DIURETICS

A Review

By H. G. LLOYD-THOMAS, M.A., M.B., M.R.C.P.

Senior Registrar, The London Hospital

All substances that increase urine flow may be classed as diuretics, and in this sense water itself is the foremost diuretic. As the main purpose of using diuretics is to promote the excretion of water, it is customary to restrict the term 'diuretic' to substances which induce a net loss of water from the body. It is also usual to exclude substances such as digitalis in which the main action of the drug is on the heart.

The chemist has provided the clinician with a large number of substances which have diuretic activity. The pharmacological actions of several of these will be considered.

Until recent years the mercurials have enjoyed an undisputed pre-eminence among the diuretics. For a long time there has been, however, a real need for an effective and non-toxic oral diuretic that would free the patient from the pain of injected mersalyl and the inconvenience of injections, and which would provide a more uniform maintenance of an oedema-free state. Many patients feel weak and unwell for 24 to 48 hours following a vigorous diuretic response to mersalyl. The search for such a drug continues. Amongst several diuretics suitable for oral administration developed since 1950, chlorothiazide ('Saluric,' 'Chlotride,' 'Diuril') has proved to be the most serious rival to the organic mercurials.

In the past, the use of diuretics was mainly restricted to the patient with congestive heart failure or oedema due to hepatic cirrhosis. Since orally-effective agents have been made available, the indications for the use of diuretics have become broader and include conditions such as premenstrual fluid retention, and pregnancy oedema.

The Organic Mercurial Diuretics

Mersalyl ('Salyrgan'), introduced in 1924, is one of the most commonly used preparations. It should be given by intramuscular injection, the usual dose being 2 ml. Intravenous injection may lead to immediate toxic cardiac reaction with ventricular fibrillation and sudden death (De Graff *et al.*, 1942).

Oral preparations such as chlormerodrin tend to cause alimentary side-effects and they produce a smaller diuretic response for the same total dosage of mercury ion.

Mercaptomerin ('Thiomerin') has the advantage that it can be given subcutaneously and can, therefore, be self-administered, but pain, ecchymosis and fibrous nodules may occur.

The primary action of the organic mercurials is to depress tubular reabsorption of certain ions. This effect can be blocked by some mercaptans. As all the transport systems in the renal tubules are not inhibited by mercury, the urine secreted in response to a mercurial diuretic has a certain pattern which will be discussed below. As a result of a proportionately greater loss of chloride than bicarbonate from the extracellular fluid there is a tendency for hypochloraemic alkalosis to develop.

The diuretic response may be potentiated by the preceding administration of ammonium chloride, which also tends to reduce excessive chloride depletion. Factors which may be responsible for unresponsiveness to mercurial diuretics, even though oedema remains, include hypochloraemia, a low glomerular-filtration rate, and the severity of the patient's condition (Stock *et al.*, 1951).

The excretion of the injected mercury is fairly rapid: 50 per cent. can be recovered in three hours, 95 per cent. within 24 hours. Measurable amounts are excreted on the second and third days and, therefore, cumulative effects may occur from injections given daily (Burch *et al.*, 1950). If there is impaired renal function the excretion may be delayed.

Contraindications

Mercurial diuretics are absolutely contra-indicated when there is an active nephritis, and when there is renal insufficiency with elevation of the blood urea above 60 mg. per 100 ml. because the drug may aggravate the existing renal lesion (Preedy and Russell, 1953), and there may be delayed excretion of the mercury. The presence

of albuminuria with casts and red cells demands caution, although these may, of course, result from congestive changes in the kidney. When there is enlargement of the prostate, urinary retention may follow a profuse diuretic response.

Untoward reactions occur infrequently. Sudden death may follow intravenous injection. Immediate non-fatal reactions may consist of flushing, chills, rigors, fever, urticaria, pruritis, skin eruptions. Dyspnoea, anxiety, palpitation, pallor and faintness may occur and should not be ignored. A different preparation of mercurial diuretic may avoid such reactions. Systemic mercury poisoning with dermatitis, stomatitis and colitis usually occurs when the diuretic response has been poor, particularly if the frequency of the injections has been injudiciously increased on this account. Fatal anuria from tubular necrosis may occur in such circumstances. Neutropenia and agranulocytosis has been reported (Silverman and Worthen, 1952). Exfoliative dermatitis has been reported after mercaptomerin ('Thiomerin') (MacHaffie *et al.*, 1958).

Secondary toxic effects are due to depletion of extracellular electrolyte. The low-salt syndrome may result and, unless corrected, may progress to oliguria and nitrogen retention. Digitalis intoxication may rarely occur after massive diuresis.

