Clinical Signs.—The general appearance of a breast is normal when the papillomata are small. When they become large they may deform the breast and even protrude from a duct orifice on the surface of the nipple. There is often a history of pain, not of a severe character. Sometimes there is a history of discharge of blood or serum from the nipple. I possess a specimen the clinical signs of which had lasted eight years and a blood discharge from the nipple was only noticed once, and that was in the middle of its history. When haemorrhage from the nipple occurs, it is a classical sign of papillomata or carcinoma of a duct. Papillomata can exist, however, without inducing haemorrhage from the nipple. On palpation one ampulla or more than one ampulla may be felt enlarged, palpation of which may induce pain and haemorrhage, or a discharge of serum. When the duct is full of papillomata an enlarged ampulla can be felt, and its ducts and branches can be distinguished tortuous and enlarged right down to the periphery. The general sensation on palpation is one of nodularity, and more than one duct may be affected.

CLASS III.—IN WHICH EPITHELIAL HYPERPLASIA APPEARS TO BE, HISTOLOGICALLY, OF LESS IMPORTANCE THAN THE HYPERPLASIA OF THE CONNECTIVE TISSUE.

A. *Hyperplasia Elastica.*

Pathology.—In this state there is a universal massive hyperplasia elastica throughout the whole lengths of all the ducts and those acini that happen to be surrounded by elastica. It is of enormous and surprising proportions and density. Hyperplasia elastica is accompanied by a loose hyperplasia extra-elastica. One never extends beyond the limits of the other, and their limit is the general supporting connective tissue of the breast. The state I discovered incidentally, on making whole microscopical sections of carcinomatous breasts, and of non-desquamative hyperplasia of epithelium (Type C). In one of the carcinomatous patients primary malignant disease and massive hyperplasia elastica were present in both breasts. Less marked hyperplasia elastica occurs in ducts that contain carcinoma and in ducts that contain a highly suspicious type of non-desquamative epithelial hyperplasia.

Clinical Signs.—Massive hyperplasia elastica gives rise to multiple solid nodules over the whole breast, which are due to tortuous, thickened ducts and the affected acini. The condition is painless, and I do not know how it can be diagnosed by clinical examination.

B. *Hyperplasia Intra-elastica.*

Pathology.—Hyperplasia intra-elastica affects mainly peripheral ducts and acini, sometimes picking out a terminal duct and its lobule. Its presence is very marked and always local. I have never seen it generalized. In the early stages the loose, delicate, cellular, fibrillous tissue inside the elastica undergoes diffuse hyperplasia. It may be evenly distributed, or it may be more marked at one place than another. The fibrillous matrix supports isolated bipolar or stellate cells. Here and there the layer shows a marked tendency to grow larger and give rise to a small intra-elastica fibro-adenoma, an intra-elastica papilloma, or only an irregularity of its surface. It usually undergoes degeneration, when only an occasional cell can be stained to prove its cellular origin. It is not a common state, and it is often associated with carcinomatous breasts. Certain types of fibro-adenomata are derived from this tissue.

Clinical Signs.—Hyperplasia intra-elastica generally occurs in women over 35 years of age. Enlarged ducts and acini give rise to local nodularity of the breast. The breasts are nodular, but there are no special clinical signs by which the state can be diagnosed. I have discovered it only on making large microscopical sections and during their examination for other diseases.

C. *Hyperplasia Extra-elastica.*

Pathology.—This type is found distributed generally throughout the gland, or only in association with the formation of the extra-elastica type of fibro-adenoma; it is an essential part in the formation of this tumour. It

is unnecessary to do more than allude to the general state of hyperplasia extra-elastica. I will deal only with the local state in connexion with the formation of fibro-adenoma. On cutting the breast in half, so that the incision passes through the affected and normal parts of the breast, a difference in the structure between these parts is at once evident macroscopically. The normal part of the breast appears white, the affected part appears lightish grey. The affected part usually occurs in the smaller ducts and acini at the periphery of the gland, and macroscopically looks definitely limited. Microscopically the limitation is not so definite. On cutting whole sections of these breasts for microscopical examination three things may be seen in the affected part: First, the fibro-adenoma, which attracts attention to the breast, is quite obvious. Secondly, a small, definite, unsuspected fibro-adenoma may be discovered in juxtaposition to it, or separated from it by a small area of breast tissue. Thirdly, the parts that appear lightish grey on macroscopical examination show marked hyperplasia extra-elastica, which is an essential part in the growth of this tumour. The parts of the breast that appear white are normal on microscopical examination.

