DRUG TREATMENT OF HYPERTENSION

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Hypertension is the commonest cause of heart failure and apoplexy. Untreated, the most severe form, malignant hypertension, kills within 6 to 12 months in 90 per cent. of the cases (Keith, Wagener and Barker, 1939; Schottstaedt and Sokolow, 1953). There are few diseases in which treatment requires more of the medical attendant in terms of knowledge and attention to detail, but there are few diseases, even with the most modern therapeutic advances, in which such a dramatic improvement in prognosis and in the relief of distress can be achieved. The principle of treatment, recognition of which changed the whole outlook, is the effective reduction of blood pressure, in most cases to near normal levels.

In nephritis, pyelonephritis, Cushing's syndrome and coarctation of the aorta the nature of the disorder causing the hypertension is known, though the mechanisms whereby the blood pressure is actually raised are still obscure. In essential hypertension the basic causes are a matter for conjecture, but they appear to be comparatively harmless, so that the symptoms and signs of essential hypertension are restricted to those which are apparently the consequences of high blood pressure as such, or vasoconstriction.

The survival rate for untreated hypertensive patients grouped according to the appearances of the fundi as classified by Keith, Wagener and Barker (1939) is shown in Fig. 1a. Fig. 1b

FIG. 1.—Survival under treatment of patients grouped according to severity of fundal changes. Dunedin series includes all cases continuing treatment to death or present time.

shows the survival rate for our treated series and includes all cases continuing treatment to death or to the present time. A number of these had marked impairment of renal function at the time of initiation of therapy and cases of known nephritis are included. Group 2 in the treated series included a number of unusually severe cases, particularly of heart disease. The improvement in prognosis dates from the introduction of effective methods of blood pressure control, in this clinic initially with hexamethonium bromide by injection (Restall and Smirk, 1950), and later with pentolinium orally (Smirk, 1952a, b) and by pentolinium in combination with reserpine (Doyle, McQueen and Smirk, 1954; Smirk, Doyle and McQueen, 1954). Elsewhere, improvements in prognosis have been demonstrated with varying degrees of blood pressure control by sympathectomy (Morrissey, Brookes and Cooke, 1953; Smithwick, 1955). Claims have also been advanced for other hypotensive agents such as veratrum alkaloids (Freis and Stanton, 1948; Hoobler, 1954), and 1-hydrazinophthalazine (Schroeder, 1952; Taylor *et al.*, 1954).

The very great improvement in the outlook for severely hypertensive patients, as shown in Fig. 1, and in their comfort, has been brought about by effective reduction of the blood pressure—to fully normal levels in the trough of the blood pressure fall, and to very much reduced levels at other times. It is insufficiently realized that the benefits to which reference will be made can be obtained only by attention to the strictest detail of management. The standard of care required is more exacting than that of a well run diabetic clinic. It is probable that the necessary experience can best be gained by special clinics to which large numbers of cases can be referred. Such clinics, furthermore, can justify the appointment of technical assistants and the development of other facilities.

Methods

Many substances capable of reducing the blood pressure therapeutically are now available. Of these the methonium compounds are the most effective and their use will be considered in detail. Rauwolfia alkaloids have also demonstrated their value, in particular as adjuvants to the methonium compounds. Other substances which have been widely employed, but whose use is considered to be of limited value, will be considered briefly. Amongst this group are:

1. *Hydrazinophthalazine* (*Apresoline*). This substance is an effective hypotensive agent and has been used chiefly in association with the methonium compounds. It may cause headache and other immediate side effects. Additionally, there

is a significant risk of delayed toxicity, as shown by the development of a syndrome resembling rheumatoid arthritis and lupus erythematosus. This, in our opinion, renders it unsuitable for routine use. It may have a special place in the management of a few exceptional patients who develop a state of resistance to the methonium compounds.

2. *Veratrum compounds*. The veratrum alkaloids are powerful hypotensive agents. Parenteral doses of as little as 0.1 mg. of the pure alkaloids may reduce the blood pressure to normotensive or even to hypotensive, levels, even in severe hypertensives. Unfortunately, doses effective in reducing the blood pressure to satisfactory levels frequently induce vomiting and other toxic effects. The most careful control of dosage is necessary, and then only about one in four patients obtain a useful fall of blood pressure without excessively troublesome side effects (Smirk and Chapman, 1952; Doyle and Smirk, 1953). The patients whose blood pressure can be satisfactorily controlled are usually mild cases and even in these the gap between the hypotensive and toxic doses seems to narrow with continued administration. Although in our clinic some 80 patients underwent a trial of treatment with these substances, they have not proved sufficiently satisfactory for their use to be continued in any of them.

3. *Thiocyanates*. The effect of thiocyanates alone in controlling blood pressure is limited and the attainment of effective blood pressure levels carries a risk of toxic side effects. When thiocyanate is administered in association with methonium compounds equal degrees of blood pressure reduction can be obtained with smaller doses of methonium and at blood levels of the thiocyanate well below those likely to be effective alone (McQueen, unpublished). In clinical practice Rauwolfia alkaloids are preferred for this purpose.

