weighing or measuring an unduly wasted body. I prefer to reckon how much the patient ought to weigh if in good health; for this purpose age, height, sex, and the general tendency of the patient's family should be taken into consideration. Having decided on this basis approximately how much the patient should weigh, I prescribe a diet which shall contain 1 gram of protein and 35 calories per kilogram of the assumed weight.

I use Woodyatt's formula for the proportions of protein, fat, and carbohydrate—namely, that the fat in the diet shall be equal to twice the carbohydrate *plus* half the protein. On this formula the minimal diet for a weight of 50 kilos (or 8 st.) is: fat 139 grams, carbohydrate 57 grams, and protein 50 grams. It is advisable to start immediately with the full adequate diet; there is no time when infection is present or an operation is about to be performed to commence with diets of the "ladder" type. The patient must be well fed from the start, and sufficient insulin must be given to keep the blood sugar at a safe level. It is not a bare subsistence the patient requires, but an allowance (of carbohydrate at any rate) which would nourish him if in good health and give a reasonable margin for combating the infection or facing the shock of an operation. I have already described how, in the after-treatment of operation cases, the surgeon is permitted to give the patient as much glucose, and in such a manner, as he would do if the patient were non-diabetic. Subsequently, as the surgeon modifies the diet, the insulin is adjusted to keep pace with it. But there must be no diminution of carbohydrate because the patient is diabetic. The insulin must be pushed in surgical emergencies as fearlessly as in the dreaded emergency of coma. For the treatment of coma the method recommended by Campbell[12] should be followed.

"Patients in diabetic coma who have not received treatment require larger doses of insulin. As speed is essential and the rate of action of insulin is only doubled by taking ten times the dose, we commonly use 100 units of insulin intravenously as the initial dose. Most of the coma patients are dehydrated and fluid must be supplied liberally. Some of this may be given intravenously as 10 per cent. glucose solution, at a rate not greater than 10 c.cm. per minute. If the pulse rises ten beats per minute, discontinue the injection. Normal saline or 5 per cent. glucose may be injected interstitially and given per rectum by the Murphy drip method after a cleansing enema has been given. Many patients difficult to rouse will respond by automatic swallowing movements when a teaspoonful of fluid is poured into the mouth. Except by direct injection into the circulation it is doubtful if too much fluid can ever be administered to a diabetic in coma. Warmth must, of course, be provided. The room should be warm and warm blankets and hot-water bottles used. Circulatory stimulants should be begun early, digitalis and coffee by mouth or per rectum being the most satisfactory stimulants, pituitrin and ether being used for more acute emergencies. In my opinion alkalis in moderate doses, 15 to 30 grams $NaHCO_3$, are of value when administered by mouth or per rectum in 5 per cent. solution. The intravenous injection of sodium bicarbonate solution is to be employed with caution as it may induce cardiac dilatation and failure. Hypoglycaemia must be avoided and carbohydrate must be available to replace the defective fat metabolism as well as to burn up the ketones already produced. This is provided by giving the patient approximately 1 gram of sugar for each unit of insulin. The use of a retention catheter and testing the urine for sugar each hour will give ample warning of a deficiency of available carbohydrate."

The Transmission of Blood Samples.

I have been asked how blood may be sent by post for purposes of blood sugar estimation. The following plan is one that I have found useful and effectual. With a hypodermic syringe withdraw 1 c.cm. of blood and empty it into a small glass tube (such as is used in laboratories for precipitation tests—Widal, Wassermann, etc.) containing a few crystals of neutral potassium oxalate. Shake the blood thoroughly to mix it with the oxalate and prevent clotting. Wash the hypodermic syringe well with plain water and then absolute alcohol. Draw up into the syringe exactly 0.2 c.cm. (or 5 minims) of oxalated blood, then fill the syringe exactly to the 1 c.cm. mark (or to the 20 minim mark) with absolute alcohol. Shake well and empty the contents of the syringe into a second small glass tube. Cork tightly and dispatch, properly packed, by post. The mixture of oxalated blood and alcohol will contain a 1 in 5 solution if the syringe was graduated in cubic centimetres, and a 1 in 4 solution if graduated in minims. The blood sugar can be estimated accurately from the alcoholic solution.

References.

