DIURETICS.

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THE importance of the kidneys was recognized almost as soon as the structure of the human body began to be studied. Inspection of the urine was undertaken in the earliest days of medicine, and before the Christian Era a number of treatises were written dealing with the urine. In the first century, A. D. Galen taught that urine was a filtrate of the blood ; and now, after centuries of observation and through steadily elaborating means of investigation, we have reached our present very complete knowledge of the constituents of urine—normal and abnormal ; and our much less satisfactory information of renal physiology.

Although it is true that the excretion of a watery fluid is the most obvious duty of the kidneys, it is entirely wrong to regard the urine as a filtrate or the kidney as a relatively simple filter, for, however important elimination of water may be, the excretion of the solid constituents of the urine is at least as essential to life ; and the great variation in the quantity and quality of the urine assures us that the kidneys are complicated chemical machines which do a very large amount of chemical work in their daily routine. Unfortunately, renal activity is very complex, so that we do not yet understand exactly how it is performed, and we are still perplexed by conflicting theories of kidney function.

A diuretic is usually defined as a substance which increases the quantity of the urine, and as it has been suggested that certain diuretics may act by causing direct damage to renal cells, thereby rendering them more permeable, it seems essential to give a brief résumé of renal physiology before considering the desirability and usage of diuretics.

The kidneys remove from the body :—

- (1) All the waste products of nitrogenous metabolism, chiefly urea and uric acid.
- (2) Unmetabolized inorganic salts.
- (3) The end products of most organic substances which are partly broken down in the body.
- (4) Excess of acid or alkali.
- (5) Excess of fluid.

Thus the kidneys maintain a very nice balance in the osmotic pressure of the blood (so that there is a fixed ratio between protein and other elements) and an amazingly constant alkaline reserve in the blood, so that it is certainly true to say that no piece of modern laboratory apparatus approaches the delicacy of the kidney in its reactions to variations in osmotic pressure or hydrogen ion concentration.

In carrying out these functions the kidneys do work—they use up oxygen in considerable quantities, nearly 1,000 c.c. per hour. This fact is of tremendous importance because it demonstrates what an exceptionally large blood-supply the kidneys need. Barcroft has calculated the renal blood-supply at 2 c.c. per gram per minute. This means that more than 12 per cent. of the blood which leaves the left ventricle passes through the kidneys. The work done in excreting the various urinary constituents

is considerable, and the work of the kidneys is increased when the concentration of the urine is greater. This fact explains the dilute urine and the polyuria of chronic renal disease, where the damaged kidneys cannot do the work of concentrating urea, &c., and so manage by eliminating larger quantities of dilute urine. In such cases the kidneys have to work both by night and by day, and the patient finds that he has to rise to pass a considerable quantity of urine once or more in the night.

Cushney thought that the renal function was performed by : (a) The glomeruli acting as filters and passing a fluid which contained all the noncolloidal substances of the blood-plasma ; and (b) the tubules reabsorbing fluid and some normal constituents of blood-plasma (e.g., sugar). This theory is almost certainly inadequate as an explanation of kidney activity, because under normal circumstances at least 60 litres of fluid would have to be filtered through the glomeruli for each litre of urine passed, and secondly, because the concentration of various substances in the urine is so different. Urea is concentrated 60 fold from 0.03 per cent. in blood to 2 per cent. in urine. Uric acid is concentrated 25 fold from 0.002 per cent. in blood to 0.05 per cent. in urine. A third difficulty is that Cushney's theory fails to explain how the urine may be more dilute than blood-plasma, for if Cushney was correct in his assumptions this could only be accounted for by the tubules reabsorbing solids without fluid from the glomerular filtrate.

We may fairly suggest that this theory is inadequate and that the filtrate which comes from the glomeruli is modified as it passes down the tubules by : (1) reabsorption of fluid by the tubules ; (2) excretion of various substances by the tubules ; (3) absorption of other substances by the tubules.

