C O N T E N T S.

THE ACTIVE PRINCIPLES OF ERGOT.

I.

Introduction.

One of the most interesting drugs, from both a
pharmacological and therapeutic point of view, is ergot,
and recently this interest has been increased owing to the
isolation of certain new active principles.

Apart from its importance in medicine, ergot has
claimed attention as the cause, through its présence in
rye-bread, of epidemics of ergotism once common throughout
Europe.

There are few drugs more familiar to the physician;
there are few of which his knowledge is more inexact or
the uses more empirical.

There are many different views accounting for this
condition of affairs.   It is generally admitted that ergot
is of unstable character and uncertain composition.

Preparations of this substance rapidly lose their
active properties and become inert, "the quantity sufficient
to produce very marked effects in Autumn may be found
entirely inert in the Spring" (Cushny), whilst its known
and unknown active principles, even in the fresh drug, vary
in their relative strengths, readily decompose, and are
inconstant in their presence.

That the incidence, of the relative strengths and
proportions of the active principles of ergot, is irregular,
is supported by the fact that in some cases of ergotism,
the most notable feature is convulsions, whilst in others,
gangrene is mostly present. This shows that the composi-
tion of ergot is variable, sometimes one, and sometimes the
other active principle preponderating.

Further, whilst it has been generally accepted that
the action of ergot is the resultant of the actions of certain
active principles, there is a great difference of opinion as
to the identity of these active principles.

The characteristic action and uses of ergot are in
connection with the uterus, and it is just on these points
that the results of experimental research and the experiences
of obstetricians disagree.

This difference of opinion, between clinical and
scientific workers, is probably due to the fact that, whilst
the former are working with a mixture of active principles
whose actions may, in some respects, be antagonistic, the
latter are working with more or less pure substances of
definite pharmacological action.

On the one hand ergot is said to cause peristaltic
contraction of the uterus (Hale White); whilst on the
other, obstetricians contend that it causes tetany of the
uterus in labour, and on that account, owing to its dangers
to the foetus and the course of labour, hold that it should
never be given until after the expulsion of the uterine

contents (Jellett).   Some, indeed, think that these fears
are exaggerated, that it is a question of dosage (Cushny);
others, that it may be given before expulsion of the
placenta as a preventive against "flooding", though it has
been thought that when so given, it is apt to cause the
irregular contraction of the uterus known as "hour-glass"
contraction, in which there is retention of the placenta
in the upper segment (Galabin).   (The writer has had
personal experience of these two conditions as the result
of ergot so given.)

Again, its therapeutic use in haemorrhage, except in
that from the uterus, is at variance with its action in
raising the blood pressure, by constriction of the arter-
ioles.

It has been sought in these remarks to shew the
chaotic state of our knowledge of the chemistry and phar-
macology of ergot, which has its corollary in the empiricism
of its therapeutics.

It is a valuable drug with a specific action on an
organ specially subject to disease from its great physio-
logical activity, but it is essential that we should use
it intelligently if we are to gain its fullest service.

The subject of this thesis is to give a review of
present day knowledge of ergot, with special reference to
active principles recently isolated, illustrated by cases
in which these have been used.

II.

HISTORICAL OUTLINE.

For many years, those who were engaged in the investigation of the active principles of ergot, only succeeded in isolating some of its inert constituents. The physiologically active preparations they were able to obtain were simply crude resinous mixtures, which their discoverers regarded as acids or alkaloids according to their methods of preparation.

In 1814, Pettenkofer isolated some crystals from ergot which he thought resembled those of morphine.

In 1826, Combes, working on ergot, stated that he found starch but could not separate any active principle, and down to about 1830, practically nothing was known of its chemical composition.

The first important contribution on the subject was made by Wiggers in 1831. He found, in his analysis of ergot, a waxy substance which he called cerin, 35 per cent. of oil, sugar and phosphates.

He, also, found in it a resinous body soluble in alcohol but insoluble in ether and water, which he called ergotin. This resin he thought to be an active principle from its toxic action on cocks.

Further, he shrewdly suggested that the therapeutic properties of ergot preparations were due to a water soluble principle.

In 1842, Bonjean published the results of his researches. He found two active principles in ergot, one of which was a powerful poison, and the other a valuable medicinal substance.

He called the former oil of ergot, and the latter ergotin. Ergotin soon came into general use as a drug in various diseases such as haemoptysis, dysentery, etc., and to this day is still known as Bonjean's Ergotin.

A long time after - in 1864 - Wenzell discovered two alkaloids, ergotine and ecboline; and, later, in 1874, Buchheim declared that "the putrid and septic substances" were the sole source of the action of ergot, a theory that in the light of latest knowledge on the subject, was not so far astray as would at first sight seem.

The first approach towards the isolation of a pure active principle from ergot was made by Tanret in 1875, who first described the crystalline alkaloid "ergotinine", and an amorphous alkaloid which he regarded as a mere physical modification of the crystalline.

Although the alkaloid was found by subsequent workers it was not always recognised as such - hence its variety of synonyms, e.g. picrosclerotine, Dragendorff and Podwyssotski, 1877; sclerocrystalline, Podwyssotski, 1883; secaline, Jacobi, 1897.

In 1884, Kobert published the results of his important investigations.