Chlorothiazide

Chlorothiazide, synthesized by Novello and Sprague in 1957, is designated chemically as 6-chloro-7-sulfamyl-1, 2, 4-benzo-thiadiazine-1, 1-dioxide. It contains an unusual fused-ring system wherein sulphur is in its highest oxidation state, as well as a sulphamyl group attached to a benzenoid ring. The compound possesses a high order of activity as an inhibitor of carbonic anhydrase *in vitro* (Beyer *et al.*, 1957).

Oral absorption is excellent as measured by the prompt electrolyte and water excretion responses, and excretion occurs rapidly via the kidney.

Although it has carbonic anhydrase inhibitor activity *in vitro*, its diuretic action in man is largely due to increased excretion of chloride ions with an almost equal loss of sodium. In its chloruretic action it resembles closely the organic mercurial compounds (Pitts and Sartorius, 1950). Increase of bicarbonate excretion may occur in the earlier hours of the action of the drug, but compared with acetazolamide the effect is neither marked nor constant (Ford and Spurr, 1957; Bayliss *et al.*, 1958a). The excretion of potassium in the urine, which may be sufficiently great to produce a state of potassium depletion, may be due to carbonic anhydrase inhibition.

It is most unusual for mercurial diuretics to

induce hypokalaemia. As mercurials may induce a greater loss of chloride than of sodium, hypochloraemia may occur and make the subject unresponsive to further mercurials. Such refractoriness is unlikely to be induced by chlorothiazide, as this drug produces almost equimolar loss of sodium and chloride. The action of chlorothiazide is likely to be maintained and because of this it is more likely to produce potassium depletion.

Chlorothiazide will frequently effectively relieve oedema and the pulmonary congestion due to heart failure (Moyer *et al.*, 1957; Bayliss *et al.*, 1958a; Bayliss *et al.*, 1958b; Slater and Nabarro, 1958; Davies and Evans, 1958; Dinon *et al.*, 1958). It is of value in causing the reduction or disappearance of oedema in nephrosis and chronic glomerulo-nephritis (Slater and Nabarro, 1958; Schreiner and Bloomer, 1957). In patients with cirrhosis of the liver with ascites, a good diuretic response was obtained in nine out of 13 cases (Read *et al.*, 1958), poor responses being obtained in those with an initial urinary output of sodium of less than one mEq. daily. Finnerty *et al.* (1958) found the drug to be useful in the treatment of the oedema and of the hypertension present in pre-eclamptic toxemia. Premenstrual oedema may be completely relieved (Bayliss *et al.*, 1958b; Dinon, 1958).

Dosage of chlorothiazide must be determined for each patient individually: 2 g. produces a maximum diuresis and this is approximately equal to the effect of 2 ml. of mercurial (Davies and Evans, 1958). It is rarely necessary to give 2 g. daily, and such a dose is probably better not continued for longer than five days without careful electrolyte control. Many patients do well on 2 g. per day given on alternate days or on two days a week. Even smaller doses may be sufficient. Disturbance of the patient's sleep may be avoided if the drug is given in the early part of the day.

Patients who are refractory to mercurial injections respond well to chlorothiazide and the reverse effect may also occur (Bayliss *et al.*, 1958b; Davies and Evans, 1958). The use of ammonium chloride with chlorothiazide may lead to a better diuresis (Watson *et al.*, 1958).

Untoward effects are uncommon. Direct toxic effects that may be attributed to the drug itself are extremely rare. Drerup (1958) reported a patient in whom jaundice occurred which he thought might have been related to chlorothiazide. Dinon *et al.* (1958) reported neutropenia and thrombocytopenia in one patient receiving chlorothiazide, and a nearly fatal allergic reaction in a second patient.

The most important side-effect of chlorothiazide is due to its effect in causing potassium loss leading

to potassium depletion which need not be accompanied by symptoms (Goodkind *et al.*, 1958; Laragh *et al.*, 1958). Hypokalaemia is of great importance in patients with cirrhosis of the liver and ascites as it may precipitate hepatic coma (Read *et al.*, 1958; Mackie *et al.*, 1958). Increased sensitivity to the toxic effects of digitalis occurs when there is potassium depletion. Hypokalaemia usually occurs in the seriously ill patients, especially those with a low dietetic intake of potassium. It is best avoided by using intermittent dosage of chlorothiazide and by supplementing the intake of potassium, using a mixture rather than tablets, which may be passed unchanged in the stool. A suitable mixture is as follows:—

Potassium chloride 1 g.
Syrup simplex 2 ml.
Alcohol, 95 per cent. 2 ml.
Raspberry flavouring qs.
Chloroform water to 15 ml.

