general parasitological reasons; (b) in contradiction with a number of biological and anatomo-pathological facts (for example, the incapability on the part of the miracidium to resist the action of acids, even if very diluted; the part played in the infection by the liver, etc.).

4. The theory of infection by the skin is in accordance with all the facts thus far known (a) of the biology of the parasite, (b) of the distribution of the disease among the population (native and foreign, town and rural) of Egypt. It shows (c) how the chief sufferers—the children in town, the adult males in the country—live under conditions which, from the epidemiological point of view, are essentially the same, and give the miracidia (d) the opportunity of passing, within the short time of their life, from man to water and from water back to man.

THE SCIENCE COMMITTEE OF THE British Medical Association.

REPORT CXII.

OBSERVATIONS ON THE PHYSIOLOGY OF THE FEMALE GENITAL ORGANS.

BY

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IV.—UTERINE CONTRACTIONS.*

SINCE uterine muscle consists of involuntary muscle fibres, one may take it as an accepted fact that most of those chemical substances which cause contraction of other involuntary muscle fibre throughout the animal body, whether produced by metabolic process normally or in specific circumstances or by experimental and therapeutic means, will also cause uterine contractions.

The object of our investigation was to discover what substance or substances, which might be said to exist in the blood normally, influenced the contraction of the uterus in respect to the ordinary contractions which are supposed to occur in the unpregnant uterus, and also those of the pregnant organ. In all our experiments we used rabbits, and our technique was as follows:

The rabbit was anaesthetized with ether, and, when fully under the influence of this anaesthetic, laid upon a heated table. The trachea having been exposed, tracheotomy was

Fig. 1.—Uterine cannula.

performed, and a tube connected with an electric bellows tied in position. The skull-cap was then trephined and the rabbit pithed, the brain being entirely destroyed, and the cranial cavity packed with wool plugs saturated with hot saline solution.

The abdomen was next opened with a 1-in. incision and the uterus and vagina identified. A small incision was made in

* The experiments recorded in this paper were carried out in the Physiological Laboratory in the University of Liverpool, and we are much indebted to Professor Sherrington for the facilities afforded.

the posterior wall of the vagina, close to the insertion of the cervix, and a special glass cannula, with a rubber-covered neck (see Fig. 1), connected with a one-arm water manometer, was carefully passed through the vulva, up the vagina, through one of the cervixes, and into a uterine cornu. This was easily accomplished by directing the progress of the cannula through the small incision in the vagina. Before being passed into the uterus saline solution was allowed to flow through the cannula in order to prevent the entrance of air.

As soon as the head of the cannula was well in the uterus a soft worsted ligature was tied firmly round the cervix above the vagina, binding it against the rubber-covered neck. On one or two occasions elastic was used as the ligature material. The uterus was then returned to the abdominal cavity, placed in a normal position, and the abdomen closed. Enough saline was allowed to flow into the uterus to distend it slightly, but only so far as to support a column of saline solution 1 in. or 2 in. in height in the single-arm manometer. This manometer was next connected with a special bellows apparatus, very kindly made for us by Professor T. G. Brodie (see Fig. 2). This apparatus consists of a membrane finger-cot attached to a glass tube which is passed through a cork, the front of which is cut at an angle. To the lower end of this a card lip is attached to support the finger-cot. A card lid with a membrane hinge rests upon the protruding rounded end of the finger-cot. To the centre of this lid is fixed a piece of cork, to which a straw lever is attached by means of a needle. A glass writing point swinging from the distal end of the straw records the uterine contractions upon smoked paper revolving on a Brodie's kymograph apparatus, for it will be clear that as the uterus contracts the saline solution is driven up the manometer tube and the finger-cot distended. In all tracings the writing points were travelling from right to left, as indicated by the arrows below the blood pressure tracings.

The carotid artery was next connected with the mercury manometer, and the blood pressure recorded. The time was marked in seconds by means of an electric connexion with a clock.

The reagents used were in all cases injected intravenously, and the smallest doses compatible with a definite result employed. Control injections of simple saline solutions were frequently used.