He stated that ergot contained three active principles - ergotinic acid, sphacelinic acid, and cornutine, an alkaloid.

Ergotinic acid is a glucoside, soluble in water.
It depresses the central nervous system, and lowers the
blood pressure.   It has been described by Kraft as a mixture
containing secale-amino-sulphonic acid.   Kobert stated that
it had no therapeutic value.   He claimed that sphacelinic
acid and the alkaloid cornutine were the therapeutic prin-
ciples of ergot: that both cause contraction of the uterus
and raise the blood pressure, but that they differed in
their toxic effects, the acid giving rise to gangrene whilst
the alkaloid had a convulsant action like strychnine.

Later, Kobert, in 1889, held cornutine to be the best
active principle for therapeutic use.   Tanret's ergotinine,
he said, was inactive, - an opinion which was strongly
combated by Tanret.

Keller in 1894 declared that Tanret's ergotinine
and Kobert's cornutine were one and the same.   He, later,
in 1896, withdrew this opinion, and maintained that cornutine
was a product of decomposition of ergotinine.

Jacobi published his important results in 1897.
He agreed generally with Kobert on the composition
of ergotinic acid and cornutine but differed from him on that
of sphacelinic acid.   He found from his analysis that
sphacelinic acid was a mixture containing an active principle,
a nitrogen free resin which he called "sphacelotoxin" in
combination with an elementary principle "ergochrysin" and
and inactive alkaloid "secalin" to form "chrysotoxin" and
"secalintoxin" respectively.

Jacobi's conclusions were generally accepted up till the recent discoveries of Barger and Carr, and Kraft.

In 1904, Vahlen published the results of his experiments with a water soluble principle which he claimed to have discovered, and to which he gave the name of Clavin.

In 1906, Barger and Carr isolated a highly active aklaloid from ergot which they named ergotoxine, and which, though itself amorphous, can in the form of its crystalline salts be prepared in a state of chemical purity.

Independently and co-incidently, Kraft isolated an amorphous alkaloid identical in every respect with ergotoxine.   He called it "hydroergotinine".   It has since been shown that "ergotoxine" or "hydroergotinine" is the hydrate of Tanret's crystalline ergotinine, and that either can easily be converted into the other;   and also, that the active principles prepared both by Kobert and Jacobi owe their activity to the presence in them of ergotoxine.

The latest discovery is that of Barger and Dale in May 1909.   They announced the discovery of the active principles parahydroxyphenylethylamine and a trace of isoamylamine in aqueous extracts of ergot:

These substances are active pressor principles which are produced by the action either of the ferments normally present in ergot or by bacterial action.

Still more recently — in July of 1909 — Tanret isolated an alkaloid from ergot which he termed ergotionine,

but there is no evidence that it is physiologically active. This brings us up to the present time, and ergotoxine, parahydroxyphenylethylamine, and a trace of isoamylamine may be considered in the light of our present knowledge as the active principles of ergot. periments on a decerebrated cat under artificial respiration, that some ergot preparations give rise to the following specific effects:-

(1) A primary stimulation of plain muscle, especially of the arteries, the uterus, and the sphincter iridis.

(2) A secondary paralysis of the motor elements of the nerve endings or myoneural junctions which are served by the true sympathetic system and are stimulated by the suprarenal active principle, the normal functions, at the same time, of the inhibitor elements and of the autonomic cranial and sacral root nerves not being affected.

This double action is best brought out on the vaso-motor system.

If a strong dose of an ergot preparation such as chrysotoxin or commercial ergotinine (which is chiefly ergotoxin) be injected into a vein, there is a marked and well sustained rise in the blood pressure. If during this rise, the sympathetic nerve supply is excited by faradisation of the spinal cord or by the intravenous injection of suprarenal extract or nicotine, there is a fall instead of the usual rise: there is a vaso-motor reversal.

Cushny with pharmacopeial preparations obtained similar results although in a less marked form, the secondary or paralytic effect being relatively slight.

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PHARMACOLOGY OF ERGOTOXINE.

It has been found from experiments on a decerebrated
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He, like Barger and Dale, in the absence of a better explanation, concluded that the primary effect was due to one active principle and the secondary to another.

The discovery, however, by Barger and Carr, of the alkaloid ergotoxine and its isolation in the form of pure salts, showed that this was not the case.

It was found that these, when given in very small doses, gave rise to results identical in every way with those produced by large doses of chrysotoxin; the logical conclusion therefore being that both primary and secondary effects were due entirely to ergotoxine.

The strength of any given dose of the alkaloid in the form of a pure salt may be approximately estimated by its depressor action when opposed to that of a pressor as suprarenal extract or other excitant of the vaso-motor system: thus, in a decerebrate cat under artificial respir-ation, 0·5 mgm. per Kilo. reverses the pressor effect of 0·1 mgm. of suprarenal extract on the sympathetic system.

The most typical results were obtained in the decerebrated animal under artificial respiration, as by these means the results were free from the vitiating influence of the higher centres in the medulla, upon which the alkaloid had a depressant effect.

The action of ergotoxine is peripheral. It first stimulates, then paralyses the sympathetic motor myoneural junctions in plain muscle, as is proved by the fact that it reacts to barium chloride but not to suprarenal extract;

or again, if the myoneural junctions are paralysed by
apocodeine, the primary or pressor effect on the injection
of ergotoxine does not follow.

