cells lining the renal tubules is actively to reabsorb water and chloride from the glomerular filtrate, and, if we suppose that they share with the cells of the other tissues a diminished affinity for these substances, there would be no difficulty in understanding why both renal and extra-renal factors should not be concerned. Further observations upon the changes in blood volume by more trustworthy methods than those hitherto employed are called for, while a study of the chloride threshold and the blood flow through the kidney is necessary in order further to elucidate the problem.

Digitalis produces no diuresis in the healthy individual, but it increases the secretion of urine in cardiac failure through augmenting the output of the left ventricle and improving the circulation in the kidneys and other tissues. The diuretic action is most marked in those instances where digitalis has the most striking effect in improving the efficiency of the heart—for example, in auricular fibrillation—and is less pronounced in cases where the influence upon cardiac action is less conspicuous, as in aortic disease and interstitial myocarditis. With the increased efficiency of the circulation the blood flow and capillary pressure in the glomeruli of the kidneys return towards the normal, and more fluid filters off from the blood plasma through the glomerular membrane. If, at the same time, the improved nutrition of the tissues leads to the reabsorption of oedema, the diuresis may be enormous.

If, in spite of the administration of digitalis, the output of urine be low, diuretics of the purine series may increase the volume of urine. When effective they would seem to be the most desirable diuretics to employ, as the mechanism of their action is not such as to involve the performance of work and an increased oxygen consumption in the kidneys. They appear to act, as already indicated, by increasing the permeability of the glomerular membrane, and perhaps, as Richards and Schmidt have observed, by increasing the number of active glomeruli. Considering their mode of action, it is not surprising that they should sometimes fail, especially when the glomerular capillaries are dilated from chronic venous stasis and the permeability of the glomerular membrane is altered as a result of anoxaemia, so that albumin appears in the urine.

When the purine diuretics fail urea may still cause diuresis. Urea filters through the glomeruli, but is reabsorbed with difficulty from the urinary tubules. Consequently the urea in the tubules, in virtue of its osmotic pressure, opposes the reabsorption of water by the tubule cells, so that a greater proportion of the water which filters through the glomeruli escapes in the urine. Thus, the volume of urine may be increased even when the rate of filtration is lessened, as in cardiac failure. Urea, however, undergoes concentration in the tubules, the tubular cells having to reabsorb water in opposition to the osmotic pressure exerted by the urea. But the process of concentration involves the performance of work, together with an increased oxygen consumption, in an organ which is being poorly supplied with oxygen. Urea, therefore, cannot be regarded as the ideal diuretic to employ, though no harm appears to result from its use, over short periods at any rate. The large doses administered in the cases above cited are not necessary in most instances, but when it is remembered that the normal output of urea, resulting from protein katabolism, is about 25 grams a day, the extra amount necessary to make an appreciable difference must be considerable, as ordinary dosage goes. When urea is no longer effective, novasurol may yet be capable of producing a large diuresis. There is no evidence that this action is obtained at the expense of damage to the kidneys. The drug is therefore a useful addition to our armamentarium.

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BIBLIOGRAPHY.

- Bohn, H.: Erfahrungen ueber die Novasuroidiurese. *Klin. Woch.*, 1922, i, 1940.
- Brunn, F.: Zur Wirkung des Novasurols als Diuretikum. *Munch. med. Woch.*, 1921, lxxviii, 1554.
- Crawford, J. H., and McIntosh, J. F.: Observations on the use of Novasurol in Edema due to Heart Failure. *Journ. of Clin. Investigation*, i, 1924-25.
- Fodor, E.: Ueber das Indikationsgebiet des Novasurols als Diuretikum. *Med. Klin.*, 1923, xix, 684.
- Gilchrist, A. R.: Novasurol, a New Diuretic, *Lancet*, November 14th, 1925, p. 1019.
- Muhling, A.: Studie ueber die diuretische Wirkungsweise von Quecksilber. Ausgefuehrt mit dem organischen Quecksilberpraeparat Novasurol. *Munch. med. Woch.*, 1921, lxxviii, 1447.
- Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese. *Munch. med. Woch.*, 1921, lxxviii, 1282.
- Richards and Schmidt: *Amer. Journ. Physiol.*, lxi, p. 178.
- Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjectionen. *Wien. klin. Woch.*, 1920, xxxiii, 943.
- Saxl, P., and Heilig, R.: Ueber die Novasuroidiurese. *Wien. Arch. f. inn. Med.*, 1921-22, iii, 141.
- Saxl, P., and Heilig, R.: Ueber die Novasuroidiurese. *Zeit. f. ges. exper. Med.*, 1923, xxxviii, 94.
- Zeiler, K.: Novasurol ein neues Quecksilbersalz zur Syphilisbehandlung, mit Bemerkungen ueber die Grundsätze der Quecksilberhandlung. *Munch. med. Woch.*, 1917, lxiv, 1257.

BETA-EUCAINE BORATE.