Clinical Signs.—The fibro-adenomata are seen mainly in young people from 15 to 25 years of age, but may occur in breasts of much older people. Attention is drawn to the breast by the fibro-adenoma. On palpation the surrounding parts are nodular; the nodules are about the size of small shot. There is very little pain connected with this type, and it is usually localized to one segment of the breast.

I have not dealt with the management and treatment of these diseases, for these reasons—namely, that the correct management and treatment frequently depend absolutely on the most careful judgement and laborious and precise preliminary microscopical examination. The detailed description would take me so long that I must reserve this part of my subject for another time.

Finally, I hope I have said enough to show you that the term "chronic mastitis" is a misnomer, and does not correctly indicate the states to which it is universally applied; that the clinical signs on which its diagnosis now depends can only indicate the possibility of many, without specifying one, of the various lesions they hide, and that these lesions may include carcinoma in its earliest as well as in its late stages.

PSICAINE: A NEW LOCAL ANAESTHETIC.*

BY

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THIS cocaine substitute is an optically active isomer of ordinary cocaine prepared by Willstätter in collaboration with the firm of E. Merck of Darmstadt.

Cocaine is formed from the combination of l-ecgonine with methyl alcohol and benzoic acid. L-ecgonine contains four asymmetric carbon atoms, so that sixteen optical isomers are possible, eight of which are the mirror images of the other eight. One isomer of l-ecgonine is d-ψ-ecgonine, which differs from the former in the arrangement in space of the H and OH groups. D-ψ-cocaine is built up from this in exactly the same way as cocaine is built up from l-ecgonine, and the acid tartrate of this substance is known as "psicaine."

In Germany psicaine is approximately twice as expensive as cocaine, but it is said to have double the anaesthetic power, half the toxicity, and to be free from addiction properties. Psicaine is freely soluble in cold water up to 25 per cent., and is not precipitated by saline solution, Ringer, nor by proteins.

On the cornea psicaine in my experiments has approximately one-sixteenth the anaesthetic power of cocaine. The minimal effective concentrations to give complete anaesthesia after instillations lasting one minute are—for cocaine 0.25 per cent., and for psicaine 2.5 per cent.; on the other

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hand, a 0.5 per cent. solution of cocaine and an 8 per cent. solution of psicaine are equally effective in giving complete anaesthesia averaging thirteen minutes under the same experimental conditions. Psicaine moderately dilates the pupil in rabbits for twenty-four hours; it causes slight vascular congestion, but no drying of the cornea.

In my earlier experiments for determining the activity of local anaesthetics on nerve fibres I chose the vagus, and estimated the duration of the loss of conductivity of the cardiac fibres. In the present investigation I have adopted also the method of using true sensory nerves. The most satisfactory nerve in rabbits was found to be the anterior crural, both because of its small size and the ease with which a long portion can be separated.

For the quantitative comparison of the anaesthetic action of different local anaesthetics it is necessary to choose some nerve peripheral stimulation of which produces an effect which can readily be estimated. It is clearly of great importance that this nerve should be small in size. The American and German observers have, for the most part, used the sciatic nerve of animals; the objections to this are obvious, because the nerve is so big that before a complete anaesthesia is produced the drug has to penetrate a considerable thickness of nerve tissue—that is to say, the rate of penetration or absorption comes into play. When a drug is injected subcutaneously it acts on only the very finest of the nerve fibrils, and therefore to obtain any result comparable with the effect of a subcutaneous injection the finest nerve possible should be chosen for experiment.