This may be given two to six times per day as needed.

It may, however, be difficult to control hypokalaemia while continuing therapy with the drug (Slater and Nabarro, 1958). Prolonged hypokalaemia should be avoided because of the risk of renal (Follis, R. H., 1948; Perkins *et al.*, 1950; Conn *et al.*, 1956) and cardiac injury (McAllen, 1955).

Care should be exercised when this preparation is to be given to patients already on hypotensive therapy because of the marked potentiating effect chlorothiazide may have on many of the hypotensive drugs now in use.

Hydrochlorothiazide

Hydrochlorothiazide ('Hydrosaluric, Esidrex') is a new preparation which is undergoing trial at present. The electrolyte excretion pattern following its use is similar to that produced by chlorothiazide but the effect on potassium and bicarbonate excretion is less. The effective dose is smaller, as hydrochlorothiazide appears to be five to ten times more potent on a milligram for milligram basis.

Drugs of the Amino-Uracil Group

Of the active diuretics in the amino-uracil series of drugs, aminometradine ('Mictine') (Kattus *et al.*, 1952; Platts and Hanley, 1956; Hanley and Platts, 1956) and amisometradine ('Rolicton') have been the most widely investigated. They are believed to act by direct inhibition of tubular reabsorption of sodium. Aminometradine given orally is generally found to be at least 50 per cent. as effective as mersalyl by injection, but effective doses cause epigastric discomfort, nausea, vomiting or diarrhoea in a consider-

able number of subjects. Headache, tinnitus and albuminuria are less common side-effects.

Jose and Wood (1958) tested the effect of amisometradine in 20 patients with heart failure using a dose of 400 mg. three times daily for two consecutive days. They found that the diuretic potency of the drug was approximately 40 per cent. that of 2 ml. of mersalyl given intramuscularly. Apart from nausea in one patient and tinnitus in another, no toxic effects were observed in this short-term study. Diarrhoea was reported in two patients of a series of 47 cases reported by Settle (1957). He found that there was a decrease of 88 per cent. in the number of mercurial injections required in patients who were maintained on regular therapy with amisometradine.

The author has observed several cases with chronic cardiac oedema in whom neither mercurial diuretics (2 ml.) nor aminometradine (200 mg. q.d.s.) alone produced a diuretic response, but when these drugs were administered on the same day, a massive diuresis occurred with loss of oedema. The loss of potassium in the urine is usually little increased by this group of drugs, and they may, therefore, be of use particularly in those patients in whom the use of chlorothiazide causes excessive potassium wastage. The slight tendency toward depression of the serum sodium, potassium and chloride, which occurs with the daily administration of aminometradine, never becomes significant, since the drug ceases to be effective on continued daily use (Ford *et al.*, 1958). This problem of absence of effectiveness (in spite of the presence of oedema) on repeated daily use because of drug tolerance is a problem common to this group of drugs and to the carbonic anhydrase inhibitors.

Drugs which inhibit Carbonic Anhydrase

Acetazolamide ('Diamox'), designated chemically as 2-acetyl-amino-1,3,4-thiadiazole-5-sulphonamide, a carbonic anhydrase inhibitor, produces a diuresis by increasing the urinary loss of bicarbonate, which is accompanied by increased excretion of sodium, potassium and water. Its action is not as rapid, nor as dramatic, as that of an organic mercurial. After a few days' continued administration the drug loses its natriuretic effect and its action is self-limiting because a metabolic acidosis develops and the amount of bicarbonate filtered by the glomeruli is reduced (Counihan *et al.*, 1955). Hanley and Platts (1956) found it less effective than mersalyl. Relman *et al.* (1954) concluded that in patients with severe congestive heart failure, it was of little or no value. Gold *et al.* (1958) found that acetazolamide in a dose of 125 to 1,000 mg. had a diuretic effect approximately equal to 0.5 ml. of injected meralluride, while

ethoxzolamide (6-ethoxy-2-benzothiazole-sulphonamide) had a diuretic effect equal to 0.7 ml. of meralluride. In a dose of 62.5 to 250 mg. it gave rise to diarrhoea, colic and vomiting.

If acetazolamide is to be used as a diuretic it is best to use it as a single dose of 250 to 500 mg. every other day, perhaps combining it with an intramuscular mercurial diuretic given once or twice a week. Oedema associated with renal damage is a contraindication, since the kidney may be unable to compensate sufficiently for the metabolic acidosis. The drug should not be used when the oedematous state is associated with potassium-losing conditions such as steroid oedema, cirrhosis or nutritional oedema. Webster and Davidson (1956) report on the precipitation of hepatic coma by acetazolamide and this may be partly related to potassium deficiency.

