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 the patient's ideal weight, I prescribe a diet which shall contain 1 gram of protein and 35 calories per kilogram of the assumed weight.

I use Woodward'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 content of the diet. For instance, the formula for the minimum diet is: 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 sugar 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 any outside influence such as 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 insulin in the diet is diminished. But there must be a 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 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 metabolism is only doubled by taking ten times the amount, 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 minims per minute. If the pulse rises ten beats per minute, discontinue the injection. Normal saline or 5 per cent. glucose may be injected intravenously and given per rectum by the Murphy drip method after a cleansing enema has been given. Many patients difficult to wine 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 such 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 in the case. If coffee is not contraindicated, the most satisfactory stimulants, pituitrin and ether being used for acute emergencies. In my opinion alcohol in moderate doses, 15 to 20 grams NaHCO₃, are of value when administered by mouth or per rectum. Solution of sodium bicarbonate 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 lesting 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.c.m. 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 in order to prevent the oxalate and prevent clotting. Wash the hypodermic syringe with plain water, then absolute alcohol. Draw up into the syringe exactly 0.2 c.c.m. (or 5 minims) of oxalated blood, then fill the syringe exactly to the 1 c.c.m. mark (or to the 20 minims 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 centimeters, and a 1 in 4 solution if graduated in minims. The blood sugar can be estimated accurately from the alcoholic solution.

References:

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 be 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 10 per cent. of mercury, and the dose is 1 c.c.m. of a 1 per cent. solution. The amount of mercury, therefore, in one dose is comparatively small—only 0.0359 gram, or about that contained in 1½ grams of pil. hydrarg.; nevertheless, the diuretic action is much stronger than the injection 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, gripping 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 1.

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 producing a pronounced diuresis when all other diuretics, including metallic mercury, had failed. The patient was a man, aged 86, suffering from syphilitic aortitis, syphilitic arthritis and mental irritability. Prognosis was grave, together with some ascites. The urine contained traces of albumin, while the blood urea nitrogen was 22 mg. per cent., and the blood calcium was 10.50 mg. per cent. and the blood phosphorus was 4.10 mg. per cent. The patient had been suffering from the chronic nephritis. He was put on a light dry diet and the intake of water was kept approximately constant. During the first few days digitalis were given in small doses. Then tincture of digitalis 80 t.i.d. was administered, and no increase in the urine was noted. On the twenty-sixth day caffeine gr. ii t.i.d. was added, but little if any change in the output of urine followed. The digitalis and caffeine were then discontinued and ura in large doses, 15 grams three daily, was given over a period of five days, when the volume of urine increased from 600 to 2,500 c.c.m., after which it gradually returned to the previous level. When the output had decreased to about 400 c.c.m. digitalis and
 mercury in the form of Gury's pill were administered during eight days, but no diuresis resulted. Later, inure of digitalis and caffeine were 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 variable results. The urine volume, the sodium salicylate and theophylline sodium salicylate plus urea, likewise failed, as also did thecine. Novasul, 0.5 c.m. intravenously, was administered, but the urine increased only to 1.350 c.m. on the day of the injection and returned to the original level the next day. A second injection of 0.5 c.m. three days later, caused a profuse diuresis, the urine volume rising to over 24 litres. During the subsequent three days the output was almost the usual level, but by the fourth day the diuresis had completely ceased. The loss of water in the urine was accompanied by marked diminution in the oedema of the legs and back, which had accumulated at the bases of the lungs had disappeared. No ill effects were observed, and the general condition of the patient appeared to be much improved for several days. Novasul was then administered three times a day, and the oedema increased once more, and later injections of novasul (not shown in the chart) had less effect. The patient ultimately died, and at the post-mortem examination the lesions of syphilis arteritis, 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 nova- sul exerted any deleterious influence upon the kidney, and no increase in the albuminuria followed its administration.

CASE II.