The method adopted is a modification of that recently described by Schmitz and Loevenhart.⁶ The rabbit first receives an injection of urethane (1.5 gram per kilo), and one hour later ether is administered and a cannula is inserted into the trachea. The anterior crural nerves are isolated and are cut as near to the periphery as possible. Ether is now discontinued, the urethane giving adequate and uniform anaesthesia. Each anterior crural nerve is held by a protected electrode at a point 2 cm. from the cut end, and is excited by the weakest current necessary to produce a definite effect on respiration. A tambour connected to the tracheal cannula records the respirations on a moving drum. In all experiments, both with the vagus and with sensory nerves, the drug is applied over 1 cm. of nerve for thirty seconds. The nerve is stimulated immediately after painting, and subsequently every few minutes, the absence of any effect on respiration denoting complete anaesthesia. By using a double key in the secondary circuit the other anterior crural nerve can be excited by the same current and serve as a control, and subsequently used for a comparative test with another drug.

The results of experiments given in Table I show that the activity of psicaine compared with that of cocaine and tutocain is very weak for both sets of fibres. Novocain in 0.05 per cent. solution has the remarkable action of paralysing sensory nerve fibres in a degree equal to that of cocaine, but in double this strength it has no effect on vagal cardiac fibres. Dixon has shown⁷ that cocaine has certain specific effects in that it paralyzes sensory fibres before motor in mixed nerves, and efferent before afferent fibres in the vagus. Novocain has a strong affinity for sensory fibres and relatively little action on the cardiac fibres of the vagus.

TABLE I.—Effect of Local Anaesthetics on Nerve Fibres.

(Figures refer to the duration of complete loss of conductivity, in minutes.)

	Cocaine Hydrochloride.	Tutocain.	Psicaine.	Novocain.
Vagus nerve: cardiac fibres	0.1 % 12	0.1 % 10	0.1 % 5-8	0.1 % 0
Anterior crural nerve: sensory fibres	0.05 % 15-20	0.05 % 5-8	0.05 % 0	0.05 % 15-20

The toxicity of psicaine was estimated by determining the minimum lethal doses for rabbits, guinea-pigs, and mice, and also, in rabbits, the minimal doses required to produce convulsions lasting five minutes. The results are given in Tables II and III.

TABLE II.—Minimum Lethal Doses Compared.

	Cocaine.	Psicaine.	Novocain.
Rabbit— Intravenous: 1 per cent. solution (1 c.cm. in 18 s. cs.)	mg. per kilo. 12†	mg. per kilo. 1†	mg. per kilo. 90
Subcutaneous: 5 per cent. solution	75 (200*, 90†)	40	600
Guinea-pig— Subcutaneous: 2 per cent. solution	30	40	Ove: 350
Mouse— Subcutaneous: 2 per cent. solution (dose in mg. for .0 gm. mouse)	5	7-10	18

* See Reference 11.

† See Reference 6.

TABLE III.—Minimum Convulsant Dose for Rabbits.

	Cocaine.	Psicaine.	Novocain.
Intravenous: 1 per cent. solution (1 c.cm. in 18 secs.)	mg. per kilo. 8	mg. per kilo. 8	mg. per kilo. 45
Subcutaneous: 5 per cent. solution	40	3-40	120

The figures for cocaine given in my previous paper⁹ have been modified, and represent the results of experiments made with a sample of cocaine hydrochloride having a melting point of 182° C. (normal 183° C., Martindale).

The Abbott Laboratories, Chicago, U.S.A., the manufacturers of butyn, inform me that they have found "considerable variation in the toxicity and efficiency of different samples of cocaine." They consider that the inequality of samples probably accounts for discrepancies in the results obtained by different investigators, and they suggest that there may be a relation between melting point and toxicity.

In rabbits psicaine, injected subcutaneously, was found to be more toxic than cocaine, whereas injected intravenously the two drugs are of almost equal toxicity. Guinea-pigs and mice are relatively less susceptible to psicaine.