Ergotoxine also acts on the stomach and intestines,
and bladder.

Dale found ergotoxine to have very slight action on
the isolated heart.   On the intact animal with medullary
centres and vagi complete, there is a marked slowing of the
pulse, and even when the vagi are cut, there is some
slowing.

This action is less after atropine.   These results
have been confirmed by those of Cronyn and Henderson.

GENERAL PHYSIOLOGICAL ACTION OF ERGOTOXINE.

Having dealt with the results on decerebrate animals
under artificial respiration, which specially demonstrate
the action of ergotoxine on the vascular system, we will
now consider its general toxic action on the intact animal,
in relation to the other active principles of ergot.

Kobert found cornutine even in minute doses e.g.
1/32 mgm. produce spastic rigidity in the frog.

In the same animal, Barger and Dale, with a large
dose of ergotoxine phosphate, obtained a slight reaction,
the main features of which were an initial excitability
followed by muscular weakness, specially marked in the
hind legs.

Similar results followed the injection of small

doses, e.g. 1/10 to 1/30 mgm.

The action of ergotoxine on mammals was of a more marked character, and resembled more closely than on the frog, the convulsive action of cornutine.

In the rabbit, one to two mgms. gave rise to general restlessness, muscular weakness and twitchings, accelerated breathing, and paralysis.

Susceptibility varied to a certain extent with the individual, whilst tolerance seemed to follow repeated doses.

One rabbit, after having had 56·5 mgms, of the phosphate of ergotoxine in 47 days, showed no sign of gangrene, and was little the worse for its experience.

The full physiological activity of the alkaloid was well shown in the cat.

Five mgms. of the phosphate gave rise, in the order of their occurrence, to the following general effects: hypersensitiveness, profuse salivation, somnolence, "pin-point" pupils, paralysis of sphincters and death.

Whilst these were the characteristic effects generally resulting from the injection of ergotoxine phosphate in the cat, one of the most important and interesting was its influence on the gravid uterus.

Three mgms. given to a large cat in the last week of pregnancy, was found to produce well marked and sustained contraction of the uterus on the foetuses as felt through the abdominal wall.   Next morning the cat gave birth to three dead but well developed kittens.   A practically similar result was obtained in another pregnant cat.

The active principles concerned in the production of the two classical forms of ergotism, the convulsive and the gangrenous, have, until the discovery by Kraft, and Barger, Carr, and Dale, of the alkaloid ergotoxine, been commonly believed to be cornutine (Kobert 1884) and sphacelotoxin (Jacobi 1897) respectively.

As has been already remarked, ergotoxin has a superficial resemblance to cornutine by its action on the central nervous system, but differs from it in that it does not give rise to spastic rigidity in the frog, and that it causes gangrene in the cock's comb.

Cornutine is a mixture of alkaloids (Sollman), an alkaloidal resin which probably contains some ergotoxine, and, from its convulsive action, some other active body, which may be a product of decomposition of ergotoxine (Barger and Dale).

The experiments of Dale with ergotoxine on the cock are important from their bearing on the relation of the alkaloid to sphacelotoxin in the causation of gangrene.

Whilst the results varied to some extent with the breed of cock, where slow absorption was provided for, gangrene of the comb was a typical and specific effect.

According to Cronyn and Henderson the gangrene produced by ergotoxine is not so marked as that produced by the galenical preparation of ergot, an opinion, they state, confirmed by the experiments of Vahlen.

Whilst they admit this difference may be due to the rate of absorption, they suggest that it may depend on the action of

another toxic principle.

Sphacelotoxin is an impure substance corresponding chemically and physiologically to ergotoxin which is present to the extent of 50 per cent.   This composition accords with the fact that Dale obtained with 2 mgms. of ergotoxine similar results in the cock to those of Jacobi with 5 - 8 mgms.of sphacelotoxin.

We will now consider the composition of the various substances which have been put forward from time to time as active principles of ergot, and contributed so much to the confusion on the subject.

Ecboline and ergotine (Wenzell) - Mixtures of alkaloids containing
   choline (Meulenhoff).

Amorphous ergotinine (Tanret) - Impure mixture of ergotinine
   and ergotoxine.

Picrosclerotine (Dragendorff) - Ergotinine, possibly mixed
   with ergotoxine.

Sclerocrystalline (Podwyssotski) - Ergotinine.

Sphacelinic Acid (Kobert) - Inactive resin with adherent
   alkaloid.

Cornutine (Kobert) - An alkaloidal resin, probably containing
   some ergotoxine and some other active substance which may
   be a product of decomposition of ergotoxine.

Cornutine (Keller) - Impure mixture of ergotinine with ergotoxine.

Chrysotoxin (Jacobi) - Inactive yellow pigment with a small
   quantity of alkaloid.

Secalintoxin (Jacobi) - Mixture of ergotinine and ergotoxine.

Sphacelotoxin (Jacobi) - Impure ergotoxine.

Hydroergotinin (Kraft) - Synonym for ergotoxine.

