A Preliminary Report ON COCAINE, BUTYN, TUTOCAIN, AND OTHER LOCAL ANAESTHETICS.

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Introduction.

Few drugs are of greater importance at the present time, both on account of their clinical interest and their habit-forming properties, than the group of local anaesthetics. The object of the present experiments was the investigation of the properties of local anaesthetics already well known, together with the action of such others as have not been thoroughly investigated, with a view to deciding whether any of these drugs could be regarded as satisfying the ideal of what a local anaesthetic should be, while at the same time producing relatively little action on the central nervous system such as might give rise to their abuse as habit-forming drugs.

The laboratory investigation of the action of these drugs, whilst all-important and, indeed, conclusive in some respects, is restricted in others—as, for example, by the difficulty in making reliable observations of subjective phenomena such as those of habit formation, etc. Before proceeding to give my experimental results it is necessary to make clear the properties which the ideal local anaesthetic should possess, and these may be briefly summarized:

1. Powerful local anaesthesia.
2. Low toxicity in proportion to anaesthetic power.
3. No irritating action, or power of causing local damage to tissues. This is another method of saying that it should possess a highly selective affinity for nerve fibrils, and relatively none for other tissues.
4. Sufficient solubility; stability on keeping; not destroyed by boiling.
5. Absorption by mucous membranes; should not be precipitated by saline solution or tissue fluids.
6. Relatively no central stimulating effect on the cerebral cortex, which is the property that induces habit formation.
7. Expense.

It must be remembered that a local anaesthetic suitable for one purpose may not be suitable for another; for special purposes other qualities are required. Thus, for the eye the anaesthetic should not cause lachrymation, smarting, or desiccation of the cornea; for certain operations dilatation of the pupil is also undesirable. For nasal work the drug must cause shrinking of the nasal mucous membrane. It is certain that any local anaesthetic capable of fulfilling all these conditions will not merely supersede cocaine; it will also extend the field of local anaesthesia.

For the purposes of this investigation experiments were made on dogs, cats, rabbits, guinea-pigs, and mice, with cocaine, beta-eucaine lactate, alypin, novocain, stovaine, holocaine, tropacocaine, apothesine, phenolaine, butyn, and also with a new cocaine substitute named "tutocain," to which my attention was directed by Professor H. H. Dale. Tutocain is the newest of the substitutes, having some chemical relationship with alypin. It has the constitutional structure shown¹—

Tutocain is not decomposed by boiling, and has the advantage over butyn that it can be dissolved in saline. It is prepared by the Bayer Company, who have kindly furnished me with a supply for experiments.

Surface Anaesthesia: Comparative Efficiency.

A good method for investigating "surface anaesthesia" for the rabbit's cornea is described by Sollmann^{13 14 15}; I have slightly modified the method. Several tests must be made for each concentration, using different animals, as individual differences in the animals sometimes occur.

The animal is confined in a comfortable stall, the head being free. All eyelashes and long hairs around the eye are clipped. The lower conjunctival sac is kept flooded with the solution for exactly one minute, and subsequent tests for anaesthesia are made by touching and stroking the centre of the cornea with the blunt point of a pencil. Anaesthesia is considered to be complete when no winking reflex is obtained on moderately firm stroking. The time of onset and the duration of this complete anaesthesia are noted, and are considered to be a fair criterion of the depth of anaesthesia. In Sollmann's experiments the animals were released for ten minutes immediately after the application of the drug. This procedure considerably weakens the effect of the anaesthetic, as is shown by the following experiments:

Rabbit.—The right eye received one instillation of 1 per cent. butyn for one minute, and the rabbit was then released for ten minutes. Result: Anaesthesia incomplete ten minutes after butyn. Immediately after the first experiment an equal quantity of the same solution of butyn was instilled into the left eye of the same rabbit, for one minute; after this the rabbit was kept confined. Very little winking occurred, the cornea thus receiving the full effect of the anaesthetic (as when eyelid retractors are used clinically). Result: Complete anaesthesia, to firm stroking of the cornea, up to twenty-nine minutes, and passing off at thirty minutes.