Untoward Effects

Numerous side-effects from the use of acetazolamide have been reported. The most common side-effects are paraesthesiae and drowsiness (Friedberg and Halpern, 1952). Fever, leucopenia, skin rashes, may occur. Other manifestations of sulphonamide reaction, such as haemolytic anaemia, bone-marrow depression with agranulocytosis (Pearson *et al.*, 1955) and thrombocytopenia (Reisner and Morgan, 1956), as well as crystalluria with renal colic and anuria (Yates-Bell, 1958; Glushien and Fisher, 1956; Persky *et al.*, 1956), may arise.

Xanthines

When given in large doses these substances result in increased cardiac output, renal blood flow and glomerular filtration rate. They are also capable of depressing renal tubular reabsorption of electrolyte (Walker *et al.*, 1937).

The xanthines are little used as diuretics at present as there is a wide choice of more effective preparations. Theophylline is included in most preparations of organic mercurial injections with the object of increasing the rate of absorption of the mercurial from the site of injection.

Acid-forming Salts

The most widely used of these substances is ammonium chloride which is a combination of a labile cation and a fixed anion. The ammonium ion is converted to urea which leaves excess chloride ion. This displaces bicarbonate ion which is converted to CO_2 and excreted. The total electrolyte concentration of the extracellular fluid is unchanged as a labile anion and a labile cation disappear, but the chloride concentration in the extracellular fluid tends to rise and, as a result, the chloride load delivered to the renal

tubule is increased. That amount of chloride which escapes reabsorption in the tubules is excreted together with an equivalent amount of cation (mostly sodium) and water.

The main use of ammonium chloride is in combination with mercurial diuretics (and possibly chlorothiazide). By increasing the concentration of extracellular chloride the action of the mercurial is potentiated and the tendency to the production of hypochloraemia counteracted.

Evans and Paxon (1941) found that the best way to use ammonium chloride was to administer 30 gr. in enteric-coated tablets two hours before the injection of mercurial.

Acid-forming salts are contraindicated if there is impairment of renal function because of the danger of causing uncompensated acidosis.

Osmotic Diuretics

Two only are discussed.

Potassium Salts

The renal tubular secretion of potassium markedly depresses $\text{H}^+\text{-Na}^+$ exchange on the renal tubule. This results in the excretion of alkaline urine containing sodium salts, and a net loss of extracellular electrolyte and water can thereby result (Berliner *et al.*, 1951).

They are generally not very effective as diuretics, and the maximum benefit is achieved when a diet low in sodium chloride is used. Their use is contraindicated when renal failure is present.

Urea

This substance is now little used as a diuretic. It has to be given in large doses of 20 g. two to five times per day. Its use is contraindicated when there is impairment of renal function.

Steroidal Antagonists of Aldosterone (Spirolactone)

Aldosterone has been implicated in the pathogenesis of abnormal sodium and water accumulation which occurs in oedematous states such as congestive heart failure, cirrhosis of the liver with ascites and nephrosis. Many patients with these conditions excrete abnormally large amounts of aldosterone in the urine (Axelrad *et al.*, 1955; Chart and Shipley, 1953; Duncan *et al.*, 1956; Leutscher and Johnson, 1954; Wolff and Koczorek, 1955; Wolff *et al.*, 1958; Leutscher *et al.*, 1954). The excessive secretion of aldosterone may indicate over-production of this steroid which may be at least in part responsible for sodium retention. Measures that combat the effects of excess aldosterone may, in those cases where this mechanism is operating, be of use in relieving the oedematous state.