Much of the confusion which has arisen in establishing
the identity of Tanret's ergotinine and its physiological
character, has been due to physical and chemical changes in
it, the result of the crystalline alkaloid taking up one
molecule of water and becoming the amorphous hydrate, i.e.
ergotoxine.

$$\text{Ergotinine} \qquad\qquad \text{Ergotoxine}$$
$$(C_{35}H_{39}O_5N_5) + H_2O = C_{35}H_{41}O_6N_5$$
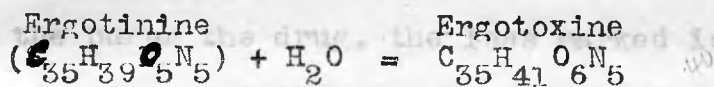
Barger and Carr give $C_{35}H_{39}O_5N_5$ and Tanret $C_{35}H_{40}O_5N_5$ as
the formula for ergotinine.

Closely related to ergotoxine in its chemical con-
stitution, ergotinine differs from it in its physical and
Physiological qualities.   Physiologically inactive, ergotinine
is crystalline, very slightly soluble in alcohol, and very
soluble in chloroform.

It forms amorphous salts.

Ergotoxine is physiologically very active, amorphous,
forms crystalline salts, and is readily soluble in alcohol.
Its phosphate is soluble in 313 parts cold and in 14 parts
boiling 90 per cent. alcohol, and forms colloidal solutions
with water.

The relation of ergotoxine to the galenical preparations of
ergot.

The galenical preparations of ergot vary to a consider-
able extent quantitively in their physiological action, which

seems, however, to be essentially similar to ergotoxine
except in the following detail.

When a galenical preparation is injected into a vein,
the rise in blood pressure in preceded by an initial fall.
(Sollman & Brown; Cronyn & Henderson).

This does not occur with ergotoxine. According to
Dixon, it is probably due to choline and other impurities,
as the purer the drug, the less marked is the fall, and it
is absent when injected subcutaneously.

The fall and rise in blood pressure were produced by
all the galenical preparations experimented with by Cronyn
and Henderson, but varied in degree and duration with the
preparation.

Dixon states that ergot has an action on the heart,
causing it to contract more vigorously and completely and
increasing its outflow.

Its action is similar to suprarenal extract, but
differs from it in that it is more sustained in character,
from which he infers that the suprarenal extract acts on the
nerve endings whilst ergot acts on the heart muscle.

As the salts of ergotoxine are but slightly soluble
in water, Barger and Dale, Kraft, and Cushny, are of opinion
that the aqueous preparations of ergot have a greater phar-
macological activity than can be accounted for by the amount
of ergotoxine in them.

Cronyn and Henderson have suggested that the solubility
of the alkaloid may be greatly increased by the presence of

other substances in the crude drug.

Barger and Dale state that ergotoxine is more soluble in the presence of salts and that ergotoxine is probably present as the phosphate in the aqueous preparations of ergot.

Is the greater activity of the galenical preparations relative to the small amount of ergotoxine in them, due to a water soluble principle?

As far back as 1831, Wiggers, as has already been remarked, expressed his belief that the therapeutic activity of the aqueous preparations of ergot was due to a water soluble principle, and at various times since then in the history of the subject do we find evidence of the search for this hypothetical substance, and with which the names of Wernich (1874), Zweifel (1875), Dragendorff and Podwyssotski (1877), and Denzel (1884) are specially associated.

In 1904, Vahlen announced the discovery of a water soluble principle which he called "clavin". He claimed for it the physiological action of ergot, but that, in contra-distinction to other active principles, it did not cause gangrene nor convulsions.

Barger found it to consist of leucin and asparaginic acid, whilst Dale, Kehrer, Cushny, and Cronyn and Henderson. from the results of their experiments, have stated that it has no action on the uterus.

Vahlen[*] has vigorously replied to his critics. He

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[*] E. Vahlen, Archiv. für Exp. pathol. u. pharmacol. Bd.60. 1908, p. 42.

does not accept as correct the analysis of Barger and Dale, and claims clavin to be a salt of a nitrogenous base with leucin.

In 1906, Abelous found that extracts from putrid meat raised the blood pressure when injected into the circulation.

Barger and Walpole, in 1909, identified, as the active principles responsible for this effect, isoamylamine, phenyl-ethylamine, and parahydroxyphenylethylamine, the last having its origin from tyrosine, and the first and second in all probability from leucin, and phenyl-alamine respectively.

With the knowledge of these results, Rosenheim analysed substances derived from placental extracts, which had been found by Dale and Taylor to increase the blood pressure and cause contraction of the gravid uterus. He showed that one was certainly, and the other probably, identical with the substances found by Barger and Walpole, and that they were probably, also like them, the result of incipient putrefaction.

In May 1909, Barger and Dale found that isoamylamine and p. hydroxyphenylethylamine were normally present in the aqueous extracts of ergot, They claimed for the latter base the whole of the pressor action of the liquid extract except that which is due to the small amount of exgotoxine in it.

In July of the same year, Dale and Dixon gave the results of their investigations into the physiological action of these water soluble principles.

As isoamylamine was not obtainable by the writer, his experience has necessarily been confined to p. hydroxyphenyl-ethylamine, the pharmacology of which will now be considered.

PHARMACOLOGY.