Table I gives approximately the duration of complete anaesthesia in minutes, the minimum effective concentra-

TABLE I.—Anaesthetic Efficiency on Rabbit's Cornea.
(Figures refer to the duration of complete anaesthesia, in minutes.)

DRUG.	1/20 per cent.	1/10 per cent.	1/8 per cent.	1/4 per cent.	1/2 per cent.	1 per cent.	2 per cent.	5 per cent.	8 per cent.	10 per cent.	Minimum Effective Concentration.	Complete Effect of Cocaine = 1.
1. Holocaine hydrochloride ...	—	I.A.	6	14	19	31	50	Over 40*	—	—	Per cent. 1/8	2½
2. Butyn	N.A.	I.A.	4	11	16	30	42	Over 40	—	—	1/8	2
3. Cocaine hydrochloride ...	N.A.	I.A.	I.A.	2	13	18	30	Over 40	—	—	1/4	1
4. Tropacocaine hydrochloride	—	—	I.A.	I.A.	8	14	19	25	40	—	1/2	4/5
5. Alypin	—	—	—	I.A.	2	10	22	34	—	—	1/2	7/10
6. Eucaine	—	—	—	N.A.	I.A.	10	16	23	—	—	1	1/2
7. Tutocain	—	N.A.	N.A.	I.A.	I.A.	6	16	21	37	—	1	1/3
8. Stovaine	—	—	—	—	—	I.A.	12	18*	—	—	2	1/4
9. Apothesine	—	—	—	—	—	—	4*	—	—	—	2	—
10. Novocain	—	—	—	—	—	N.A.	I.A.	2	8	11	5	1/20

I.A. = Incomplete anaesthesia. N.A. = No anaesthesia. * Signifies marked irritation. Phenolaine is too irritant for eye work.

TABLE II.—*Anaesthesia of Cornea: Side Actions.*

DRUG.	Vascular Reactions. Rabbit.	Drying of Cornea. Rabbit.	Sensory Irritation.		Pupil Reaction.	
			Rabbit.	Human.	Rabbit.	Human.
<i>Severe Irritants.</i>						
Apothesine (2 per cent.) ...	Marked dilatation	Moderate drying	Very considerable		No effect	
Holocaine (1 to 5 per cent.) ...	Marked dilatation	Desiccation	Very considerable	Burning irritation	No effect	
Stovaine (2 to 5 per cent.) ...	Dilatation		Very considerable		No effect	
Phenolaine ...			Too irritant for cornea			
<i>Irritants.</i>						
Alypin (1/2 to 5 per cent.) ...	Dilatation	Desiccation			No effect	
Butyn (1 to 5 per cent.) ...	Dilatation	Desiccation			No effect	No effect.
Cocaine (1/2 to 5 per cent.) ...	Primary dilatation, then constriction	Moderate drying		Smarting at first; lacrymation Slight smarting 30 secs.	Dilated	Dilated.
Eucaïne (1 to 5 per cent.) ...	Dilatation	No drying			No effect	
Tropacocaine (4 to 8 per cent.) ...	Moderate dilatation	Moderate drying			No effect	
<i>Mild Irritants.</i>						
Tutocain (2 to 5 per cent.) ...	Moderate dilatation	Moderate drying		Smarting lacrymation, slight	No effect, or slightly dilated	Slightly dilated 2 hours
Novocain (5 to 10 per cent.) ...	Moderate dilatation	No drying		No irritation	No effect	

tions, and the ratio of efficiency. Table II shows the more important side actions. All solutions were made with distilled water for comparison with butyn, which is precipitated by Ringer's solution or saline.

Holocaine, stovaine, apothesine, alypin, and phenolaine are all too irritant for ocular anaesthesia. Tropacocaine, eucaïne, and novocain, although less powerful than cocaine, are useful for minor operations. They are mildly irritant and cause moderate vaso-dilatation, which can be controlled by adrenaline.