It may be urged that pithing produces a condition of intense shock and low blood pressure. This, of course, is true; at the same time it is probable that the blood pressure is acted upon in much the same way, if in less degree, under these conditions by the reagents we employed, as would have been the case had pithing not been performed. Certainly pithing seems to have little effect on uterine contractions. On the other hand, we found it absolutely impossible to get satisfactory results under ordinary anaesthesia, owing to the variations in blood pressure, and the irregularity of uterine contractions—probably due to the impossibility of keeping the animal all the while in the same state of anaesthesia.

In regard to our method of recording uterine contractions, we consider it the most perfect yet utilized, in that alterations of the total uterine content only are recorded; and, further, that the uterus is acting under practically normal conditions—the slight stimulus of saline solution under a low pressure being negligible from a practical point of view. The methods used by Cushny,¹ Dale,² and others are open to the objection that the uterus is exposed—even though it be in a bath—and, further, that isolated muscular contractions only are recorded, instead of altera-

Fig. 2.—Recording bellows.

tions in the total content. Now we have found that contractions of the uterus may occur without the uterine content being altered at all. That is to say, the uterus may relax at one part while contracting at another. In our opinion the total alteration in the content, or, in other words, the expulsive force of the uterus, is the most important result of uterine contraction, and it was this we wished to measure; hence our employment of the method already described.

Before passing on to a consideration of the results obtained, we would like to point out, in addition to the fact just mentioned of peristaltic contraction, in which a relaxation compensates a contraction, that we have found the contractile power of different uteri to vary enormously according to the size of the rabbit and its age. In regard to the former point, it will be noticed that a great variation occurs in the size of the contractions in

Fig. 3.—Inactive uterus showing no contraction. (Reduced about one-half.)

the different tracings. This is almost entirely dependent, subject to the conditions to be mentioned directly, on the size of the uterus, or, in other words, on the age and size of the rabbit. In addition to these factors, we must also point out, however, that the non-menstruating and non-pregnant uterus does not normally contract at all (see Fig. 3 and subsequent figures of inactive uteri). We have reason to believe that this applies to the uteri of wild

Fig. 4.—Menstruating uterus showing normal expulsive contractions. Note—Drum revolving faster than in Fig. 5 and in most of the other tracings. (Reduced about one-half.)

rabbits in winter months (see Paper III). We shall for the sake of brevity refer to these as "inactive" uteri.

The menstruating uterus appears to be in a state of more or less regular expulsive contraction (see Fig. 4), and likewise the pregnant uterus (see Fig. 5), once the uterus when in this condition is interfered with. Unfortunately it is impossible to measure contractions without some interference, but we obtained conclusive evidence in one instance, in which the sacs were unruptured, that leads us to believe that the pregnant uterus does not normally contract expulsively. That is to say, any contractions which normally occur are compensated by relaxation at the same time. Our tracings of the contractions of the pregnant uterus are, therefore, from those experiments in which the membranes had been ruptured.

Fig. 6 (continued).—Menstruating uterus: effect of ovarian extract in repeated doses. (Reduced about one-half.)

In our experiments we have used all three varieties of uterus: The pregnant, the menstruating, and the virgin non-menstruating.

We have tried the effect of the following reagents upon these uteri by intravenous injection:

1. Ovarian extract.	5. Placental extract.
2. Thyroid extract.	6. Uterine secretion.
3. Pituitary extract.	7. Calcium salts.
4. Adrenal extract.	

In general, we may say that in some cases the virgin non-menstruating uterus was affected, but that in those

cases where any contraction was obtained it was more marked in the case of the menstruating uterus, and most marked in the pregnant uterus. That is to say, a uterus that can be caused to contract by any reagent reacts more readily and violently during menstruation and pregnancy.

Fig. 5.—Pregnant uterus showing normal expulsive contractions. (Reduced about one-half.)

We have, in short, been unable to obtain those paradoxical effects, noted by some observers using different methods, of relaxation in the non-pregnant and contraction in the pregnant uterus.* Such results seem foreign to what one would expect, and are not, as we say, borne out by our

Fig. 7.—Menstruating uterus: effect of ovarian extract. (Reduced about one-half.)

results. In most of the experiments we were also able to note the effect of our reagents upon the blood pressure.