Cats, dogs, and rabbits, in every case decerebrated and anaethetised, were employed by Dale and Dixon in their experiments, but as the results were essentially the same, those on the cat will be taken as typical.

When p. hydroxyphenylethylamine is injected into the circulation, there is a sudden and rapid rise in the blood pressure which resembles the action of suprarenal extract, but differs from it in having a slower development and a longer duration.

P. hydroxyphenylethylamine is much less active than suprarenal extract, their relative activities having been estimated at 1 - 20.

As might naturally be expected of an active principle which is normally present in aqueous preparations of ergot, the action of p. hydroxyphenylethylamine resembled that of the liquid extract on the circulation as described by Dixon.

The rise in blood pressure which follows the administration of the active principle is due to its action on (1) the heart, (2) the arterial system, and (3) other organs containing plain muscle, e.g. uterus, spleen, etc.

(1) Cardiometer records show that there is an increased output of blood from the ventricles as the result of the greater frequency and amplitude of their contractions. That these effects are due to direct action on the heart muscle, is evident from the fact that they are also produced when the heart is

perfused with a Ringer-Locke solution containing para-hydroxyphenylethylamine.

(2) The vaso-constriction of the arterial system has a large share in the causation of the increase in vascular tension, and as this also follows when the method of adminis-tration is by perfusion, its origin is largely peripheral.

P. hydroxyphenylethylamine, like suprarenal extract, constricts the pulmonary arterioles.

(3) Whilst the increase in blood pressure is mostly due to the augmented power of the heart and the constriction of the arterial system, the contraction of plain muscle throughout the body in such organs as (a) the spleen, and (b) the uterus, must, by diminishing their bulk as the result of the expression of blood from them, contribute to that effect.

(b) Parahydroxyphenylethylamine caused contraction of the spleen by its action on its muscular capsule.

(b) Its action on the uterus of the rabbit and the cat presented an important difference which is related to the fact that that organ in some animals is peculiarly susceptible to vaso-motor influences. (Langley and Anderson) (Langley).

In the rabbit p. hydroxyphenylethylamine caused contraction of the uterus in its pregnant and non-pregnant states. In the cat, on the other hand, its action had a definite relation to the physiological state of the uterus; it caused, like suprerenal extract, inhibition

of tone and rhythm in the non-pregnant and contraction in
the pregnant uterus.

Its motor action, however, was much stronger that its
inhibitory, thus differing from suprarenal extract in which
the reverse obtains.

Whilst p. hydroxyphenylethylamine has a decided
action on the pregnant uterus, Dale and Dixon were unable,
even with strong doses, to induce abortion in a cat and
goat, both of which were near the end of pregnancy.

The inhibitory action on the non-pregnant uterus is
also seen on the bladder and the stomach and intestines of
the cat.

Here again, as in the non-pregnant uterus, the inhibi-
tion of the tone and rhythm of these organs was much less
marked with p. hydroxyphenylethylamine than with suprarenal
extract.

On the eye p. hydroxyphenylethylamine gave rise to
effects similar to those which follow excitation of the
cervical sympathetic, e.g. dilatation of the pupil, widening
of the palpebral fissure, protrusion of the eyeballs, etc.

P. hydroxyphenylethylamine, like suprarenal extract,
excited secretion in the lachrymal, salivary and sudoriparous
glands of the cat: also of the kidneys, but in this case it
was probably due to the increased vascular tension.

Whilst the vaso-motor effects of p. hydroxyphenyl-
ethylamine which give rise to an increase in blood pressure
are very largely, they are not altogether the result of

peripheral innervation; for, if the sympathetic nerve cells be paralysed with injection of nicotine, the subsequent rise in the blood pressure after the injection of the active principle is of a less marked character than usual.

As paralytic doses of nicotine do not affect the pressor action of suprarenal extract, the action of the latter is more wholly peripheral that p.hydroxyphenylethylamine. Suprarenal extract, as we have seen, is much more active than p.hydroxyphenylethylamine, but this only obtains when the method of administration is by intravenous injection; when given by the mouth or hypodermically, owing to the great local anaemia it causes, absorption is slow, and much of its action is dissipated before it can be observed, whereas p. hydroxy- phenylethylamine has a very slight local effect on absorptive tissues and membranes and consequently retains its activity as the following results shows.

100 mgms. of p. hydroxyphenylethylamine hypodermically produced in a cat within two minutes, in a marked degree, all the effects of its physiological action.

Dale and Dixon also record the results of an experiment on one of themselves with the active principle.

Ten grains taken by the mouth on an empty stomach, within five minutes, gave evidence of rapid absorption in its physiological activity as shown by an increase in the blood pressure, which was distinctly observable 85 minutes later.

And in connection with the part played by putrefaction in the production of amines, and the fact of the ready absorption

IV.

GENERAL CONSIDERATIONS.

parahydroxyphenylethylamine from mucous surfaces, it is inter-
esting to note that according to Barger and Walpole, p. hydroxy-
phenylethylamine may result from the action of faecal bacteria
on tyrosine and be absorbed from the intestinal tract, and
produce its effects.

Further they suggest that dilatation of the pupil of the
enucleated eye of the frog, which occurs by injection of the
urine and blood serum in certain morbid states, may be due to
amines and not suprarenal extract as has been stated by some
authorities.