Tutocain has one-third the anaesthetic power of cocaine and seven times that of novocain, on the rabbit's cornea, but the anaesthesia is slow in onset. On the human cornea a few drops of a 2 per cent. solution of tutocain give complete anaesthesia in about four minutes, which lasts about five minutes to firm pressure with the eye spud; slight smarting and some lacrymation occur, but the irritant effect passes off in one minute. The anaesthetic efficiency of tutocain is less than that of eucaïne and tropacocaine, and it shows less irritation and vaso-dilatation; the pupil dilates fifteen minutes after the application and remains slightly dilated for about two hours. Tutocain may be a useful anaesthetic for minor operations.

Butyn is twice as powerful as cocaine, and has no mydriatic effect, for which reasons it is preferred to cocaine by some surgeons. The disadvantages of butyn are the drying effect on the cornea, sometimes followed by desquamation, smarting and slight vaso-dilatation, and its expense. The choice for major operations must therefore lie between cocaine and butyn.

Effect on Nerve Fibres.

A simple method for determining the effect of these drugs on nerve fibres is to paint a definite length of the vagus nerve of an anaesthetized rabbit or other mammal with the various solutions. The vagus was then stimulated with the faradic current at intervals above the part painted; the duration of complete paralysis was determined by the absence of cardiac inhibition.

Table III shows that holocaine, butyn, cocaine, stovaine, phenolaine, alypin, and tutocain all give prolonged anaesthesia when brought into direct contact with nerve fibres. Eucaïne, novocain, apothesine, and tropacocaine give a much more evanescent anaesthesia. When the whole nerve is immersed in a solution of the drugs, as in Sollmann's experiments on frogs,⁸ novocain and tropacocaine give as good anaesthesia as cocaine; obviously, however, such a method gives no information as to the rapidity with which the drug is absorbed from the seat of action, or whether the drug is destroyed by the tissues.¹⁰

Blood Vessels.

It is an advantage that local anaesthetics should constrict vessels, and certainly it is a grave disadvantage when they dilate them. I therefore tested the action of the various substances on the blood vessels of the limb and lung, using Dixon's artificial perfusion method⁴ with defibrinated blood; the drugs were also injected intravenously into anaesthetized cats and rabbits, and the effect on blood pressure and on splanchnic vessels as determined by the oncometer was investigated.

By the perfusion method it was found that cocaine caused very marked vaso-constriction, and was the only local anaesthetic to induce constriction of vessels by a peripheral action. In these experiments all the other drugs, with the exception of butyn, acted as vaso-dilators, especially

TABLE III.—*Effect of Local Anaesthetics on Nerve Fibres.*
(Solutions painted on 0.5 cm. of nerve for 15 seconds.)

DRUG.	0.1 per cent.		0.5 per cent.		2 per cent.	
	A.	R.	A.	R.	A.	R.
Holocaine hydrochloride ...	15	40				
Butyn	10-17	30-40	40	50	2 hours	
Cocaine hydrochloride ...	12	30	More than 2 hours			
Stovaine	10	23	24	50		
Phenolaine			30	45	35	60
Alypin	10-16	15-20				
Tutocain	10	16				
Beta-eucaine lactate ...	1	3	12	20	20	30
Novocain	1	5	12	16		
Apothesine	0	0	8	15-20		
Tropacocaine	0	0	5	6		

A. Duration of complete paralysis in minutes.
R. Length of time for recovery in minutes.

stovaine, phenolaine, apothesine, alypin, holocaine, eucaïne, and tropacocaine, the effect being less marked for novocain and very slight in the case of tutocain. Butyn, a drug which dilates vessels, especially those of the splanchnic area, behaved in all perfusion experiments like a vaso-constrictor, a result thought to be due to its precipitation by tissue fluids in the smaller vessels.

Equal small doses (5 mg.) injected intravenously into a cat caused: with cocaine, a marked rise in blood pressure with some constriction of splanchnic vessels; with tutocain,

a much smaller rise in blood pressure, with no obvious effect on splanchnic vessels; with butyn, a fall of blood pressure followed by a more gradual recovery, with marked dilatation of the splanchnic vessels.

Nasal Mucous Membrane.