BY

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IN a previous communication¹ H. E. F. Notton and I have described the action of a borocaine (ethocaine borate). One other of these borocaines seems to me to require some further comment.

Beta-eucaine borate (formula, $C_{15}H_{21}NO_2 \cdot 5HBO_2$) is now prepared (under the name "beta-borocaine") by the British Drug Houses, Ltd., who have kindly furnished me with a supply of the drug. It is a white crystalline powder, soluble in water up to 20 per cent., and not precipitated by saline, Ringer's fluid, nor by proteins. It is stable in cold or warm solutions—that is, an excess of boric acid is not required in the solution to prevent the separation of the base. Solutions are therefore on the alkaline side of neutrality, with a high pH value of 8. A little of the base separates on boiling, but redissolves on cooling. The following experiments show that the efficiency of beta-eucaine borate is weakened but not destroyed by boiling.

Rabbit's Cornea.—Beta-eucaine borate, 0.5 per cent., 20 c.cm., was boiled for five minutes. Distilled water, 7 c.cm., was subsequently added to replace fluid lost by evaporation. Duration of complete anaesthesia in minutes, after an instillation lasting one minute: normal solution, 30+; boiled solution, 12. *Cocaine hydrochloride*, 0.5 per cent., 20 c.cm., was boiled for two minutes. Distilled water, 3 c.cm., was then added to replace the fluid lost. Duration of complete anaesthesia in minutes, after an instillation for one minute: normal solution, 13; boiled solution, 0.

If placed in an autoclave at 120° C. and 15 lb. excess pressure for twenty minutes it undergoes little change as regards appearance of solution and pH value, and the physiological activity is only slightly diminished. Beta-eucaine borate is at least two to three times as powerful as cocaine hydrochloride on the rabbit's cornea. After instillations lasting one minute the minimal effective concentrations to give complete anaesthesia are, for cocaine hydrochloride 0.25 per cent., and for beta-eucaine borate 0.1 per cent. A 0.5 per cent. solution of cocaine hydrochloride and a 0.125 per cent. solution of beta-eucaine borate are equally efficient.

A few drops of a 0.25 per cent. solution of beta-eucaine borate on the human cornea produce in a few seconds complete superficial anaesthesia, which lasts several minutes. It causes no smarting, but the vessels are slightly congested. A 2 per cent. solution causes definite smarting and pronounced vascular congestion. The pupil is not affected.

The experimental toxicity of beta-eucaine borate was investigated by subcutaneous injections into rabbits, and was found to be approximately one-tenth that of cocaine hydrochloride. Very large doses are required to produce convulsions. For example, using a 5 per cent. solution, a dose of 400 mg. per kilo caused weakness for thirty minutes, but no convulsions, whereas the minimum convulsant dose of cocaine hydrochloride under the same conditions is 40 mg. per kilo. I am indebted to Dr. S. W. F. Underhill for permission to refer to the following experiment.

Experiment.—A rabbit, weight 2.25 kilos, received 18 c.cm. of a 10 per cent. solution of beta-eucaine borate (=800 mg. per kilo). The animal had convulsions in the intervals between which it lay

stretched out immobile and rigid; later it passed through a period of inco-ordination on movement. Next day it was less rigid, but was not well and died the same night, about thirty-six hours after the injection.

In one of my experiments a rabbit, weight 1.38 kilos, received 20 c.cm. of a 5 per cent. solution of beta-eucaine borate (=720 mg. per kilo). This dose is approximately ten times the minimal lethal dose of cocaine hydrochloride. The animal had convulsions lasting twenty minutes, but recovered.

Beta-eucaine borate is not more irritant for rabbits than cocaine hydrochloride, and it is less irritant than beta-eucaine lactate. Thus, in a rabbit 0.5 c.cm. of a 10 per cent. solution of beta-eucaine borate injected subcutaneously caused slight thickening and hyperaemia lasting three days; the same dose of beta-eucaine lactate in equal concentration caused much thickening and ecchymosis lasting seven days, and this was followed by sloughing, as in Le Brocq's experiment.² This irritation may not be of practical importance when the greater dilution of the solutions as compared with cocaine hydrochloride is taken into account. Beta-eucaine borate is a vaso-dilator, and, in the cat, a 2 per cent. solution causes marked congestion of the nasal mucous membrane.

Conclusions.

1. Beta-eucaine borate has three times the surface anaesthetic action on the rabbit's cornea, and one-tenth the experimental toxicity, as compared with cocaine hydrochloride.

2. It is mildly irritant, causes some congestion, especially in the nose, and, in very large doses, excites the central nervous system.

This research was carried out during my tenure of the Ernest Hart Memorial Scholarship of the British Medical Association. I desire to express my thanks to the Medical Research Council for the special grant it made for the expenses.

REFERENCES.

¹ Copeland and Notton: *BRITISH MEDICAL JOURNAL*, September 26th, 1925, p. 547. ² Le Brocq: *Ibid.*, 1909, i, p. 783.

THE CLINICAL VALUE OF BOROCAINE IN OPHTHALMOLOGY.