P.hydroxyphenylethylamine also occurs in old ripe cheese
as the result of the action of bacteria on tyrosine; whilst
both it and isoamylamine have been found in cod's liver as the
result of putrefactive processes, and were therefore present
in cod-liver oil prepared by the old method.

IV.

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The specimens of ergotoxine and p.hydroxyphenylethylamine used in these cases were those introduced and vended as "Ergotoxine" and "Tyramine" respectively by Burroughs, Wellcome & Co.

The method of administration in each and every case was by intramuscular injection, e.g. into the gluteus muscle.

Ergotoxine: Analysis of Results.

In estimating the value to be attached to a diminution in the pulse rate, it is to be borne in mind that there is commonly, especially in nervous subjects, an ante-partum acceleration of the pulse which very quickly falls post-partum; hence the pulse next day or some hours later was noted.

In cases 1, 2, 4 and 6, there was no change in the pulse rate other than that due to excitement of the occasion.

In cases 3, 5, and 14(III) a progressive diminution in the pulse rate was accompanied by an increase in tension. This is especially well shown in case 3, in which a normally slow pulse fell to 48 per minute.

A diminution in the volume of pulse was noted in cases 5 and 14(III).

A distinct increase in vascular tension was noted in cases 3, 5, and 14(III), coincident with a diminution in the pulse rate.

Action of Ergotoxine on the Uterus.

Ergotoxine had absolutely no action of any kind on the uterus, e.g. Cases 2, 4, 6, 14(I).

Parahydroxyphenylethylamine.

The results obtained with this active principle were of such a negative character as to be quite devoid of any significance.

In case 9, there was a slight diminution of the pulse rate and increase in tension; also, in case 14(II), but in it the changes were probably due to greater composure of the patient.

On the uterus p.hydroxyphenylethylamine had no action of any kind, e.g. cases 12, 13, and 14(II). This inactivity of p.hydroxyphenylethylamine on the uterus is especially well seen in the twin birth, i.e. case 13.

Conclusions.

In considering the results obtained with ergotoxine and parahydroxyphenylethylamine, as set forth in these cases, it is to be admitted that they are from the circumstances of private practice, necessarily of a somewhat rough character. However desirable, it is difficult, indeed impossible, to make use of the mechanism of the laboratory in the lying-in room.

The results obtained with p. hydroxyphenylethylamine were of such a negative kind as to furnish no suggestions as to its therapeutic use; whilst those obtained with ergotoxine, only

less negative, suggest from its action on the circulation,
that it might be useful in cases characterised by low blood
pressure, e.g. shock.

These results on the human subject do not bear out the
high promise of therapeutic value contained in those obtained
on the animal, but allowance must be made for the physiological
differences, as also for the fact that the method of adminis-
tration in the latter was the more active form of intravenous
injection.

Further, it may be that the doses of ergotoxine and p.
hydroxyphenylethylamine employed in these cases, although
greater than the maxima recommended by Burroughs, Wellcome &
Co., are too small to yield appreciable results.

V.

CLINICAL TRIALS.

Ergotoxine   1/100 grain (0·00065 gm.)

F. Mrs. aet. 27. III para.   Case I.

	Vertex, pains good and regular.
3.10 a.m.	Pulse 84, moderately full and strong.
3.20 "	Birth. Ergotoxine injected.
3.22 "	Uterus midway between umbilicum and symphysis pubis; which position, alternately relaxing and contracting, it maintained.
3.24 "	Placenta expressed.
	Pulse 78, otherwise unchanged.
3.30 "	Pulse 75, unchanged.
3.40 "	Pulse 72, "
3.50 "	Pulse 72, " Uterus well contracted.
12 noon.	Pulse 74. Moderate in size and good tension.

Comments: Nothing unusual noted in pulse or uterus.

Ergotoxine 1/100 gr. (0·00065 gm.)

L. Mrs. aet. 25. II para.   Case 2.

5   a.m.   Labour began, vertex.

11   "   Pulse 120 small and soft.   Patient not been
                      well for some time.   Heart normal.

2   "   Pulse 100, small and soft.

2.10   "   Head in cavity; "pains" frequent but small.
                      1/100 gr. Ergotoxine injected.

2.15   "   )   Pulse 1001 as above.
)
2.28   "   )   No change of any kind in character of pains.

2.30   "   Birth, normal.

2.35   "   Pulse 84, tension firmer.

2.40   "   Placenta expressed; uterus well contracted;
                      pulse 84, small.

                  Next day, pulse 80, small.

Ergotoxine 1/50 gr. (0·0013 gm.).

T. Mrs. aet.28. primipara.   Case 3.

5   a.m.   Labour began, vertex.

5.30 p.m.   Pulse 60, fair volume and good.   Chloroform
                   administered – partial anaethesia to deaden
                   pain.

4.5   "   Birth.   Ergotoxine injected.

4.7   "   Pulse 60.

4.10   "   Placenta expressed.

              Pulse 64.   )

4.17   "   "   56.   )   No change in volume of

4.23   "   "   54.   )   pulse, but increase in

4.30   "   "   54.   )   tension pari passu with

4.35   "   "   52.   )   diminution in frequency.

4.40   "   "   52.   )

4.45   "   "   48–50)

9. p.m.   Pulse 65.