1. Ovarian Extract.

The ovarian extract used was kindly prepared for us by Mr. H. H. Dale, of the Wellcome Laboratories. It was made by extracting fresh sheep's ovaries with cold saline solution containing a little chloroform. The extract was filtered first through paper, and then under pressure through a Berkefeld candle. A crystal of thymol was added to act as an antiseptic; 1 c.cm. of this extract contained 0.25 gram of fresh ovary.

(a) This extract has no effect upon the inactive uterus.

(b) Upon the menstruating uterus the effect is well marked, as illustrated by the gradually increasing effect of

Fig. 6.—Menstruating uterus: effect of ovarian extract. (Reduced about one-half.)

a series of intravenous injections of 1 c.cm. of the extract. This is shown in Fig. 6. The action is not excessively energetic, but still it is quite evident. Fig. 7 illustrates the effect in another rabbit, whose uterus was also menstruating. In this case a more or less tetanic spasm was produced.

(c) The pregnant uterus is affected in a somewhat remarkable manner by ovarian extract. The strength of the contractions are in no way lessened, but the immediate effect of an injection appears to be the stopping of the

* Verbal communication, Dr. F. E. Taylor.

impending contraction. This is shown in Fig. 8, in which only one injection is illustrated. A subsequent injection produced the same effect, but with a slightly shorter interval, and a third injection hardly showed the effect at all, antibodies being probably formed in the blood by that time. We may say, however, that in the case of other

uterine contractions. In Fig. 9 this result is seen after one injection. The results of a subsequent injection into the same animal are illustrated in Fig. 9 *continued*, where a general convulsion was noted after the third injection.

(c) On the pregnant uterus the effect is the same as that upon the menstruating uterus, only more marked.

Fig. 8.—Pregnant uterus: effect of ovarian extract. (Reduced about one-half.)

pregnant uteri an increase in the strength of the contractions only was observed.

The effect of the ovarian extract upon the blood pressure is hardly noticeable; if anything, there is a tendency to a gradual, uniform decline, as is shown in the lessening of the force of the heart-beats, and gradual progression towards the abscissa in Fig. 8.

The effect of thyroid extract upon the blood pressure is shown in Fig. 9. There is always a distinct drop; this may be followed by a rise with the onset of a convulsion (see Fig. 9 *continued*)

3. Pituitary Extract.

The extract used was, in this case, also kindly prepared

Fig. 9 *continued*.—Menstruating uterus: effect of thyroid extract. (Reduced about one-half.)

2. Thyroid Extract.

For these experiments we used a solution of thyrocol of a strength of 1 in 10 in normal saline.

(a) There was no effect upon the inactive uterus.

(b) Upon the menstruating uterus the effect of thyrocol was to cause an increase in the strength and number of

Fig. 9.—Note: The contraction marked *c* followed the injection, the uterine marker being a little behind the proper line in this figure and in Fig. 9 *continued*. (Reduced about one-half.)

for us by Mr. H. H. Dale, of the Wellcome Laboratories; 1 c.cm. of the solution contained 0.1 gram of fresh infundibulum. As previously stated (see Paper I), it is only this portion of the pituitary gland which is active in the respect shown here.

(a) Upon the inactive uterus pituitary extract will pro-

duce a slight effect. This is shown in Fig. 10, where an evident wave of contraction is seen to occur in a uterus which had not previously contracted.

(b) Upon the menstruating uterus pituitary extract produces a very marked effect, causing much more powerful,

Fig. 10.—Inactive uterus: effect of pituitary extract (0.5 c.cm.). (Reduced about one-half.)

frequent, and prolonged contractions than those occurring normally.

(c) Upon the pregnant uterus the extract produces the same effect as upon the menstruating organ, with the qualification that the contractions are, as always obtains in this condition, more forcible because of the increase in the muscular structure in the walls, and the greater sensitiveness to stimulation which is exhibited during pregnancy. This effect is shown in Fig. 11.

In Figs. 10 and 11 the effect of pituitary extract upon the blood pressure is well seen. There is an immediate and extensive rise. This rise is maintained for a considerable time. In Fig. 10 secondary rises—three in number, with two less important ones—are very prettily shown. These occurred during the act of defaecation, brought about, no doubt, by the effect of the pituitary extract on the intestinal muscles.