BY

T. HARRISON BUTLER AND R. U. GILLAN.

RECENTLY there appeared in the *BRITISH MEDICAL JOURNAL* (1925, ii, p. 547) a most interesting account of borocaine, showing that it should be an efficient substitute for cocaine in operations demanding surface anaesthesia. I at once procured a supply for trial. The tests were made at the Birmingham Eye Hospital, at the Coventry and Warwickshire Hospital, and at the Warneford Hospital, Leamington. Borocaine was used for the removal of foreign bodies from the eye and for tonometry.

At the Birmingham Eye Hospital, where anything up to eighty cases of foreign body in the eye are treated daily, I asked the out-patient sister to try borocaine in 2 per cent. solution. She reported to me that were she to go on with it it would be impossible to finish the cases, for the drug took such a long time to act, and that even then it was ineffective.

At the Warneford Hospital borocaine was investigated by my house-surgeon, Mr. Mackenzie, and by the out-patient sister. The report was that even in 4 per cent. solution borocaine was ineffective. I myself tried it upon two cases for the purpose of finding the intraocular tension with the Schiötz tonometer. I found that after twenty minutes' anaesthesia the cornea was still sensitive, and that repeated instillation of borocaine was ineffective. I put in a drop of holocaine, and at once was able to use the instrument. Another case gave three minutes for the induction with borocaine, three seconds for cocaine.

At the Coventry Hospital I suggested to my house-surgeon, Mr. R. U. Gillan, that he should carry out a research upon the value of borocaine. His results were the following.

AN INQUIRY INTO THE VALUE OF BOROCAINE AS A SURFACE ANAESTHETIC FOR THE EYE: A COMPARISON WITH COCAINE.

Observations were made on over 200 eyes, attention being given to the following considerations:

1. The practical value of borocaine in the removal of foreign bodies lodged on the surface or in the superficial layers of the cornea.
2. The comparative value of cocaine for the same purpose.
3. The extent and duration of the anaesthesia induced by borocaine and cocaine respectively.
4. The after-effects of borocaine upon the condition of the eye compared with the after-effects of cocaine.
5. The effect of borocaine and cocaine upon the state of the pupil and upon the tension of the eye.

Under the first heading 44 cases of foreign body in the cornea were tested with 2 per cent. solution of borocaine with glucose and adrenaline in normal saline. The results were very variable.

In 2 cases repeated instillations failed to abolish corneal sensation and cocaine had to be used. In 2 cases a second instillation had to be made to allow painless removal. In 3 cases spasm of the lids made removal difficult. In 5 cases the patient felt the operation but did not complain. In 3 cases the patient complained of pain during removal. Six cases were treated with ease, and the removal was in all respects satisfactory. The remainder were treated without difficulty, but there was a tendency to spasm. A foreign body embedded in the conjunctiva was removed with the aid of scissors without pain.

In the next series of 36 cases 4 per cent. borocaine was used in the hope that anaesthesia might be more consistent and complete, but the results were still variable. The outstanding feature was the spasm induced by the drug before the onset of anaesthesia. This was present in all cases. The anaesthesia was generally complete. The average time occupied by the operation was 116 seconds.

In 21 cases the removal was easy and unattended by any unpleasant symptoms. In 13 the removal was made difficult by palpebral spasm. In 4 there was actual sensation of pain.

The results obtained with 2 per cent. cocaine in normal saline with glucose were steadily uniform. There was no sensation of pain and no spasm of the lids. The average time occupied was fifty-eight seconds (20 cases).

Under the third heading 42 cases were treated with 2 per cent. borocaine. The average time of induction was found to be from ten to twenty seconds, usually fifteen seconds. The anaesthesia was complete in most cases to light touch, pressure, and to the pain sense.

In 7 cases anaesthesia was complete to light touch, but pressure was felt and the pain sense was not abolished. In 2 cases light and deep touch was not felt, but pain was not abolished. In 4 cases all forms of corneal sensation were still present.

Eleven cases were treated with 4 per cent. solution of borocaine. The induction period was usually fifteen seconds. Before this time had elapsed the corneal surface could not be touched because of the initial spasm. One patient retained the feeling of pressure and the pain sense.

The induction period for 2 per cent. cocaine was found to be ten to fifteen seconds for light touch and from fifteen to thirty seconds for deep touch and pain. Anaesthesia was complete in all cases.

Duration of the Anaesthesia.—This was tested by the corneal reflex and by the sensations of the patient. Under 2 per cent. borocaine the corneal sensation returned in a period of from 30 to 210 seconds, the average being 120 seconds. The corneal reflex returned in from 75 to 300 seconds, the average being 180 seconds. Under 4 per cent. borocaine corneal sensation returned in from 150 to 500 seconds, the average being 370 seconds. The corneal reflex was in most cases not present in ten minutes, the earliest return being 240 seconds. Under 2 per cent. cocaine the period of anaesthesia lasted from 90 to 300 seconds, the average being 200 seconds. The reflex was in most cases not present in five minutes, the lowest period