A man, aged 78, 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 cleared up and more than two stools were passed in the day. On rest in bed alone and liberation of fluids along with the theophylline the output increased to between 500 and 800 c.m., and the oedema diminished somewhat. The theophylline was discontinued and urea, 15 grams twice a day, was substituted, when the urine increased to between 900 and 1,400 c.m. This dose of urea was continued for fifteen days, and the urine volume remained at the above level, although on the twelfth day the digitalis had been stopped owing to the development of the pulse size. After a period without diuretics the output fell to about 500 c.m., and again administered, with a similar response. After discontinuing the urea for a few days, theophylline alone was given, but the output of urine steadily diminished to 396 c.m. Plasma hydrargyrum, gr. t. d. was then given instead of theophylline, when the urine increased to 1,000 c.m. and remained at about this level for a week. It was then that the following day a dose of novasul, 0.5 c.m., was administered, when the urine secreted during the following twenty-four hours amounted to 1,000 c.m. Digitalis, which had been discontinued since the development of the irregularity above referred to, was now recommenced (tinct. digit. n.t.d.), but the urine volume remained at 450 c.m. A second dose of novasul (0.5 c.m.) given along with the digitalis ten days after the previous dose, gave a greater response, 1,932 c.m. 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 novasul, because during the period preceding and second dose of novasul 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 less. Nevertheless, it is possible that the novasul in this case, only one day, the output of urine reaching 450 c.m. two days after, and a still lower figure (owing probably to loss of water in later phase.) gr. t. d. was ineffective.

To summarize, it may be said in this case that digitalis and urea, or mercurial, given alone, caused diuresis, while novasul gave a still greater response. The administration of novasul was in each instance followed by nausea and a feeling of weakness and general malaise. The use of the colloids of chloride, 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 novasul. Three doses of 0.5 c.m. 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.

<table>
<thead>
<tr>
<th>Date</th>
<th>Novasul</th>
<th>Urine, litres</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 18, 1924</td>
<td>0.5 c.m.</td>
<td>1,874 c.m.</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>730</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>730</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>2,831</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>709</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>568</td>
</tr>
</tbody>
</table>

Though the oedema was lessened as a result of the diuresis, the jaundice increased on the days immediately following that of novasul, 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 novasul an interval of about three to four hours elapsed before the common symptoms of diuresis, which reaches its height between the eighth and twelfth hour, and almost entirely passes off by the end of twenty-four hours. Analysis of the urine shows that the constituents whose elimination is most markedly increased are those after the chlorides, while the urea is increased only to a very small extent. Controversy has centred around the question as to whether novasul 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 hyaemura, 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 corpuscular volume, and haemoglobin percentage, occurred during the period immediately preceding the onset of diuresis, while during the actual diuresis the hyaemura disappeared and the blood became more concentrated. The diuresis, therefore, could not have been due to the hyaemura, 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 again rose. They have thus not 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 novasul, as also after the administration of calomel, similar curves are obtained; but with larger doses of novasul 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 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 stricture disease and interstitial myocarditis. With the increased efficiency of the circulation the blood flow and capillary pressure in the glomeruli of the kidneys return toward 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 edema, the diuresis may be enormous.

If, in spite of the administration of digitalis, the output of diuretics of the glomerular series may increase, it is not necessarily 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 capillaries 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 these glomerular membranes 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 taking the reabsorbed 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 catabolism, is about 25 grams a day, the effect of such doses necessary to make an appreciable difference must be considerable, as ordinary dosage alone. 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.

BETA-EUCANAE BORATE.

by

(From the Pharmacological Laboratory, Cambridge)

In a previous communication 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, C10H12NO5HBO3) 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 strong 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, 17.

If placed in an autoclave at 120° C. and 15 lb. excess pressure for twenty minutes it undergoes no 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 concentration 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 weak convulsions in 2 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 0.10 per cent. solution of beta-eucaine borate (=450 mg. per kilo). The animal had convulsions, in the intervals between which it lay