The relations of normal blood-serum and normal urine are well seen in this table.

Blood Serum				Urine	
Serum albumin	... 2.8	per cent. not filtered by glomeruli	...	...	0
Serum globulin	... 0.9	" " " " "	...	...	0
Sodium chloride	... 0.3	" partly reabsorbed in tubules	...	...	1.0 per cent.
Urea	... 0.03	" excreted by tubules	...	...	2.0 "
Uric acid	... 0.002	" " " " "	...	...	0.05 "
Sugar	... 0.1	" completely reabsorbed by tubules	...	...	0

It is important to understand something of the circumstances which influence the quantity of the urine.

These are : (1) The quantity of blood passing through the renal arteries, as determined by (a) renal blood-pressure, (b) dilatation or constriction of renal arteries.

(2) The colloid concentration of the blood, for the greater the colloid and osmotic pressure the less will be the filtration through the glomeruli.

(3) The concentration of the glomerular filtrate, because the more concentrated the filtrate the less readily can fluid be absorbed from it by the action of the tubules.

(4) The rapidity of the filtrate flow through the tubules, for the faster the flow the less time is there for reabsorption of fluid.

It follows logically from these facts that an increased output of urine can be brought about in a variety of ways :—

(a) By increasing the blood-flow through the kidneys : (1) By dilating renal arteries ; (2) by raising blood-pressure ; (3) by any general increase in the efficiency of the circulation.

(b) By producing changes in the blood, especially alterations in colloid concentration such as are brought about by dilution.

(c) By direct stimulation of renal epithelium, a possibility which some pharmacologists have denied.

It is probable that most diuretics act in several ways at once, for instance digitalis, which is a most powerful diuretic in cases of heart failure, acts by augmenting the cardiac output, increasing the rate of blood-flow through the kidney and raising arterial pressure : thus producing a general improvement in circulatory efficiency. Such an improvement ought to augment the activity of most of the secreting glands in the body—the stomach and the salivary glands, as well as the kidneys ; and since we know that neither the stomach nor the salivary glands do extra work under the influence of digitalis, it seems fair to assume that the diuresis is due to some direct action on renal epithelium as well as to the effects produced by changes in the circulation. This same argument can be applied to most of the substances which act especially as diuretics.

Now let us consider the practical application of these theoretical considerations. Diuresis is of considerable practical importance and is used in medicine for a variety of conditions which are not uncommonly met in the daily routine of the practitioner.

(1) To reduce œdema or the collection of fluid in any part of the body in cases of heart failure, ascites, pleural effusion, &c.

(2) To reduce general blood volume in cases of aneurysm, hyperpiesis, myocardial embarrassment.

(3) To ease the work of the kidneys in excreting toxins or poisons, such as diphtheria toxin, lead, or arsenic.

(4) To dilute the urine in cases of pyelitis, cystitis, or general urinary tract infections.

(5) To augment the rate of excretion of certain substances, i.e., urea, uric acid.

The simplest of all diuretics is water, and its importance is so obvious that like Naaman we are apt to overlook its adequate use and effects. It is well-known that in hot weather, when the skin is active, the total quantity of fluid secreted by the kidneys is reduced, and the urine becomes high coloured and concentrated. A similar oliguria is seen in fevers or after strenuous exercise, and a concentrated urine may follow the ingestion of excessive quantities of food. As a general rule mankind (especially civilized womankind) drinks too little fluid, and his almost habitual constipation, at least part of his renal disease, and his tendency to formation of calculi in the urinary tract are attributable to this fact. So that it seems probable that the intake of too little water may be almost as harmful as drinking other more potent fluids to excess. One of the outstanding features of spa treatment, a feature common to the majority of spas all over the world, is the tremendous increase in the fluid intake of the pilgrims, and, without in the least discrediting the other factors in the cure, it seems reasonable to assume that some of the benefits which a visit to a spa confers upon a patient are due to the diuresis that follows the increased intake of water. In hot weather and hot countries nature in her wisdom has provided a thirst of a truly astonishing intensity which is designed to attempt to minimize the effects of a high temperature in concentrating body fluids and renal secretion. This suggests that those who have a tendency to the formation of calculi, or to the passage of uric acid crystals in the urine, would be well advised to pay at least as much attention to diuresis as to diet : for, however important diet may be, it is surely true that if the urine be sufficiently dilute calculi will not appear. In fevers and in infections of the urinary tract we ought to attempt to augment the fluid intake, and a minimum of five pints of fluid a day should be aimed at, for we must remember that as