Ergotoxine 1/25 gr. (0·00195 gm.)

W. Mrs. aet. 34. IV. para.   Case 4.

Time	Notes
1.30 p.m.	Labour began; vertex.
6.30 "	Pulse 116, fair size and tension. "Pains" have fallen off and have little expulsive force.
6.45 "	Pulse 106 - unchanged. Head close on outlet and parts lax; injected 1/25 gr. ergotoxine.
7.1 "	No change in trivial character of "pains". Since injection was given there have been 7, all under 3/4th min. in duration. Pulse 100 unchanged.
7.11 "	After quiescent interval of 10 minutes, a very slight pain of 1/4 min. duration.
4.18 "	As no progress, forceps to head and delivery.
4.21 "	Pulse 96.
4.27 "	Placenta expressed.
7.30 "	Pulse 96)
7.35 "	" 88) Fair size and tension.
Next day	" 90)

Ergotoxine 1/50 gr. (0·0013 gm.)

T. Mrs. aet. 39. IX. para.   Case 5.

3.   a.m.   Labour began; vertex.
5.5   "   Pulse 90 - 100, small and compressible.
5.17   "   Birth; ergotoxine injected.
5.19   "   Pulse 76.
5.25   "   "   68.
5.30   "   Placenta expressed.
                Pulse 65, smaller and harder.
5.39   "   Pulse 72.
5.43   "   Pulse 64.   )   Small 'wiry' pulse.
5.48   "   Pulse 64.   )   Uterus well contracted at
6   "   Pulse 60.   )   level of umbilicus.

Next day, pulse 72 and fair.

Comments: Slight diminution in calibre of radial noted.

            Increase in tension, and diminution in frequency

            of pulse.

Ergotoxine 1/50 gr. (0·0013 gm.)

S. Mrs.   aet. 25.   II. para.   Case 6.

11.30 p.m.   Labour began; vertex.

3.55 a.m.   Head in cavity.   "Pains" every three minutes
                    but short and with little force.
                    Pulse 92, moderately full and good.

4.30   "   As little progress, and no obstruction to birth,
                    ergotoxine 1/50 gr. injected.

4.42   "   Patient sick and vomited.

4.48   "   Pulse 90, not so full, nor so good.

5   "   Since injection was given there have been 13
                    "pains" varying in duration from 1/4 to $1\frac{1}{5}$
                    minutes duration (mostly 1/2 minute).

5.8   "   Forceps to head and child delivered.

5.15   •   Placenta expressed.   Pulse 74 and character as noted
                    last.   Uterus well contracted, below umbilicus.

1.30 p.m.   Pulse 72, fair volume and good tension.

Parahydroxyphenylethylamine 0·005 gm.

U. Mrs. aet. 34. II. para.   Case 7.

3	a.m.	Labour began; vertex.
7.45	"	Pulse 72, of moderate volume and good tension.
8.	"	Birth, normal.
8.5	"	Pulse unchanged.
8.10	"	Placenta expressed.
		"Tyramine" 0·005 gm. injected.
8.12	"	Uterus hard and size of cricket ball. Pulse 72; unchanged in character.
8.20	"	Uterus low in pelvis; pulse maintains its ante-
8.30	"	partum character.
1.30	"	Uterus below umbilicus. Pulse 72.

Comments: No change of any kind in pulse.

Parahydroxyphenylethylamine 0.005 gm.

W. Mrs. aet. 42. IV. para.   Case 8.

5.30 a.m.   Labour began; pains strong and frequent.

8.20 "   Birth, normal; a few minutes before arrival.

8.23 "   Pulse 72, of good tension and small volume.

8.30 "   Placenta expressed.

                 "Tyramine" 0.005 gm. injected.

                 Pulse 72.

                 Uterus at level of umbilicus, contracting later

                   to lie between pubis and umbilicus.

                     No change in pulse.

8.40 ")
)
8.45 ")   Pulse maintains its ante-partum character.
)
B.50 ")

1.   "   Patient complained of severe "after-pains"

                 setting in after birth - neurotic.

Comments: No change in pulse of any kind.

Parahydroxyphenylethylamine 0·0075 gm.

<div align="right">Case 9.</div>

S.Mrs.   aet. 28. II.para.   Patient has initial stenosis.

6.30 a.m.   Membranes ruptured spontaneously.   "Pains"

              small till 2.30 p.m., then strong till birth.

4.5 p.m.   Pulse 84, small and soft.

4.20 "   Birth.   Tyramine injected.

4.25 "   Pulse 80, unchanged.

4.30 "   Pulse as above.

4.35 "   Placenta expressed.   Pulse 75, slightly but

              appreciably stronger in tension.

4.40 "   Uterus well contracted, size of foetal head, between

              symphysis pubis and umbilicus.

4.50 "   Pulse 75, increase in tension maintained. Uterus

              as above.

             Next day pulse was 80, small and compressible.

Parahydroxyphenylethylamine. 0·01 gm.

P. Mrs. aet.24. primipara.   Case 10.

6.0 a.m.   Labour began, vertex.

7.20 p.m.   Pulse 86, volume moderate, tension good.

8.7   "   Birth.   "Tyramine" injected.

8.12 "   Pulse 80, full, good.

8.17 "   Pulse 72, smaller and harder.