Fig. 11.—Pregnant uterus: effect of pituitary extract (0.5 c.cm.). (Reduced about one-half.)

Mr. H. H. Dale also has shown the effect of this extract upon the uterus, using a different method.

4. Adrenal Extract.

The solution of 1 in 1,000 adrenalin prepared by Parke, Davis and Co. was used.

The effect upon the pregnant uterus is well known, consequently we only tried the effect of the extract upon the inactive uterus. The result is shown in Fig. 12. A distinct contraction was produced, together with the well-known rise in the blood pressure. This tracing is, in fact, almost identical with that shown in Fig. 10.

5. Placental Extract.

The preparation used was that kindly supplied to us by Dr. F. E. Taylor, who, with Professor Dixon, has recently published the results of their work with the extract prepared by them from the placenta.

(a) Upon the inactive uterus this preparation, used

Fig. 12.—Inactive uterus: effect of adrenalin (1 c.cm. of 1 in 1,000 solution). (Reduced about one-half.)

according to the instructions of Dr. Taylor, produced quite a marked effect, as is seen in Fig. 13, where two distinct contractions occurred as the result of a single dose.

Fig. 13.—Inactive uterus: effect of placental extract (1 c.cm.). (Reduced about one-half.)

(b) Upon the menstruating organs there appears to be a marked effect. The contractions are prolonged, and recur more rapidly, but their total expulsive force is not increased. This is shown in Fig. 14. It is possible the

Fig. 14.—Menstruating uterus: effect of placental extract (1 c.cm.). (Reduced by one-half.)

dose used (1 c.cm.) was rather small to produce a very decided result. Upon the blood pressure the effect is not at all marked, but there is a slight tendency for it to rise.

(c) Our supply having run short, we did not test the action of this preparation upon the pregnant organ, but in view of our other experiences we have no doubt that powerful contractions would be produced.

6. Uterine Extract.

In order to obtain this extract it occurred to us to use the secretion obtained from the uterus by ligation of the

uterine cornua in rabbits. In this way we obtained, in a concentrated form, the secretion of the glands, and it may be taken for granted, therefore, that such a secretion would resemble in its action an active extract prepared from the whole organ. We found that the most active preparation was that obtained fresh and from a rabbit capable of menstruating. The secretion so obtained was very fatal

Fig. 15.—Inactive uterus: effect of uterine secretion. (Reduced about one-half.)

in its effect unless used dilute. We used it, therefore, in a dilution of 1 to 4; even then we could readily produce fatal effects. Our records only show, of course, those cases in which no bad result, beyond perhaps clotting in the blood-pressure cannula, was produced. We found this secretion the most powerful in its effect upon the uterus of any of the animal extracts used by us.

Fig. 16.—Menstruating uterus: effect of uterine secretion. Note clotting in the blood-pressure cannula. (Reduced about one-half.)

(a) In Fig. 15 is seen the result upon the inactive uterus. There is an immediate and marked contraction, followed by several smaller ones.

(b) Upon the menstruating uterus the effect appears to be that the contractions become prolonged considerably, and occur more frequently. In Fig. 16 this is well seen, but apparently there is a slight delay in bringing about the result. This, however, may have been due in this case to fatigue.

(c) Upon the pregnant uterus, as one would expect, we obtained a very powerful reaction. The uterus was thrown into a series of violent and continuous contractions. This is seen in Fig. 17. There were no general convulsions, so that the effect appears to be specific.

Uterine secretion appears to raise the blood pressure, but owing to the marked rapidity with which clotting occurred in the cannula no very good tracings of the blood pressure were obtained. There was, however, no general intravascular clotting.

Fig. 17.—Pregnant uterus: effect of uterine secretion. (Reduced about one-half.)

in the calcium content of the systemic blood of pregnant women towards the termination of the intrauterine life of the fetus, and taking into consideration the important part played by the calcium salts in all processes associated with female genital activity (see previous papers), we thought that our work on uterine contractions would not be complete unless we endeavoured to show the effect produced upon these contractions by such an important normal constituent of the blood.