It has been found clinically that cocaine when applied directly to nasal mucous membrane will cause shrinkage, a property which is of much importance to surgeons, and which is not possessed by any well known substitute drug. Nasal mucous membrane is not merely richly vascular, but it has almost the structure of erectile tissue. Direct observation of changes in the condition of the nasal mucous membrane of animals is not feasible, and I therefore devised a special indirect method¹⁹ which was found to be suitable—namely, that of perfusing the nares of a cat or dog through a frontal sinus with warm Ringer solution at a constant temperature and pressure. A small brass tube is screwed into a trephine opening made into the frontal sinus, and by connecting this tube to a Marriotte's flask warm saline can be allowed to run through the nares, and collected and measured as it drips from the nose. When the flow is constant the connecting rubber tube is clipped and the drug is injected through it into the frontal sinus, whence it percolates into both the nasal cavities. After a given time, usually fifteen minutes, perfusion is resumed; any swelling of the mucosa will retard, while shrinkage quickly causes a marked augmentation of, the flow.

Using this method, only two local anaesthetics cause an increase in the rate of flow, cocaine and tutocain—that is, these two only cause shrinkage. Butyn causes marked swelling of the mucous membrane, which can be partly removed by adrenaline, and the swelling is less marked if the adrenaline be instilled into the nose five minutes before the application of the butyn. Other drugs which have been tested by this method are stovaine, novocain, and tropacocaine, and all cause marked congestion. Cocaine has hitherto been unsurpassed in rhinology; tutocain is the only substitute drug which causes shrinkage of the nasal mucosa; if it should prove to be an effective anaesthetic and non-toxic it may become a substitute for cocaine. Butyn is precipitated by sodium chloride, and its action is therefore uncertain. The toxicity of butyn renders the application of 5 per cent. solutions inadvisable, and a 2 per cent. solution only is recommended for the throat and nose.²⁰

Irritation.

Le Brocq¹¹ has shown that stovaine, eucaïne, and tropacocaine are too irritant to be used for subcutaneous injection, that cocaine is also irritant to tissues, while novocain is altogether free from irritant properties. I adopted le Brocq's method. Rabbits were used for the experiments: the abdomen was shaved, and the skin washed with ether. The drugs were injected in 10 per cent. solutions freshly made with twice distilled water, 0.5 c.cm. of the solution being injected subcutaneously into the upper part of the shaved area; a control injection of distilled water was made below. Cocaine immediately caused hyperaemia and slight swelling, followed later by ecchymosis and thickening for three days, and then by scab formation. Phenolaine caused hyperaemia, ecchymosis, and slight thickening immediately after injection, lasting four days, and followed by scab formation. Butyn caused slight hyperaemia lasting one day, but no thickening; there was no scab formation, but some desquamation of the skin after five days. Novocain caused no ecchymosis or thickening, nor any signs of irritation, even after the injection of a 20 per cent. solution. Tutocain caused hyperaemia and slight thickening immediately after the injection. The thickening lasted for two days and was followed by scab formation. In the above experiments all the control areas were normal. Cocaine and phenolaine act as irritants to tissues when injected subcutaneously, butyn has very little irritant action, and novocain none. Tutocain is certainly as irritant as cocaine. Experiments were made on three men, subcutaneous injections being made with 2 per cent. solutions. Marked hyperaemia and thickening of the skin is caused immediately after the injection, and some ecchymosis and tenderness persist for

about two days. Tutocain would therefore appear to be quite unsuitable for subcutaneous injection; the toxicity of butyn and cocaine²⁰ renders these drugs also undesirable, and for this purpose novocain most nearly approaches the ideal local anaesthetic.

Specific Action on the Central Nervous System.