Dr. Shipley pithily remarks, even the Archbishop of Canterbury is 57 per cent. water, and that a highly acid or concentrated urine with a heavy deposit of urates suggests an inadequate supply of fluid.

In 1785 William Withering introduced **digitalis** as a diuretic of especial utility in cases of dropsy. He says: "These cases must be considered as the most hopeless and deplorable that exist . . . so that upon the whole the instances I am going to adduce may truly be considered as cases lost to the common run of practice and only snatched from destruction by the efficacy of the digitalis, and this in so remarkable a manner that if the properties of the plant had not been discovered, by far the greatest part of these patients must have died. . . . But it is not my intention merely to introduce a new diuretic, but one which, though not infallible, I believe to be much more certain than any other in present use." Withering used either an infusion of the leaves or the powdered leaf, and he ordered far bigger doses than are common now, pressing it until diuresis, purging, vomiting, or blurred vision ensued.

He recognized its action in slowing the pulse but did not know that it was in cardiac dropsy that it was particularly useful, indeed he states that it commonly cured dropsy as a sequel to scarlet fever or sore throat which was epidemic in 1779.

There is no doubt that digitalis is the most generally useful diuretic in the oedema of congestive heart failure, and that, when the condition of the heart is recognized early, the judicious use of the drug will prevent the onset of oedema and the more severe symptoms of failure. Unfortunately, cardiac patients are inclined to be optimistic about their symptoms, to take little notice of the early signs of a failing circulation, and to fail to recognize the progressive nature of their troubles until a severe grade of failure is present. Under these circumstances large doses of a potent preparation of digitalis are urgently needed.

In heart failure digitalis should always be tried in adequate doses. It is worth remembering that Wenckebach states that he owes his reputation to the fact that he orders digitalis in just those cardiac conditions in which the textbooks say the drug is either contraindicated or useless. Withering and Wenckebach have both preferred the powdered leaf, and it is difficult to see the advantage of the many and varied modern preparations which have been put on the market. These preparations are not more palatable nor more potent than the powdered leaf, they are merely more expensive. The dosage is important, and before definite effects can be expected at least 10 gr. of the powdered leaf must be given, to which 5 drm. of the tincture are approximately equivalent. Patients who have not had any digitalis or strophanthus for a week may be given the 10 gr. of the powdered leaf or an equivalent dose of some other preparation in the course of two or three days, and effects may be expected at the end of this time; if there has been a previous but inadequate use of a digitalis preparation it is safer to use smaller doses than those mentioned above. The infusion of digitalis is often said to be a better diuretic than the tincture; this may be so, or the statement may be due to the general use of a larger and more effectual dose of the infusion.

Mercury, which is itself a diuretic, may be combined with digitalis, and **Guy's pill** has stood the rest of time as a useful preparation. This pill contains 1 gr. each of powdered digitalis, extract of squill and mercury pill, and is a powerful diuretic in adequate doses. In the same way **other diuretics** may be combined with **digitalis**,

and a modern practice is to give one of the acid salts which **alters the acid base equilibrium**—ammonium chloride, calcium chloride or ammonium nitrate. The last is the least objectionable to the patient as being less salt than the chlorides; it should be given in doses of about 15 gr. five or six times a day, each dose dissolved in an ounce of sweetened flavoured water. At times there is a marked diuresis within three or four days of commencing such treatment, and this may continue until all oedema has disappeared. These acid salts may be safely used in renal as well as cardiac oedema. There are numerous other useful diuretic drugs which may be used as alternatives or in combination with those already mentioned.