Recently, two synthetic steroids, 3-(3-oxo-17 β -hydroxy-4-androsten-17 α -yl) propionic acid γ -lactone (SC 5233) and its 19-nor analogue (SC 8109), have been shown to possess natriuretic activity consequent upon their anti-aldosterone activity (Cella and Kawaga, 1957; Kawaga *et al.*, 1957) and therefore manifested only in the presence of sodium-retaining steroids, endogenous or exogenous (Liddle, G. W., 1957). In patients with Addison's disease, maintained only on a high salt intake alone, SC 8109 had no effect on the excretion of sodium, potassium, chloride, phosphate, ammonia or titratable acid (Liddle, G. W., 1957, per Kerr *et al.*, 1958), but, when given during treatment with DOCA increased excretion of water, sodium and chloride and decreased excretion of potassium, phosphate, ammonia and titratable acid occurred. Normal subjects on a high sodium intake do not show significant responses to spirolactones, but when a state of high aldosterone output is induced in the same subjects by restriction of sodium intake, significant responses follow the administration of the spirolactones. No changes in the output of aldosterone occur in short-term studies, but continued administration of the spirolactones may be associated with a rise in aldosterone excretion. Salassa *et al.* (1958), in a study on a patient with primary aldosteronism, found that SC 8109 caused a marked effect on the excretion of sodium when a large amount of aldosterone was being excreted; it caused a negligible effect when, following removal of an adrenal cortical adenoma, only a trace of aldosterone was being excreted. These findings suggest that the spirolactones act as antagonists to aldosterone at end-organ level (the renal tubule). Liddle (1957) found a consistent natriuresis in seven patients with congestive heart failure treated with spirolactone. Kerr *et al.* (1958) obtained a sodium and water diuresis in two cases of cirrhosis of the liver with ascites and failed to do so in a third patient treated with SC 8109. The negligible potassium loss is an important feature of the diuretic response during treatment with SC 8109. Diuretics which cause a heavy loss of potassium should be avoided in patients with cirrhosis of the liver who have a tendency towards hepatic coma. The best method for the administration of these new drugs has yet to be defined. Oral and intramuscular preparations are obtainable. They are not commercially available because of prohibitive cost.

Urinary Electrolyte Excretion Patterns

Precise knowledge concerning the mechanism of action of the main diuretics used today is not complete. The principal action is the inhibition of renal tubular reabsorption of sodium. Evidence that the fundamental method by which this is

accomplished differs among various diuretic drugs is afforded by study of the urinary electrolyte excretion that follows their use. Ford (1958) studied patients with incipient heart failure and obtained the following results.

The urinary electrolyte patterns which follow the oral or intramuscular administration of the *organic mercurials* are similar. Sodium and chloride excretion are increased for 12 to 18 hours with the maximum effect occurring during the first two to six hours. Potassium excretion shows no significant alteration. Ammonia excretion is slightly depressed during the period of maximum sodium and chloride loss, but is elevated after the period of greatest sodium loss. During the period of maximum chloride loss, there is suppression of bicarbonate loss which returns to normal or greater than normal when the chloride loss begins to fall off, this action lasting for 12 to 18 hours. The response of phosphate excretion is similar to that of bicarbonate.

The urinary electrolyte pattern which follows the oral administration of drugs of the *amino-uracil group* (amisometridine and aminometridine) shows an increase in sodium and chloride excretion with little or no effect on potassium or bicarbonate excretion. The onset of action of these drugs occurs within two to four hours and continues for approximately 12 hours. There are no significant changes in phosphate or ammonia excretion.

The urinary electrolyte pattern following the administration of *chlorothiazide* alters within two hours and continues for approximately 12 hours. There is an increase in the excretion of sodium and chloride, with an increase in the excretion of potassium amounting to about one half that of sodium. Ammonia excretion is not changed during the period of sodium loss but shows some increase after 12 hours. The increase in excretion of bicarbonate is about a quarter that of chloride. Phosphate excretion shows no significant change.

The urinary electrolyte pattern following the administration of *acetazolamide* shows an increase in the excretion of sodium with an almost equal effect on potassium and bicarbonate. Chloride excretion is depressed during the period of maximum loss of bicarbonate but increases as the bicarbonate excretion diminishes. There is no significant change in ammonia excretion nor in phosphate excretion. The onset of action of the drug occurs within six hours and lasts for six to twelve hours.

The urinary electrolyte pattern following the administration of spirolactones has already been indicated.

When assessment of a diuretic response is made, it is essential to consider the formidable difficulties involved (Spencer and Lloyd-Thomas, 1953). The

test subjects differ in the nature of their disease, in the causation of their oedema, in renal function and in many other variable factors important in the differential distribution of their body fluids, such as the concentration of serum albumin and plasma sodium. Not only do patients differ among themselves, but there is a considerable daily variation of the renal excretion of water and electrolytes in the same patient which is still the case when the intake is constant, within the limits of a standard low-sodium diet.

The Comparative Potency of Diuretic Drugs

Ascribing a 'potency' of one to an organic mercurial given by intramuscular injection, the following degrees of potency may be ascribed to chlorothiazide, aminometridine, and acetazolamide respectively, 0.8, 0.7 and 0.25 (Ford, 1958). These values are based on the results of single doses and do not, therefore, accurately reflect the usefulness of the drugs. Both acetazolamide and aminometridine lose their efficiency with continued administration and this is a very important factor which seriously limits the value of these drugs as therapeutic agents.