Both cocaine and psicaine give rise to symptoms identical in character though not in degree. Experiments on frogs show that psicaine is a more powerful stimulant than cocaine, since it will more readily increase reflexes and will even produce convulsions, which cease when the cerebrum is destroyed. In rabbits, following a preliminary stage of excitement during which reflexes are increased, there is a sudden tonic spasm, and this is succeeded by a stage of marked clonus in which there are violent spasms of the limb muscles, together with twitchings of the muscles of the head area. The head is retracted and the corneal reflex is lost. With larger and lethal doses the clonic spasms are very violent and are quickly followed by death from failure of respiration. Convulsions do not occur when the cerebrum is destroyed, nor after the administration of a general anaesthetic.

The irritant effect of psicaine is less than that of cocaine, and for practical purposes should not be of any significance. In rabbits 0.5 c.cm. of a 10 per cent. solution of psicaine injected subcutaneously causes slight hyperaemia, followed by thickening lasting two days and some desquamation on the fifth day, whereas cocaine in similar concentration produces ecchymosis and thickening lasting three days, followed by scab formation.

Psicaine has relatively little effect on blood vessels, and its action suggested that psicaine would not cause any swelling of the nasal mucous membrane. This, however, is not the case in the cat, since, using my perfusion method,¹⁰ it was found that after an application of a 5 per cent. solution of psicaine lasting twenty-five minutes the mucous membrane became so swollen as almost completely to obstruct the flow of fluid—an effect which lasted for several hours.

In this series of experiments I have been unable to verify the claims for efficiency and low toxicity which have been made for psicaine. If these experimental results are confirmed psicaine is unlikely to be useful as a substitute for cocaine.

I desire to express my thanks to the Medical Research Council for the special grant it made for the expenses of this research, and to Professor W. E. Dixon, to whom I am greatly indebted for help and advice throughout the investigation.

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PSICAINE: AN ARTIFICIAL COCAINE.*

BY

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PSICAINE is said to be the acid tartrate of a pseudo-cocaine, a dextro-rotatory artificial isomer of natural cocaine.¹ (Formula, $C_{17}H_{21}O_4N.C_4H_6O_6$; molecular weight, 453; alkaloid content, 67 per cent.). It is a white crystalline powder, very soluble in hot water, soluble in cold water up to 20 per cent.; the solution is acid in reaction, 1 per cent. solution giving a rather pinkish orange tint with dimethylamino-azo-benzene—pH about 3.3; the solution is also dextro-rotatory. (This is mentioned, as other properties of the substance I have examined differ somewhat from those described in Continental reports.¹) The powder is sparingly soluble in alcohol.

Anaesthesia.—Applied to the nasal mucous membrane a 5 per cent. solution gives very good anaesthesia. As compared with 5 per cent. solution of cocaine hydrochloride, the time taken for full anaesthesia is rather longer; the depth of anaesthesia ultimately obtained is the same. The duration of anaesthesia without adrenaline is over fifteen minutes, after packing. If 7 per cent. solution is used, the time required for anaesthesia is practically the same as with 5 per cent. cocaine hydrochloride solution. (The alkaloid content of 7 per cent. psicaine solution is 4.7 per cent., that of 5 per cent. cocaine hydrochloride solution being 4.5 per cent.) I have made over fifty observations with uniformly good results, performing such operations as puncture of the antrum, cauterization, etc. I have not found that the anaesthetic value is twice that of cocaine as claimed.

Toxicity.—No cases of toxicity in the human subject have been brought to notice. Experiments have shown that doses up to 70 mg. do not produce excitement or fainting when injected into men.¹ This dose (containing less than gr. 3/4 of alkaloid) is too small for deductions of value; many men might escape symptoms after the same quantity of cocaine.

Shrinkage.—Psicaine is said to be a vaso-dilator, but I have found uniform good shrinkage after spraying the nose with mv of 5 per cent. solution. This strength also checks bleeding. If it is desired to use adrenaline the solutions mix well.