For the purpose of intravenous injection we found that a solution of 0.1 gram in 1 c.cm. of calcium chloride was the best suited to our purpose.

(a) We were unable to produce any effect upon the inactive uterus.

(b) Upon the menstruating uterus a marked effect was produced, as is seen in Fig. 18. From a somewhat weak and prolonged contraction the character was changed so that the expulsive contraction became more powerful and definite, without much loss in the length of the total contraction. We noticed, however, that when the uterus was tired the contraction was apt to be of a more prolonged and tetanic character in addition to being increased in force, and further that the effect was somewhat delayed after the injection. (See Fig. 19.) This delay we frequently noticed when trying the effect of calcium salts upon the uterus.

(c) Upon the pregnant uterus the effect is, as we should expect from our previous observations, very well marked. This is seen in Fig. 20. In some of the tracings obtained the effect was more violent than in the case illustrated.

Calcium salts cause the blood pressure to rise. This, though not nearly so marked as with pituitary and adrenal extracts, is often quite distinct, as is well shown in Fig. 20.

As we have said elsewhere, we have not found that injections of calcium salts cause intravenous clotting.

REMARKS AND CONCLUSIONS.

Such, then, are the results of the investigations which have occupied much of our time and exercised much of our patience. On account of limitations in the former we have not been able to carry out other experiments on the same lines as we had hoped. Some day we may be able to return to the subject; if so, we shall try the effect of extracts made from the whole uterus in order to see if a marketable extract can be made which will have the same definite effects upon uterine contractions as the uterine

secretion has without, possibly, the marked effect of the latter upon the coagulation of the blood, an effect possibly produced by nucleo-proteids.

We should like to test the action of fresh blood from a parturient rabbit upon one less advanced in pregnancy.

7. Calcium Salts.

One of us (W. B. B.) having already observed an increase

Also, if possible, to have discovered some substance circulating in the blood which definitely inhibits uterine contractions.

Our results, then, indicate that all those substances—most of them being extracts prepared from the ductless glands—which we have investigated appear to increase uterine contractions, and that most raise the blood pressure, some much more than others.

We do not know whether it is quite logical to come to such a conclusion, but it seems to us that probably those extracts such as the pituitary and adrenal—we will omit

been found to contain. We have ourselves no first-hand knowledge upon this point.*

Uterine secretion, we venture to think, however, must be specific to some extent, as we have used it straight from the living rabbit to the one under experimentation. Indeed, it seems only feasible that it should have some such action, and the fact that during menstruation, when this substance is being excreted, marked contractions are constantly in progress makes it a fair assumption that these contractions are caused by the direct stimulation of the compound substance we may call "uterin" which

Fig. 18.—Menstruating uterus: effect of calcium chloride (0.1 gram in 1 c.cm.). (Reduced about one-half.)

placental and uterine extracts for the moment—which cause contractions in the inactive uterus act not specifically upon the uterine muscle, but upon involuntary muscle in general. In regard to these, their marked effect upon the blood pressure gives further proof of this.

Of the others, thyroid extract lowers the blood pressure but increases the uterine contractions. In this case, however, the contractions may form part of a general convulsion. Should this occur the blood pressure rises. We think, therefore, that thyroid extract may be dismissed from the competition for specific effect.

Fig. 19.—Menstruating uterus: delayed effect of calcium chloride. (Reduced about one-half.)

Next we have to consider the claims of ovarian extract; and we must confess at once that we wish we had been able to extend considerably our observations in this direction, especially in the matter of using more than one preparation of this organ. We should have liked to note the comparative effect of the extract prepared from rabbits' ovaries during the inactive, menstruating, pregnant, and lactating periods, for we should not be surprised to find different results would be obtained with preparations obtained in the different circumstances. That result in which delay in the contraction of the pregnant uterus occurred is full of significance, and it may be that the ovary of pregnant animals controls uterine contractions, especially in their expulsive effects.

In regard to the secretion obtained from the uterus we were much interested. That it has an effect upon the inactive uterus is undoubted, so that one might be tempted to class it with pituitary, adrenal, and placental extracts. It does not, however, raise the blood pressure in the way that the two first do.