Additional Measures for the Mobilization of Oedema

Restriction of sodium intake is still essential in a large number of oedematous patients.

A fundamental problem is that concerned with water intake in patients with oedema. It is now generally agreed that the intake of extracellular electrolytes rather than water is important in this regard, and that if sodium salts are sufficiently restricted nothing is gained by the simultaneous restriction of water. If, however, the patient will not accept adequate restriction of sodium intake, it is probably beneficial to restrict the intake of water.

In certain patients, who show no response to the diuretic agents described above, it may be necessary to resort to drainage of the legs by means of multiple punctures or by the use of Southey's tubes under systemic antibiotic cover. After a satisfactory drainage, it may often be found that the patient will again respond to diuretics. Occasionally a diuresis will follow venesection and a similar event may occur after a period of fever.

The use of cation-exchange resins is now rarely required in the treatment of cardiac oedema. Their use in treatment had been described by Spencer and Lloyd-Thomas (1954) and their place in the treatment of the nephrotic syndrome evaluated by Rosenheim and Spencer (1956). The place of cortisone and its analogues in the treatment of the nephrotic syndrome has been reviewed by Smart (1958). Ross and Ross (1957) recorded deaths

from cellulitis in two nephrotic patients treated with cortisone.

Radó and Blumenfeld (1958) record the use of ACTH to restore responsiveness to mercurial diuretics.

It may in certain patients be necessary to use a combination of diuretic agents in order to obtain a satisfactory diuretic response. The use of ammonium chloride to increase the effect of mercurials and to reduce the incidence of hypochloraemia in long-term therapy is well known. The use of potassium salts instead of ammonium chloride may be more effective occasionally. Mercurials, when given together with chlorothiazide, may succeed in producing diuresis when neither drug alone is effective. The successful use of mercurials together with aminometridine has been referred to.

Failure to obtain satisfactory mobilization of oedema fluid may be due to electrolyte derangements which should be corrected as far as possible.

The use of salt-poor albumin (Thorn *et al.*, 1945; Patek *et al.*, 1948) and of the plasma-expanders such as dextran in hyperoncotic solution to increase the colloid osmotic pressure of the plasma is of value on occasions. Space does not allow of further consideration of these substances.

Choice of Diuretic Agent

The majority of patients who require diuretic therapy will obtain satisfactory results from the use of intramuscular mercurials which are well tried and relatively free from toxic effects. They are still the standard to which other diuretics are compared. Where ease of administration is required, the most potent available oral diuretic should be used. At present this drug is chlorothiazide.

The regular use of a small intermittent dose of chlorothiazide or other oral diuretic may often allow the patient to ingest more salt and more highly salted foods than he would otherwise be able to do. The psychological advantages of being allowed a more normal diet are obvious. Many patients, however, will have to continue with moderate or even severe restriction of sodium intake.

The clinician should bear in mind the pharmacological properties of the various diuretics available, so as to make an intelligent choice of the proper drug or combination of drugs to fulfil the therapeutic need of the particular patient, and avoid untoward effects.

BIBLIOGRAPHY

- AXELRAD, B. J., CATES, J. E., JOHNSON, B. B., and LEUTSCHER, J. A. (1955), *Brit. med. J.*, **1**, 196.
 BAYLISS, R. I. S., MARRACK, D., REES, J. R., and ZILVA, J. F. (1958a), *Ann. N.Y. Acad. Sci.*, **71**, 442.
 BAYLISS, R. I. S., MARRACK, D., PIRKIS, J., REES, J. R., and ZILVA, J. F. (1958b), *Lancet*, **1**, 120.