[1] Joslin: *Treatment of Diabetes Mellitus*, third edition, London, 1924, p. 320. [2] Fitz and Murphy: The Cause of Death in Diabetes Mellitus, *Amer. Journ. Med. Sci.*, vol. 168, September, 1924, p. 313. [3] Macleod and Banting: Beaumont Foundation Lectures, 1923. [4] Joslin: Loc. cit. ([1]), p. 638. [5] McCay: Coma as a Cause of Death in Diabetes, *Indian Journal of Medical Research*, xii (1919-20), p. 22. [6] Rosenfeld: *Zentralbl. f. inn. Med.*, 1906, xxvii, 986. [7] Joslin: Loc. cit. ([1]), p. 600. [8] Treves: *System of Surgery*, London, 1896, vol. i, p. 268. [9] Lawrence: *The Diabetic Life*, London, 1925, p. 95. [10] Joslin: *Trans. Assoc. Amer. Phys.*, xxxix, 1924, p. 307. [11] Vignes and Barbaro: *Presse Médicale*, December 20th, 1924, p. 1018. [12] Campbell and Macleod: *Insulin*, Medicine Monographs, Baltimore, 1925, p. 112.

NOVASUROL AND OTHER DIURETICS IN CARDIAC OEDEMA.

BY

C. G. LAMBIE, *M.C.*, F.R.C.P.Ed.,

ASSISTANT PHYSICIAN, ROYAL INFIRMARY, EDINBURGH; LECTURER IN CLINICAL MEDICINE, UNIVERSITY OF EDINBURGH.

The value of mercury as a diuretic in the treatment of cardiac dropsy has long been recognized, the drug being usually prescribed along with digitalis, as in Guy's pill. The combination of digitalis with mercury was so much the rule that some doubt existed as to whether mercury possessed any diuretic action independent of its association with digitalis. This point may be said to have been settled, as mercury in the form of metallic mercury (pil. hydrarg.), for example, will increase the elimination of urine in cardiac dropsy apart from the administration of digitalis, though the diuresis may not be so marked as when the latter is given as well. The appearance, therefore, of an organic compound containing a large percentage of mercury, capable of being injected intramuscularly or intravenously, and exhibiting powerful diuretic properties, is of interest.

Novasurol has been studied in America and in Germany, but, save for a recent article by Dr. A. R. Gilchrist of Edinburgh, observations upon its clinical use do not seem to have been reported in this country. It contains 33.9 per cent. of mercury, and the dose is 1 c.cm. of a 10 per cent. solution. The amount of mercury, therefore, in one dose is comparatively small—only 0.0339 gram, or about that contained in $1\frac{1}{2}$ grains of pil. hydrarg.; nevertheless, the diuretic action is much more pronounced than in the case of metallic mercury administered in the usual way by the mouth. As the mercury in novasurol is not in an easily ionizable form, it possesses a low toxicity and is non-irritating locally, provided that none escapes into the subcutaneous tissues. Moreover, griping and a tendency to diarrhoea—drawbacks attendant upon the oral administration of mercury—are obviated. The solubility of the drug, permitting of its rapid absorption from the site of injection, probably favours a more intense and rapid action than that exhibited by metallic mercury or calomel.

Case I.

This case appeared to be peculiarly suitable for the study of various diuretics. The cardiac failure was progressive, little influenced by digitalis and not complicated by any abnormal rhythm. A record of the output of urine over a period of 109 days, during which different diuretics were administered (see graph), shows that novasurol was capable of causing a profuse diuresis when all other diuretics, including metallic mercury, had failed. The patient was a man, aged 68, suffering from syphilitic aortitis, with aortic and mitral incompetence and oedema of the legs, together with some ascites. The urine contained traces of albumin, while the blood urea nitrogen was 22 mg. per cent., and the blood chlorides 450 mg. per cent., showing that there was no evidence of chronic nephritis. He was put on a light dry diet and the intake of water was kept approximately constant. During the first week no drugs were given and the effect of rest in bed was observed. Then tincture of digitalis ♏x t.i.d. was administered, and no increase in the urine was noted. On the twentieth day caffeine gr. iij t.i.d. was added, but little if any change in the output of urine followed. The digitalis and caffeine were then discontinued and urea in large doses, 15 grams thrice daily, was given over a period of five days, when the volume of urine increased from 600 up to 2,590 c.cm., after which it gradually returned to the previous level. When the output had decreased to about 400 c.cm., digitalis and

mercury in the form of Guy's pill were administered during eight days, but no diuresis resulted. Later, tincture of digitalis and caffeine were again tried, and there appeared to be a very slight increase in the elimination of urine. This was followed by urea in doses similar to those previously employed, but with very little influence upon the urine volume. Theobromine sodium salicylate and theobromine sodium salicylate *plus* urea, likewise failed, as also did theocin. Novasurol, 0.5 c.cm. intramuscularly, was then administered, when the urine increased to 1,350 c.cm. on the day of the injection and returned to the original level the next day. A second injection of 0.5 c.cm., three days later, caused a profuse diuresis, the urine volume rising to over 3½ litres. During the subsequent three days the output was also above the usual level, but by the fourth day the diuresis had completely passed off. The loss of water in the urine was accompanied by marked diminution in the oedema of the legs and back, while some fluid which had accumulated at the bases of the lungs disappeared. No ill effects were observed, and the general condition of the patient appeared to be much improved for several days. The gradual failure of the heart, however, caused the oedema to increase once more, and later injections of novasurol (not shown in the chart) had less effect. The patient ultimately died, and at the *post-mortem* examination the lesions of syphilitic aortitis, together with aortic and mitral incompetence, were found; the kidneys were of normal size, the cortex of each organ being broad and well defined, while the capsule stripped readily, leaving a smooth surface. There was no evidence that novasurol exerted any deleterious influence upon the kidneys, and no increase in the albuminuria followed its administration.