The uterine secretion and placental extract are somewhat similar, then, in their action, and possibly may contain the same substance which effects uterine contractions. We are informed, however, that the specificity of placental extract has been disproved, and that its effects are produced by the products of decomposition it has

is in process of excretion, and which may in some form exist in the blood.

Finally the calcium salts are shown to exert a definite influence upon uterine contractions, with a slight but definite rise of blood pressure. This action is well illustrated, both upon the heart and upon the uterus. A slow, forcible, and rhythmical contraction is produced—the very type that is seen in labour.

We admit that we have been unable in our experiments so far to show definitely that labour is produced by the action of calcium salts in the blood, but we have gone some way towards this, especially in that we have previously shown (see Paper II) that uterine secretion is rich in calcium salts. Consequently of the various substances used uterine secretion and calcium salts appeared to us to possess most points in favour of specific action.

This question of specificity in the matter of uterine contractions is, then, at once of considerable difficulty and of great importance. We do not think that until the further investigations indicated have been carried out it can be authoritatively stated that one reagent alone is responsible therefor—for the contractions in menstruation and labour.

So far as we have gone we incline to the belief that calcium salts circulating in the blood, or excreted by the

Fig. 20.—Pregnant uterus: effect of calcium chloride. (Reduced about one-half.)

uterus, play the most important rôle in this connexion. At the same time we are alive to the probability that they

*Since writing this we have been favoured with a letter from Dr. O. Rosenheim in which he confirms the above statement. This disposes of the claim put forward by Professor Dixon and Dr. F. B. Taylor in regard to the specific action of placental extract.

may act in conjunction with other substances elaborated by such glands as the infundibular portion of the pituitary, either in a harmonic or conjunctive manner. We feel assured, however, that the secret is not now deeply hidden in view of the observations already made.

Contractions of the Human Uterus.

From our observations upon the uteri of rabbits, we may assume that the contractions of the human uterus are governed by the following circumstances:

First, that the normal non-menstruating, non-pregnant uterus does not contract at all. Secondly, that the menstruating uterus is in a state of constantly recurring expulsive contractions. And thirdly, that the normal pregnant uterus contracts and relaxes in a complementary fashion, no expulsive force being exercised; but that during labour violent expulsive contractions occur.

Therapeutics.

In regard to any therapeutic suggestions we might make we feel that the subject is too big and too uncertain to do justice to here, so that we will content ourselves with one or two remarks only. Until a satisfactory uterine extract is upon the market or the specific (?) calcium salt synthesized, we think that we have a very efficient therapeutic product in the pituitary extract, which we have reason to believe Messrs. Burroughs and Wellcome will shortly put upon the market in hypodermic form. We have ourselves used this preparation clinically with satisfactory results. A dose of 2 c.cm. of the infundibular extract (0.1 gram. in 1 c.cm.) should be given hypodermically and repeated if necessary. In addition to the effect upon the uterus it is most valuable in cases of shock in which the blood pressure must be raised, the protracted period during which the pressure is kept up adding considerably to its value.

We also think that it might be used in the place of physostigmine in paralytic distension of the bowel, its action upon the intestinal muscle being well shown in Fig. 20.

Lastly, we would call the attention of physicians to the effect of the calcium salts upon the heart as shown in the series of tracings made by us for Sir James Barr's paper on Mitral Stenosis (see BRITISH MEDICAL JOURNAL, December 19th, 1908, p. 1797). It appears to us that where it is necessary to slow the heart and strengthen the heart beat, calcium salts administered hypodermically or intravenously should form an ideal drug. In further connexion with this point our remarks on exophthalmic goitre in Paper I may be referred to.

* * * * *

While much remains to be learnt in regard to many of the problems upon which we have endeavoured to throw some light, we hope that the results we have already obtained, and summarized in these four papers, will not only justify the time, thought, and labour expended upon them, but also induce others to complete and extend the work we have so imperfectly performed in the much-neglected branch of gynaecological physiology.

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¹ Cushny, A. R.: On the Movements of the Uterus, *Journ. Physiol.*, vol. xxxv, Nos. 1 and 2. ² Barger, G., and Dale, H. H.: Ergotoxine and Some other Constituents of Ergot, *Bio-chemical Journal*, vol. ii, Nos. 5 and 6.