Irritation.—I have found no case of primary or late irritation with solutions of the strengths described.

Habit Formation.—In common with all cocaine substitutes, psicaine is said not to lead to addiction. Deductions from animal experiments support this view—the dose required to produce excitement would probably be so near the lethal dose as to prevent the drug ever making a popular appeal.

Stability.—A 5 per cent. solution of psicaine grows "moulds" just as does cocaine solution; the addition of 1/4 per cent. salicylic acid prevents this. Time has not allowed an investigation of keeping powers; the solution is unaltered after two months. Psicaine can be boiled for

five minutes, or steamed for an hour, with only slight loss of power; fifteen minutes in the autoclave at 134° C. seriously diminishes the anaesthetic power and the experimental toxicity.

Dangerous Drugs Acts.—It appears that psicaine comes under the Dangerous Drugs Acts. (The Home Office is investigating this point, and will give a decision when the work is complete.)

Experimental Work.—Subcutaneous injection into guinea-pigs* was chosen as a method of comparison. The minimal lethal dose in 5 per cent. solution was found to be 53 mg. per kilogram. The toxicity is therefore 19 kilograms per gram of psicaine (the toxicity of 5 per cent. cocaine hydrochloride is 25 kilograms per gram). The toxicity figure is affected by the large proportion of acid in the molecule—just under a third. In kilograms per gram of alkaloid, the toxicity is 28, the same as that of cocaine in 5 per cent. cocaine hydrochloride solution. In 1 per cent. solution, the toxicity of psicaine is 18 kilograms per gram. The new isomer therefore appears to have no advantage over the natural alkaloid as regards toxicity measured by the minimal lethal dose. The minimal convulsant dose seems to be almost the same as the minimal lethal dose: it was practically impossible to produce convulsions without killing the animal. Assuming that the same holds good in man, and further that there is some relationship between the dose required to produce excitement, nausea, fainting, etc., and that required to produce convulsions, it is seen why I consider the drug unlikely to become one of addiction: the dose necessary for excitement would be dangerously high—that is, psicaine probably has a high "danger ratio." This is important, since, if so, we shall not be warned when our clinical dosage is getting dangerously large. No one should use psicaine who has not acquired with the much safer (from this aspect) cocaine hydrochloride practice in safe dosage. When death occurs, it is from respiratory failure, the heart continuing to beat after the respirations cease. Under ether anaesthesia, deep enough to abolish reflexes, convulsions do not occur, but the same dose kills the animal, respiration gradually failing; it is not, in fact, the convulsions that cause death.

Summary.

1. Psicaine is the acid tartrate of an artificial isomer of cocaine. It is soluble in water, giving a definitely acid solution. The solution is not harmed by brief boiling. It requires the addition of salicylic acid to prevent the growth of moulds.
2. Used in the nose, 7 per cent. psicaine solution gives anaesthesia identical with that produced by 5 per cent. cocaine hydrochloride solution. The anaesthetic value of the new alkaloid is the same as that of natural cocaine.
3. The same "shrinkage" as is seen with cocaine is found in using psicaine.
4. The experimental toxicity of psicaine in 5 per cent. solution is three-quarters that of cocaine hydrochloride; the toxicity of the new alkaloid is therefore identical with that of cocaine.
5. It is probable that excitement, fainting, etc., will not be so readily produced by psicaine as by cocaine; it may therefore be useful in susceptible persons.
6. For the same reason psicaine should not be used except by those well accustomed to use cocaine; the dose of psicaine should not exceed that found safe with cocaine.
7. Psicaine is a "dangerous drug."
8. The price of psicaine has not yet been published.

I am indebted to Professor Walker Hall for permission to use the Pharmacological Laboratory of Bristol University for the experimental work on psicaine; and to Messrs. Merck of Darmstadt for supplies of the drug.

REFERENCE.

¹ *Muench. med. Woch.*, 1924, No. 26.

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