Caffeine or trimethylxanthine is a powerful diuretic, as many tea and coffee drinkers know by personal experience (it occurs in tea to about 2.5 per cent.). This alkaloid is fairly freely soluble in water and forms soluble salts with acids, but unfortunately the majority of these salts are too strongly acid for use as therapeutic agents, and for this reason only the weakest acids are used. Caffeine citrate is feebly acid, and the double salts, caffeine sodium benzoate and caffeine sodium salicylate are freely soluble in water and are neutral in reaction, so that solutions of them may be used (as may a solution of caffeine itself) for hypodermic injection. The usual dose of caffeine or one of its salts is from 2 to 5 gr., and its action as a diuretic is due to several effects. It is a definite cardiac stimulant and increases the stroke output of the heart; it also causes local vaso relaxation, and so increases the blood supply of the kidney, and there is definite experimental evidence of a direct stimulation of renal epithelium. All these properties of caffeine may prove advantageous, but there are other effects which may be definitely troublesome, for it is a direct stimulant of the central nervous system and can produce insomnia and restlessness; it also raises blood-pressure, so that in high-pressure cases with heart failure, and especially in mentally restless patients, its use is definitely contraindicated. On the other hand, it may be used in nephritic oedema without fear of damage to the kidneys. In cases in which caffeine is indicated it may be given in the form of tea.

Theobromine or dimethylxanthine forms a double salt with sodium salicylate—**diuretin**—which is a useful but not very powerful diuretic. It is chemically unstable and is readily decomposed by alkalis, and for this reason it is best prescribed as tablets in doses of 10 gr. to be chewed or crushed in a little water and taken three times a day. This salt acts as a salicylate and therefore affects those who have an idiosyncrasy for salicylates, but in such cases agurin (theobromine-sodium acetate) may be used as a substitute. Diuretin is especially useful in certain forms of heart failure; it relieves the pain of angina and is supposed to improve the coronary blood-supply.

Theophylline (another dimethylxanthine), also known as theocin, is a powerful diuretic, but is even more active than caffeine in stimulating the central nervous system.

All these xanthin derivatives increase the output of the solid constituents of the urine as well as the fluid. Urea, uric acid and chlorides are especially excreted. This may not be due entirely to the action of these compounds upon the kidneys, for some experimental work has suggested that under the influence of purin bodies there is a rise of the chloride content in the blood, a state of affairs which should facilitate the excretion of chloride in the urine.

Urea itself is a most useful and potent diuretic, but it must be given in large doses. At least 5 grm. three times a day are necessary, and larger doses are desirable. Since

urea is non-toxic and is a low threshold body which is readily excreted by the normal kidney, it may be used in considerable dosage over a long period without fear, but experience has shown that where it is going to prove effectual it begins to exert its effects within four or five days provided the dose be adequate. It has been used in renal dropsy and cardiac dropsy with marked benefit. The best way to prescribe it is in a dose of 10 grm. with 2 or 3 drms. of syrup of orange and 2 oz. of water, to be taken in a small tumbler of soda water three times a day. In this way it is not unpleasant, but in some people it does appear to induce vomiting or digestive upset. The essential oils of juniper, turpentine, copaiba, cubebs, buchu and *urva ursa* are all feeble diuretics, probably because they are all renal irritants. They are superseded now by the more generally useful and more potent modern chemical compounds.

The most modern and potent diuretics are **organic salts of mercury** with tremendous technical names, but known shortly as **novasurol**, **salyrgan** and **neptal**. Used judiciously in suitable cases, where the kidneys are relatively normal and after adequate preparation, these salts produce a remarkable diuresis, but there is no doubt that they are dangerous toxic drugs which can produce severe local and general disturbance.