- BERLINER, R. W., KENNEDY, T. J., and ORLOFF, J. (1951), *Amer. J. Med.*, **11**, 274.
- BEYER, K. H., BAER, J. E., RUSSO, H. F., and HAIMBACH, A. S. (1957), *Fed. Proc.*, **16**, 282.
- BURCH, G., THORPE, R., THREEFOOT, S., KELLY, F. J., and SVEDBORG, A. (1950), *J. clin. Invest.*, **29**, 1131.
- CELLA, J. A., and KAWAGA, C. M. (1957), *J. Amer. chem. Soc.*, **79**, 4808.
- CHART, J. J., and SHIPLEY, E. S. (1953), *J. clin. Invest.*, **32**, 560.
- CONN, J. W., and JOHNSTONE, R. D. (1956), *Amer. J. clin. Nutr.*, **4**, 523.
- COUNIHAN, T. B., EVANS, B. M., and MILNE, M. D. (1955), *Clin. Sci.*, **13**, 585.
- DAVIES, D. W., and EVANS, B. (1958), *Brit. med. J.*, **1**, 967.
- DE GRAFF, A. C., and LEHMAN, R. A. (1942), *J. Amer. med. Ass.*, **119**, 998.
- DINON, L. R., KIM, Y. S., and VANDER VEER, J. B. (1958), *Amer. J. med. Sci.*, **236**, 533.
- DRERUP, A. L., ALEXANDER, W. A., LUMB, G. D., CUMMINS, A. J., and CLARK, G. M. (1958), *New Engl. J. Med.*, **259**, 534.
- DUNCAN, L. E., LIDDLE, G. W., and BARTTER, F. C. (1956), *J. clin. Invest.*, **35**, 1299.
- EVANS, W., and PAXON, T. (1941), *Brit. Heart J.*, **3**, 37.
- FINNERTY, F. A., JR., BUCHOLTZ, J. H., and TUCKMAN, J. (1958), *J. Amer. med. Ass.*, **166**, 141.
- FORD, R. V., and SPURR, C. L. (1957), *Amer. J. Med.*, **22**, 965.
- FORD, R. V., ROCHELLE, J. B. III, HANDLEY, C. A., MOYER, J. H., and SPURR, C. L. (1958), *J. Amer. med. Ass.*, **166**, 129.
- FOLLIS, R. H. Jr. (1948), 'The Pathology of Nutritional Disease,' Charles C. Thomas, Springfield.
- FRIEDBERG, C. K., and HALPERN, M. (1952), *Fed. Proc.*, **11**, 49.
- GLUSHIEN, A. S., and FISHER, E. R. (1956), *Ibid.*, **160**, 204.
- GOLD, H., GREINER, T. H., WARSHAW, L., KWIT, N. T., and GANZ, A. (1958), *J. Amer. med. Ass.*, **167**, 814.
- GOODKIND, M. J., HARVEY, R. M., and RICHARDSON, D. W. (1958), *Amer. J. med. Sci.*, **235**, 164.
- HANLEY, T., and PLATTS, M. M. (1956), *Lancet*, **1**, 357.
- JOSE, A. D., and WOOD, P. (1958), *Brit. med. J.*, **1**, 9.
- KATTUS, A., ARRINGTON, T. M., and NEWMAN, E. V. (1952), *Amer. J. Med.*, **12**, 319.
- KAWAGA, C. M., CELLA, J. A., and VAN ARMAN, C. G. (1957), *Science*, **126**, 1015.
- KERR, D. N. S., READ, A. E., HASLAM, R. M., and SHERLOCK, S. (1958), *Lancet*, **1**, 1084.
- LARAGH, J. H., HEINEMANN, H. O., and DEMARTINI, F. E. (1958), *J. Amer. med. Ass.*, **166**, 145.
- LEUTSCHER, J. A., NEHER, R., and WETTSTEIN, A. (1954), *Experientia (Basle)*, **10**, 456.
- LEUTSCHER, J. A., and JOHNSON, B. B. (1944), *J. clin. Invest.*, **33**, 1441.
- LIDDLE, G. W. (1957), *Science*, **126**, 1016.
- MACHAFFIE, R. A., HUMOLLER, F. L., and WALSH, J. R. (1958), *Amer. J. Card.*, **1**, 505.
- MACKIE, J. E., STORMONT, J. M., HOLLISTER, R. M., and DAVIDSON, C. S. (1958), *New Engl. J. Med.*, **259**, 1151.
- MARTIN, J. D., and MILLS, I. H. (1956), *Brit. med. J.*, **1**, 571.
- MATHESON, N. A., and MORGAN, T. N. (1958), *Lancet*, **1**, 1195.
- McALLEN, P. M. (1955), *Brit. Heart J.*, **17**, 5.
- MOYER, J. H., FORD, R. V., and SPURR, C. L. (1957), *Proc. Soc. exp. Biol. (N.Y.)*, **95**, 529.
- PATEK, A. J., MANKIN, H., COLCHER, H., LOWELL, A., and EARLE, D. P. (1948), *J. clin. Invest.*, **27**, 135.
- PEARSON, J. R., BINDER, C. L., and NEBER, J. (1955), *J. Amer. med. Ass.*, **157**, 339.
- PERKINS, J. G., PETERSON, A. B., and RILEY, J. A. (1950), *Amer. J. Med.*, **8**, 115.
- PERSKY, L., CHAMBERS, D., and POTTS, A. (1956), *J. Amer. med. Ass.*, **161**, 1625.
- PITTS, R. F., and SARTORIUS, O. W. (1950), *Pharmacol. Rev.*, **2**, 161.
- PLATTS, M. M., and HANLEY, T. (1956), *Brit. med. J.*, **1**, 1078.
- PREEDY, J. R. K., and RUSSELL, D. S. (1953), *Lancet*, **1**, 1181.
- RADO, J., and BLUMENFELD, G. (1958), *Acta. med. scand.*, **160**, 15.
- READ, A. E., HASLAM, R. M., LAIDLAW, J., and SHERLOCK, S. (1958), *Brit. med. J.*, **1**, 963.
- REISNER, E. H. Jr., and MORGAN, M. C. (1956), *J. Amer. med. Ass.*, **160**, 206.
- RELMAN, A. S., LEAF, A., and SCHWARTZ, W. B. (1954), *New Engl. J. Med.*, **250**, 800.
- ROSENHEIM, M. L., and SPENCER, A. G. (1956), *Lancet*, **1**, 313.
- ROSS, I. P., and ROSS, J. H. (1957), *Ibid.*, **1**, 354.
- SALASSA, R. M., MATTOX, V. R., and POWER, M. H. (1958), *J. clin. Endocr. Metab.*, **18**, 787.
- SCHREINER, G. E., and BLOOMER, H. A. (1957), *New Engl. J. Med.*, **257**, 1016.
- SETTLE, E. (1957), *Postgrad. med. J.*, **21**, 186.
- SILVERMAN, J. J., and WORTHEN, J. F. (1952), *J. Amer. med. Ass.*, **148**, 200.
- SLATER, J. D. H., and NABARRO, J. D. N. (1958), *Lancet*, **1**, 124.
- SMART, G. A. (1958), *Postgrad. med. J.*, **34**, 325.
- SPENCER, A. G., and LLOYD-THOMAS, H. G. L. (1953), *Brit. med. J.*, **1**, 957.
- SPENCER, A. G., and LLOYD-THOMAS, H. G. L. (1954), *Ibid.*, **1**, 597.
- STOCK, R. J., MUDGE, G. H., and NURNBERG, M. J. (1951), *Circulation (N.Y.)*, **4**, 54.
- THORN, G. W., ARMSTRONG, S. H., DAVENPORT, V. D., WOODRUFF, L. M., and TYLER, P. H. (1945), *J. clin. Invest.*, **24**, 802.
- WALKER, A. M., SCHMIDT, C. F., ELSOM, K. A., and JOHNSTON, C. G. (1937), *Amer. J. Physiol.*, **118**, 95.
- WATSON, W. C., THOMPSON, T. J., and BUCHANAN, J. M. (1958), *Lancet*, **1**, 1199.
- WEBSTER, L. T., and DAVIDSON, C. S. (1956), *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 27.
- WOLFF, H. P., and KOCZOREK, Kh. R. (1955), *Klin. Wschr.*, **33**, 1104.
- WOLFF, S. J., FAST, B., STORMONT, J. M., and DAVIDSON, C. S. (1957), *New Engl. J. Med.*, **257**, 215.
- YATES-BELL, J. G. (1958), *Brit. med. J.*, **1**, 1392.