CASE II.

A male, aged 76, suffering from myocarditis, with marked oedema, without valvular disease, but in whom extra-systoles were frequently present. Some mucus and blood were present in the stools for a few days after admission, but this soon cleared up and not more than two stools were passed in the day. On rest in bed alone and a milk diet the urine volume averaged between 300 and 400 c.cm. On administering digitalis along with theobromine the output increased to between 500 and 800 c.cm., and the oedema diminished somewhat. Then the theobromine was discontinued and urea, 15 grams thrice daily, was substituted, when the urine increased to between 900 and 1,400 c.cm. This dose of urea was continued for fifteen days, and the urine volume remained at the above level, although on the third day the digitalis had to be stopped owing to the development of the pulsus bigeminus. After a period without diuretics, when the volume fell to about 500 c.cm., urea was again administered, with a similar response. After discontinuing the urea for a few days, theobromine alone was given, but the output of urine steadily diminished to 396 c.cm. Pil. hydrarg. gr.j t.i.d. was then given instead of theobromine, when the urine increased to 1,000 c.cm. and remained at about this level for a week. It was then stopped, and on the following day a dose of novasurol, 0.5 c.cm., was administered, when the urine secreted during the following twenty-four hours amounted to 1,000 c.cm. Digitalis, which had been discontinued since the development of the irregularity above referred to, was now recommenced (tinct. digit. mx t.i.d.), but the urine volume remained at 450 c.cm. A second dose of novasurol (0.5 c.cm.), given along with the digitalis ten days after the previous dose, gave a greater response, 1,932 c.cm. of urine being eliminated in the twenty-four hours. It is not possible to say whether this more marked effect was due to the digitalis having been given along with the novasurol, because during the period preceding the second dose of novasurol the urine volume had been very small and the oedema had increased, whereas before the first dose the output of urine under pil. hydrarg. had been much greater. The duration of the diuresis under novasurol was, in this case, only one day, the output of urine reaching 450 c.cm. two days after, and a still lower figure (owing probably to loss of water) later. Theocin gr. v. t.i.d. was ineffective.

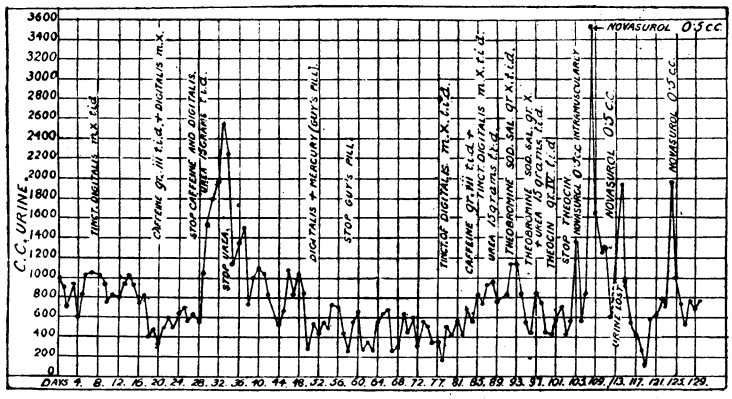

Chart showing the effect of various diuretics on the elimination of urine in Case I.

To summarize, it may be said in this case that digitalis and theobromine produced some increase in the urine to begin with, but later failed, as did also theocin. Nevertheless, urea, or metallic mercury, given alone, caused diuresis, while novasurol gave a still greater response. The administration of novasurol was in each instance followed by nausea and a feeling of weakness and general malaise. The mucus in the stools did not appear to be increased, however, though the presence of enteritis is regarded as a contraindication to the use of the drug.

CASE III.

In a man, aged 40, suffering from mitral incompetence, together with auricular fibrillation and an enlarged liver, with jaundice, a response was obtained to all the diuretics, the greatest diuresis resulting from the administration of novasurol. Three doses of 0.5 c.cm. were given at intervals of three days, with an increasing effect, although the urine volume in the interval between the doses fell to the average level, as shown by the following table.