8.23 "   Pulse as above. Uterus hard, between pubis and

             umbilicus.

8.30 "   Pulse 72.   Change in volume not maintained,

             again full.

8.35 "   Pulse 74.

8.52 "   Pulse 68, full and hard; little difference in

             its volume on pressure.

             Uterus well contracted.

             Next day, pulse 74, moderately full and good.

Parahydroxyphenylethylamine 0·01 gm.

F. Mrs. VII. para.   Case 11.

Time	Event
10 a.m.	Labour began; vertex.
1.45 p.m.	Birth (before arrival).
2.30 "	Pulse 76, rather small, fair tension.
2.40 "	Placenta expressed. "Tyramine" injected.
2.45 "	Pulse 78, slightly fuller, otherwise unchanged.
2.50 "	Pulse 74, unchanged. Uterus well contracted, level of umbilicus.
2.55 "	Pulse 72)
3. 3 "	" 74) Unchanged in character.
3.10 "	" 74)

Comments: No effects on pulse or uterus noted.

Parahydroxyphenylethylamine (0.01 gm.)

B. Mrs., aet.27. primipara.

2.0 a.m.	Labour began; vertex.
12.40 p.m.	Head at outlet but pains short and ineffective. Pulse 84, moderate volume and good tension. "Tyramine" injected.
12.45 ")	Pulse 92.
12.50 ")	Pulse 80, unchanged.
12.55 ")	
12.58 "	No change in the frequency, duration or strength of "pains" since injection given. Chloroform administered and delivery by forceps to head.
1. 5 "	Pulse 76.
1.10 "	Placenta expressed; uterus well contracted. Pulse 76, and maintains its ante-partum character.

Parahydroxyphenylethylamine 0·01 gm.
+
I.   Ergotoxine.   1/50 gr. (0·0013 0·005 gm.

II. Parahydroxyphenylethylamine.   0·01 gm.   <u>Case 13.</u>

<u>M. Mrs., aet.31, primipara.</u>   Patient very "big"; twin

pregnancy diagnosed on palpation.

M. Mrs. aet. 33, hysterical, V. para.   Case 14. (I)

10.0	p.m.	Labour began.
6.30	"	Pulse 100, moderate volume and soft. Patient anaemic.
7.35	"	As pains ineffective and patient suffering, delivery
		of child under chloroform with forceps to head.
		"Tyramine" injected, 0·01 gm.
7.37	"	Pulse 92.
7.47	"	Pulse 100, less slack in character.
7.55	"	Pulse 100, and slight improvement in tension maintained.
8. 5	"	Pulse as above. Uterus is contracted on second foetus,
		breech of which can be felt high up, with intact
		membranes. As no pains whatsoever since birth
		of first child and injection of "Tyramine" another
		injection of 0·005 gm. given with hope of inducing
		uterine contraction. ·
8.15	"	Pulse 96, and as last noted.
8.30	"	As uterine inertia persists, membranes ruptured and
		live female child delivered by traction on foot.
8.35	"	Placenta expressed. Fair amount of post-partum
		haemorrhage. Patient in rather a low state. Pulse
		variable in rate 100 - 110.
8.45	"	Pulse 100, moderate in volume and soft.
8.50	"	Uterus well contracted, pulse as above.
<u>Comments:</u>		The most notable feature in this case was the absolute
		failure of p. hydroxyphenylethylamine to promote
		contraction of the uterus and expulsion of 2nd foetus.

I.   Ergotoxine.   1/50 gr. (0·0013 gm.)

II. Parahydroxyphenylethylamine.   0·01 gm.

III. Ergotoxine.   1/25 gr. (0·00195 gm.)

J. Mrs. aet. 33, hysterical, V. para.   Case 14. (I)

Patient had had "niggling" pains throughout day but with no "show". Os size of half-crown and dilatable. Confinement due.

9.46 p.m.   Ergotoxine 1/50 gr. injected.

Pulse 100, small, fair tension.

9.55 "   Pulse 100, somewhat fuller, otherwise unchanged.

10.5 "   Pulse as above. No "pains" whatsoever since injection was given.

(II)

Next day, at 4.30 a.m. had some "pains" with "show".

1.35 p.m.   Pulse 100, small, fair tension. P.hydroxyphenyl-ethylamine 0·01 gm. injected.

1.40 "   Pulse 84, small but of stronger tension. Patient drowsy, probably from want of sleep.

1.42 "   Pulse 80, improvement maintained.

1.48 "   Pulse very irregular, 84 to 104 and smaller in volume.

2. 0 p.m.   Pulse steadier, 100.

2. 5 "   As no sign of uterine activity, membranes ruptured.

Labour set in 20 minutes after rupture of membranes.

4.25 p.m.	Birth; vertex. Ergotoxine 1/25 gr. injected.
"	Pulse 100, small, fair tension.
4.31 "	Pulse 82.
4.37 "	Pulse 80. Placenta expressed.
4.42 "	Pulse 80.
4.48 *	Pulse 70, decided increase in tension; no difference
	in volume.
4.53 "	Pulse 64.)
4.58 "	Pulse 64.) Smaller in volume and "wiry" in character.
5. 5 "	Pulse 64.)

Next day, pulse 70.

VI.

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