One factor common to most local anaesthetics is that they stimulate the central nervous system. Cocaine, butyn, tutocain, and novocain all cause convulsions in rabbits after subcutaneous injection. The convulsions are followed by muscular weakness, or even by collapse if the dose has been large. Small injections not sufficient to cause convulsions give rise to muscular twitchings, especially of the head area, and the general effect is very similar to the cerebral effects produced by tutin¹⁸ and picrotoxin.³ I have satisfied myself that these convulsions are due in each instance to stimulation of the cerebral cortex. Under the influence of deep anaesthesia the convulsions do not occur. If the animal be anaesthetized, and one cerebral hemisphere destroyed, and if it be then kept lightly anaesthetized with ether, the injection of one of these drugs causes convulsions which occur on the side opposite to the whole hemisphere; further, convulsions cannot be obtained if the crura are divided. There seems, therefore, little doubt that these drugs cause convulsions by stimulating some portion of the cortex of the brain, and that this effect is followed later by depression. When these drugs are injected subcutaneously in the amounts in which they are likely to be used as local anaesthetics, their convulsant action can be placed in the following order—cocaine, butyn, tutocain. Novocain is much less effective, and for practical purposes need not be considered. This property of giving rise to powerful stimulation and excitement of the cerebral cortex is characteristic of one of the two main groups of addiction drugs represented by cocaine, a drug which excites the "emotional and relatively lower centres in the cortex" (Dixon⁵).

Butyn in relatively small doses temporarily depresses nerve ganglion cells throughout the body: the splanchnic nerves are paralysed, though post-ganglionic fibres remain active; the vagus and sympathetic in the neck are depressed; after larger doses both vagi and sympathetic are temporarily paralysed. The cells in the spinal cord are depressed in the anaesthetized cat by even a small dose of butyn, such as 5 mg. injected intravenously, and this dose antagonizes the action of strychnine, since much larger doses of this alkaloid are now required to cause convulsions.

Relatively small doses of butyn injected intravenously may cause sudden arrest of respiration in anaesthetized cats or rabbits; this is in contrast to cocaine and tutocain, which first excite respirations.

Toxicity.

Some observations were made with the object of determining the minimum lethal doses of cocaine, butyn, tutocain, and novocain for rabbits, guinea-pigs, and mice, and the results are given in Table IV. By subcutaneous injection the toxicity of tutocain for rabbits is double that of novocain, and for guinea-pigs and mice two to three times. By rapid intravenous injection of 1 per cent. solutions the toxicity of tutocain is four times that of novocain, and nearly approximates to that of cocaine and butyn. Table V gives the minimal doses required to produce mild convulsions lasting five to ten minutes in rabbits.

TABLE IV.—Minimum Lethal Doses Compared.

	Cocaine.	Butyn.	Tutocain.	Novocain.
	mg. per kilo.	mg. per kilo.	mg. per kilo.	mg. per kilo.
<i>Rabbit</i> —				
Intravenous: 1 per cent. solution (1 c.cm. in 18 secs.) ...	12*	12*	21	90
Subcutaneous: 5 per cent. solution ...	200*	55*	300	600
<i>Guinea-pig</i> —Subcutaneous: 2 per cent. solution ...	Under 60	Over 70	120-150	Over 350
<i>Mouse</i> —Subcutaneous: 2 per cent. solution (dose in mg. for 20 gm. mouse) ...	6	3	10	22

* See Reference 8.

TABLE V.—Minimum Convulsant Dose for Rabbits.

	Cocaine.	Butyn.	Tutocain.	Novocain.
	mg. per kilo.	mg. per kilo.	mg. per kilo.	mg. per kilo.
Intravenous. Rapid injection of 1 per cent. solution into ear vein (1 c.cm. in 18 secs.)...	4	4	10-15	45
Subcutaneous. 5 per cent. solutions under skin of back ...	30	30	65	120

CONCLUSIONS.

1. These experiments show that the best of the local anaesthetics for the eye are cocaine and butyn. Tutocain may also have a use. Tropicocaine, novocain, and eucaine are less valuable for deep anaesthesia.

2. For the nose, cocaine and tutocain are alone useful.

3. For subcutaneous injection novocain is much the best.

4. Besides cocaine, it is believed that the properties of butyn and tutocain may render them addiction drugs.

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CAESAREAN SECTION.*

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THIS paper records an experience of 116 sections, the majority of which were performed to anticipate or relieve obstructed labour due to pelvic contraction, the others for less common indications.

The Operation.