		Dose.	Urine.
September 18, 1924	...	Novasurol 0.5 c.cm. ...	1,874 c.cm.
,, 19	,, ...	... ...	730 ,,
,, 20	,, ...	... ...	631 ,,
,, 21	,, ...	Novasurol 0.5 c.cm. ...	2,752 ,,
,, 22	,, ...	... ...	2,031 ,,
,, 23	,, ...	... ...	568 ,,
,, 24	,, ...	Novasurol 0.5 c.cm. ...	3,266 ,,
,, 25	,, ...	... ...	994 ,,
,, 26	,, ...	... ...	709 ,,
,, 27	,, ...	... ...	568 ,,

Though the oedema was lessened as a result of the diuresis, the jaundice increased on the days immediately following the exhibition of novasurol, and the patient suffered from feelings of exhaustion and general malaise. There was never any salivation. At the *post-mortem* examination chronic venous congestion of all the organs, including the liver, was found, there being apparently nothing else to account for the jaundice.

After the administration of novasurol an interval of about three to four hours elapses before the commencement of the diuresis, which reaches its height between the eighth and twelfth hours, and almost entirely passes off at the end of twenty-four hours. Analysis of the urine shows that the constituents whose elimination is most markedly increased are the water and the chlorides, while the urea is increased only to a very small extent. Controversy has centred around the question as to whether novasurol increases the urine through an action upon the kidneys or whether the diuresis is to be ascribed to some extrarenal action. Thus, it has been suggested by Saxl and Heilig and others that the drug brings about a diminution in the affinity of the tissue colloids for water and chloride which diffuse into the blood, causing a hydraemia, and to the latter the diuresis is ascribed. Evidence regarding the dilution of the blood has been conflicting, but the observations of Crawford and McIntosh seem to reconcile the discrepancies in the findings of other investigators. They found that dilution of the blood, as determined by the protein content of the plasma, corpuscular volume, and haemoglobin percentage, occurred during the period immediately preceding the onset of diuresis, while during the actual diuresis the hydraemia disappeared and the blood became more concentrated. The diuresis, therefore, could not have been due to the hydraemia, since the height of the diuresis sometimes coincided with increased concentration of the blood. The same observers also showed that in the dog an increased chloride percentage in the plasma occurred along with the primary dilution, but that during the diuresis the chloride rapidly fell. They did not, however, note any early increase in the chloride of the blood in man.

In the diuresis brought about by the purine diuretics, which are believed to act by increasing the permeability of the cells lining the glomerular tuft, thereby diminishing the resistance to filtration, there is an increase in the output affecting chiefly the chloride and water, but, as the output of chloride increases, the percentage falls. After small doses of novasurol, as also after the administration of calomel, similar curves are obtained; but with larger doses of novasurol there may be an increase, not merely in the total elimination of chloride, but, as Crawford and McIntosh have shown, an increase in the percentage, and this in spite of the fact that the percentage of chloride in the plasma was normal or diminished. This would seem to suggest that a change had taken place in the renal threshold for chloride, analogous to that which occurs with respect to glucose under the influence of phloridzin. The normal function of the

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.

My thanks are due to Dr. W. T. Ritchie for facilities afforded in his wards at the Royal Infirmary, Edinburgh.

BIBLIOGRAPHY.

Bohn, H.: Erfahrungen ueber die Novasuroldiurese. *Klin. Woch.*, 1922, i, 1940.
Brunn, F.: Zur Wirkung des Novasurols als Diuretikum. *Münch. med. Woch.*, 1921, lxviii, 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 Wirkungweise von Quecksilber. Ausgefuhrt mit dem organischen Quecksilberpräparet Novasurol. *Münch. med. Woch.*, 1921, lxviii, 1447.
Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese. *Münch. med. Woch*, 1921, lxviii, 1282.
Richards and Schmidt: *Amer. Journ. Physiol.*, lxxi, 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 Novasuroldiurese. *Wien. Arch. f. inn. Med.*, 1921-22, iii, 141.
Saxl, P., and Heilig, R.: Ueber die Novasuroldiurese. *Zeit. f. ges exper. Med.*, 1923, xxxviii, 94.
Zeiler, K.: Novasurol ein neues Quecksilbersalz zur Syphilisbehandlung, mit Bemerkungen ueber die Grundsatze der Quecksilberhandlung. *Münch. med. Woch.*, 1917, lxiv, 1257.

BETA-EUCAINE BORATE.

BY

A. J. COPELAND, M.A., M.B., D.P.H., B.Sc.
(From the Pharmacological Laboratory, Cambridge.)

IN a previous communication[1] 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, $C_{15}H_{21}NO_2.5HBO_2$) 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 *p*H 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-cucaine 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 *p*H 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