Novasurol is the most toxic, and is also quite easily the most powerful diuretic; **salyrgan** occupies the intermediate position both as a diuretic and as regards its toxicity; while **neptal** is the least toxic and, as a rule, produces a less striking diuresis.

These relatively new drugs may be used in cardiac dropsy, in the ascites of hepatic disease, or in other forms of local or general oedema, but the selection of a suitable case for the exhibition of one of these salts and the preliminary preparation of the patient is of considerable importance. As a general rule the less toxic diuretics should be tried first, especially in renal cases, but where the urine is relatively normal, contains no granular casts, not much albumen and is concentrated, either may be tried. As an example, let us take a case of cardiac failure with massive oedema of the legs, ascites, some oedema of the chest wall and a pleural effusion. In spite of digitalis, no marked improvement has appeared; and, as a preliminary to giving one of the mercury salts, ammonium nitrate has been given as described above for three days, but without any adequate response. If possible, the amount of fluid in the abdomen should be lessened by means of a small trocar and cannula or a Southey's tube, so that the blood-supply to the kidneys may be augmented, and then $\frac{1}{2}$ c.c. of the solution of the mercury salt is injected. This should be injected into a vein if possible, because local pain and reaction are avoided and a diuresis is favoured, while the likelihood of a bad reaction is not increased. If intravenous administration is impossible the dose must be given by deep intramuscular injection. The injection must be deep, into a muscle, not on to a bone, and never subcutaneous; for the injection given near a bone causes severe pain, and that given subcutaneously results in a severe local inflammation and may cause a painful ulcer. Any local reaction indicates a technical error in administration. Provided that diuresis follows, or in the absence of any effect of the first dose, a further quantity (usually 1 c.c.) is given next day and may be repeated on the third day. With novasurol it is advisable not to give more than three or four doses. With salyrgan the dose may be continued daily for ten or twelve days, though this is seldom necessary.

The general reactions are of three types. Within a short time—twenty minutes to two hours—a syncopal attack may occur with cyanosis, a rapid weak pulse, and a considerable degree of severe collapse. Fortunately, attacks of this kind are rare.

The second type of disturbance is characterized by bowel upset, abdominal pain, tenesmus, the passage of small, loose, mucoid or even bloody stools. Upsets of this kind are not very infrequent, they are unfortunate but do not persist, and although they upset the patient for twelve hours or so, are not dangerous. If either of these disturbances appears, a subsequent dose is not advisable, but where novasurol has caused the upset salyrgan has been used subsequently without any ill-effect. The much more usual reaction is diuresis, and this may be astonishing.

A doctor who had persisted with his work until he had massive œdema of the legs, ascites and bilateral pleural effusions—he even had œdema of the scalp so that he could not wear a hat—was given $\frac{1}{2}$ c.c. of novasurol on Monday at midday. For ten days before this he had averaged about 18 oz. of urine per twenty-four hours. On Monday, after the injection, he passed 75 oz. On Tuesday he excreted 185 oz. and on Wednesday 240 oz. of urine. He had no further dose, and within eight days he had lost the whole of his very considerable œdema.

A police officer, Irish, and over six feet in height, who had been a heavy drinker, and had hyperpiesis, finally developed heart failure with extreme œdema, and was treated in hospital for sixteen days without very marked improvement. He had not been given novasurol, as there was definite evidence of renal abnormality—casts and albumin were both present in the urine. Finally, he was given doses of $\frac{1}{2}$ c.c. of novasurol and 1 c.c. twenty-four hours later. During the first day after the 1 c.c. the diuresis was such that his bed was soaking and the total output was not measured. But during the second day he passed 316 oz. of urine, and he continued to pass over 150 oz. a day for a fortnight. During this period the urea output for twenty-four hours was nearly trebled, and his blood-urea fell from 110 to 60 mg. per cent.