Addendum

Further investigations of the properties of hydrochlorothiazide (6-chloro-7-sulphamyl - 3, 4-dihydro - 1, 2, 4 - benzothiadiazine - 1, 1 - dioxide) have confirmed that the hydrogenated derivative of chlorothiazide is usually about ten times more potent than the parent substance, although there are individual variations, in promoting a diuresis in patients with chronic heart failure (Fleming *et al.*, 1959) or in those with ascites due to liver disease (Kerr *et al.*, 1959). Since the action of hydrochlorothiazide is more prolonged than that of chlorothiazide in the majority of cases, a single dose in any one day should be adequate, while chlorothiazide usually needs to be given twice in any one day (Platts, 1959). Although increased potency based merely on a weight-for-weight basis is of no particular merit in itself, it may be that the very rare toxic effects on the bone marrow that have been reported with chlorothiazide (Nordquist *et al.*, 1959) will be even less likely to occur when a smaller total dose of a compound of similar chemical structure is used. From studies on the patterns of diuresis it appears that with the exception of rather less bicarbonate excretion after hydrochlorothiazide, the urinary electrolyte pattern produced by both drugs is the same. Potassium loss may occur just as readily with hydrochlorothiazide as with chlorothiazide (Havard and Fenton, 1959). Hypokalaemia is more likely to occur in patients previously subjected to a low dietary sodium intake. In patients with oedema of recent onset and not treated by sodium restriction the urinary potassium excretion may not be materially increased by either drug.

The maximum effective dose of hydrochloro-