AN exhibition of flying machines and internal combustion engines intended for use in connexion with the same has been open at Olympia during the current week. It was promoted by the Society of Motor Manufacturers in conjunction with the Aero Club, and of the exhibits several were duplicates of machines which have already proved their capacity for actual flight and the carrying of passengers. Others were as yet in the model stage, and though they exhibit extreme ingenuity more perhaps is expected of them by their inventors than by any one else. Of the engines, a good many seemed to be the work of firms—such as the Wolseley Tool and Motor Car Company—whose names are already familiar in connexion with automobiles. The holding of this exhibition is an event worth noting as being the first of its kind. Otherwise the exhibition was not of special interest to medical men, as flying is not yet sufficiently popular to necessitate a new entry in the indexes of text-books on surgery on the lines of "golf elbow," "tennis wrist," or "back-firing fracture." Doubtless, however, such entry will presently appear—in connexion with the cervical vertebrae.

THE THERAPEUTIC COMMITTEE OF THE British Medical Association.

REPORT ON THE LOCAL ANAESTHETICS RECOMMENDED AS SUBSTITUTES FOR COCAINE.

By C. N. LE BROCC, B.A., M.D.
(From the Pharmacological Laboratory, Cambridge.)

THE substances which have been investigated are: Stovaine, novocain, tropacocaine, beta-eucaine, alypia, beta-eucaine lactate, nirvanine, holocaine hydrochloride, acoine, orthoform (new), anaesthesine.

The points to which special attention has been paid are those laid down by Professor Braun as essential in estimating a local anaesthetic action. They are:

1. A lower degree of toxicity than cocaine in proportion to its local anaesthetic power.
2. Sufficient solubility in water. The solutions should be stable, that is, they should keep without deterioration and be capable of sterilization by boiling.
3. Absence of any sign of irritation. There should be no injury to the tissues; the local anaesthetic should be easily absorbed without causing any after-effects, such as hyperaemia, inflammation, infiltrations, or necroses.
4. Compatibility with adrenalin.
5. Rapid penetration of the mucous membrane, and suitability for medullary anaesthesia.

The only exception I would make to these postulates of Braun is that dealing with absorption. It is not obvious that easy absorption is desirable. If the drug is absorbed slowly it remains longer in contact with the nerve fibrils, and produces a more prolonged action. It has been stated that by delaying absorption, as by local vaso-constriction, we are giving the anaesthetic a longer time for action, and it is for this reason that adrenalin is injected with these substances.

If a drug can be obtained which fulfils the above conditions it can be safely said that it will supersede cocaine.

To arrive at a satisfactory conclusion it is necessary to deal with each drug separately, and to discover how closely each approaches the conditions specified by Braun.

Solubility in Water.

Solubility in water is essential for subcutaneous and intraspinal injections. If a drug is not soluble in water to the extent of forming a 2 per cent. solution, I have regarded it as unworthy of competing with cocaine. By examining the solubility of these drugs, the list is considerably diminished, for acoine, holocaine hydrochloride, anaesthesine, orthoform (new), beta-eucaine, are all more or less insoluble, and for this reason alone unsuitable for producing local anaesthesia by injection. Beta-eucaine is not completely soluble in cold water to the extent of forming a 2 per cent. solution, but if the solution is warmed a 2 per cent. solution is readily obtained. As dusting powders, these drugs may, of course, still prove useful, but I am not here concerned with that point.

Cocaine, stovaine, novocain, tropacocaine, beta-eucaine lactate, alypin, and nirvanine are freely soluble in water; their solutions are stable, and as a 2 per cent. solution they will keep for a short time without deterioration.

Sterilization of Solutions.

Cocaine cannot be boiled, as decomposition occurs, and the drug loses its activity and is gradually destroyed. Stovaine, novocaine, beta-eucaine lactate, tropacocaine, alypin, nirvanine can be sterilized at 115° C. if necessary, undergo no change, and the drug is as active after as before sterilization.

Local Anaesthetic Properties.

The determination of the local anaesthetic action is not easy, as it is not practicable to work with accuracy on the lower animals on account of the difficulty in determining when sensation is absent or merely blunted. The method