In one case of nephritis with considerable œdema novasurol was given with beneficial results, and from the evidence of the urine and the blood urea the damage to the kidneys was not increased, but the use of these salts is not to be recommended in the œdema of nephritis.

Salyrgan acts in much the same way, it produces similar if less striking diuresis, and is less likely to produce the bad reactions. In cases in which there is no objection to novasurol it is to be preferred, but in cases which are open to objection salyrgan or neptal is preferable and should be tried first. Should these fail to produce the desired effect novasurol may be used as a final resort, for at times the latter succeeds where the former proves ineffectual. By comparing daily estimations of the blood-urea and records of the daily output of urea and fluid for a period of a week or so before the use of mercury salts, with similar records obtained during diuresis, and after the loss of œdema it has been shown that no damage to the kidneys results from these salts when they are used in suitable cases and safe doses.

Salicylates and Atophan are not strictly diuretics because they do not augment the fluid portion of the urine, but they ought to be mentioned because they are valuable in augmenting the output of uric acid. Atophan is phenolquinoline carbonic acid and lowers the renal threshold for uric acid, so that to all intents uric acid becomes a non-threshold body and is totally excreted from the blood. But this action is temporary only and so it is necessary to give the drug intermittently. Moreover, atophan can cause severe damage to the liver, and has been responsible for several deaths where it has been taken injudiciously by those who have discovered its action upon gout. For

these reasons it is advisable to give it in the following manner, and to limit the dosage strictly. Atrophan should be used in doses of $7\frac{1}{2}$ gr. three times a day, on three days a week—say Monday, Wednesday and Friday, and should never be given for more than three weeks in all, in any period of three months. Used in this way it is devoid of risk and will produce good results. The mode of action is roughly that the dose on Monday causes all the uric acid present in the blood to be excreted so that some of the uric acid deposited in the tissues is mobilized or forced into solution in the blood during Tuesday. This quantity is again excreted during Wednesday, so that a further quantity of uric acid is mobilized on Thursday and so on. The effect of atophan is augmented by increasing the intake of fluid. Salicylates act in a similar manner but are much less effectual and not nearly so toxic. They may be given over a long period continuously, but probably the best salicylate to use for this purpose is diuretin.

There are many other medicines with reputations as diuretics, but they do not seem to require special mention, because they do not possess any special attributes which render them more useful than those which have been discussed.

ANÆMIA.

By H. V. MORLOCK, M.D.

THE investigation of a patient suffering from a grave anæmia demands a careful history, physical, and pathological examination.

Whatever may be the cause of the anæmia, the symptoms common to all severe degrees of anæmia will be present, i.e., weakness, lassitude, lack of concentration, dyspnœa, palpitations, œdema, often dyspeptic symptoms of varying severity, nevertheless a careful history may elicit other symptoms which may suggest the cause of the anæmia.

Marked cardiac symptoms particularly if fever is present may suggest the possibility of an infective endocarditis, a productive cough, and loss of weight. Phthisis or new growth of the lung, or if the sputum is foul, pulmonary suppuration.

Marked gastro-intestinal symptoms, the possibility of a bleeding peptic or malignant ulcer.

Marked urinary symptoms, the possibility of a chronic nephritis; symptoms referable to the central nervous system would suggest that the anæmia was one which is often associated with central nervous systemic lesions, namely pernicious anæmia.

In female patients the symptoms of pregnancy would demand special attention.

The past history may reveal a recent acute infection such as typhoid, rheumatic fever, or other fevers which are known to cause anæmia.

A recent large acute hæmorrhage, or repeated small chronic hæmorrhages (piles) may be found in the past history. The story of a recent faint may arouse the suspicion of an intestinal or gastric hæmorrhage which was passed down the alimentary tract.

Past attack of anæmia from which recovery was made.

Past attacks of jaundice.

Past residence in tropical or subtropical countries may raise the possibilities of sprue, malaria.

Past venereal disease.