The abdominal incision is median and subumbilical unless Bandl's ring is present, when it is placed higher. The uterus is opened in the upper segment, and the hand, passed between the placenta and the uterine wall, ruptures the membranes and extracts the child. After removal of the placenta 1 c.cm. of pituitary extract is injected, and the uterus is closed with four to six interrupted catgut sutures, taking up the whole thickness of the wall. A continuous suture or further interrupted sutures adjust the superficial layers and peritoneum, and the abdomen is closed. The operation takes from twelve to twenty minutes. The gaping mouths of sinuses seen while incising the uterus suggested that a safer method of approach must be adopted in septic or suspect cases.

Situation of Placenta.

The placenta in 75 cases was posterior or anterior in position in a proportion of 4 to 3, but in patients who had had previous sections the proportion was 3 to 1, suggesting that the residual scar tissue contributed to this result. It is noteworthy that the placenta was anterior in the only case of rupture of an old scar.

Rupture of Old Scar.

This risk is negligible. In many the uterus showed no trace of a previous incision, but in some there was definite scar tissue, and the wall felt dense when incised. In no case was thinning evident, although in many instances the

patient had been in labour a number of hours, and one at least has since been delivered without resort to section. The case which ruptured had had four previous sections and came in for her fifth. After several hours in labour the pain became very severe and she was operated on shortly after admission. The complete ovum was lying in the abdominal cavity, which contained much blood, and the placenta presented. The uterus, firmly contracted, appeared ready for a resuture, which was done. The mother made a perfect recovery.

Contracted Pelvis.

A large number of the patients were definitely undersized and rachitic. Three had old hip trouble with, in two cases, the limb ankylosed in such marked adduction as to render delivery difficult if not impossible, but each in addition had marked flattening on the affected side of the pelvis.

The previous obstetric histories were instructive. A 10-para with a conjugata vera of 3 in. reported the survival of one child—the others died at birth following instrumental delivery—while a 6-para and a 4-para recorded a series of stillbirths preceding the successful Caesarean section. In a number of cases when the child survived delivery it died some weeks or months later from "fits." One 7-para reported that her four children delivered alive with forceps died between six weeks and three months from this cause.

Primiparae, having no antecedent obstetric history, are entirely dependent for their safety on a pre-maternity examination. The outstanding impression gained in dealing with these cases was the extremely obvious indication that something was wrong, gained in practically every instance by abdominal examination without resort to either pelvimetry or an internal examination. The problem, viewed purely as one of elementary mechanics, was obvious: the head was above the brim and actually over-riding it; or sitting in the brim and no pressure from above could push it in; or the head was definitely engaged but a large amount was still above the brim. Since in a normal case merely the forehead can be felt above the brim some weeks before term, surely something must be wrong if more of the head is felt. Where there is the least doubt the patient should be anaesthetized, and with fingers—or even the whole hand—in the vagina, the exact relationship of the head (the ball) to the pelvis (the socket) should be decided on a purely mechanical basis. When the patient is in labour and it is believed that the head may come through, a careful watch should be kept on the mother for exhaustion, the child for distress, and the course of labour for the non-descent of the presenting part or the formation of Bandl's ring, with a view to performing an immediate section should occasion arise.

Contraction of the pelvic outlet is less common but more treacherous. In the majority the pelvis was small and the delay was at the brim or high up, but in some cases the abdominal examination suggested that all was well, and the head appeared to be well engaged. In such cases no difficulty was experienced at the operation in extracting the head from the pelvis. A certain number of cases invited the application of forceps, especially when the head was impacted in the mid-cavity in cases of funnel-shaped pelvis, and in two cases where it was actually at the outlet. A thorough examination, however, showed that the lower strait could not possibly allow the passage of a head in a condition consistent with the survival of the child, and without inflicting serious trauma on the mother.

Caesarean section as an operation is often regarded as of sole interest to the specialist, and for use in cases of marked pelvic contraction. It has not yet come into its own in minor degrees of this condition.

Obstructed Labour.

Peritoneum.—The peritoneal fluid was markedly increased in a number, and in one was blood-stained.

Uterus.—The presence of Bandl's ring as a shallow transverse groove was noted in a number, and frequently corresponded to the child's neck. In several cases the incision had to be prolonged into the lower uterine segment

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