The Methonium Compounds

Pentolinium has replaced hexamethonium as the ganglion blocking agent for routine use. It is the corner stone of treatment in severe hypertension. It is effective in smaller doses than hexamethonium (approximately 1/5th), its duration of action is considerably longer, and it is much more satisfactory for oral administration. A new ganglion blocking agent, SU 3088, resembles pentolinium in its therapeutic action (Grimson *et al.*, 1955; Smirk and Hamilton, 1955). These compounds block autonomic ganglia and, according to some recent work, they also inhibit sympathetic centres in the central nervous system (Dontas and Nickerson, 1955). Hence they reduce blood pressure by diminution in the peripheral resistance.

INITIAL DOSES AND DOSAGE INCREMENTS OF METHONIUM COMPOUNDS

	Initial dose (mg.)	Dose may be raised by increments of (mg.)	Highest final daily dose used (mg.)	Average duration of significant action (mg.)
Pentolinium bitartrate, oral	20	20	1400	8-12+
Pentolinium bitartrate, simple aqueous, 'retard,' subcutaneous	3	0.5-1.5	140	8-12+
Hexamethonium bromide, simple aqueous, subcutaneous	15	5	1200	2-3
Hexamethonium bromide 'retard,' subcutaneous	20	5-10	1200	3-5
SU 3088 ('Ecolid'), Ciba, oral	10*	10	1000	8-12+
SU 3088 ('Ecolid'), Ciba, simple aqueous, subcutaneous	1	0.5	100	8-12+

*This drug is at present available for oral administration only in the form of 50 mg. tablets. We consider these too large for safety in initial dosage and recommend they be dissolved in a measuring cylinder and the appropriate fraction measured in this way.

With large falls in blood pressure there may be a decrease in cardiac output, probably due to diminution in venous return. A fall in venous pressure may, at times, be observed to precede the fall in arterial pressure. In congestive cardiac failure the marked falls in venous pressure may be associated with an increase in the cardiac output. Cerebral blood flow is usually maintained adequately, except at very low blood pressures.

The effects on renal haemodynamics are ordinarily transient, brief falls in renal plasma flow and glomerular filtration rate being succeeded by rapid restoration to levels approximating the initial ones. In cases with severe renal damage, however, excessive reduction in blood pressure may produce considerable and prolonged reduction in function with nitrogen retention. Additionally, where there is an important impairment in the renal function, the falls of blood pressure from therapeutic doses may be prolonged because of delayed excretion. Administration of Ansolysen over a long period has not, in our experience, caused interference with renal function when this is satisfactory initially.

Many of the changes in blood pressure after methonium administration depend upon the incapacity of the sympathetic nervous system to maintain the normal circulatory reflex functions. Thus, in the erect posture, the blood pressure falls because of the absence of reflex sympathetic vasoconstriction. This additional fall of blood pressure in the sitting and standing postures is used therapeutically; by controlling the posture of patients much lower falls of blood pressure are obtained, even with smaller doses. The proper

employment of posture during treatment is essential to successful management.

In patients under the action of methonium salts an additional fall of blood pressure usually follows meals, presumably due to uncompensated splanchnic dilatation. Postural hypotension is markedly exaggerated by a salt-free diet or by loss of blood, even in quite small amounts, such as 250 ml.

Parasympathetic effects include paralysis of accommodation, pupillary dilatation, diminished secretion of saliva, diminished secretion of acid in the stomach, diminished gastric and intestinal motility, diminution of potency in the male and occasionally urinary retention. These all constitute side effects of greater or lesser severity which will be discussed later.

Rauwolfia and its Derivatives

Since direction of the attention of Western countries, particularly by Vakil (1949), to extracts of *Rauwolfia serpentina*, use of these compounds has increased with impressive rapidity. Numerous preparations of the total alkaloids are available containing varying proportions of the active principles. Amongst the score or so of alkaloids which have now been isolated in pure form from *Rauwolfia serpentina*, reserpine (Müller, Schlittler and Bein, 1952) possesses sedative and other central nervous system effects apparently closely approximating those of the crude extracts, whilst it and also rescinnamine (Klohs *et al.*, 1954) have been shown to have specific antihypertensive properties. Another alkaloid, canescine (deserpidine) (Schlittler *et al.*, 1955) from the related species *Rauwolfia canescens*, also has a hypotensive action. These three pure substances have been

employed in this clinic rather than the cruder preparations of which the constitution is uncertain.

Reserpine

Reserpine exerts its hypotensive action, at least in part, through the central portions of the sympathetic nervous system, in particular by diminishing reflex pressor vasomotor activity (Bein, 1953; Trapold *et al.*, 1954). Its sympathetic vasomotor depressor function can be seen in the rabbit with one sympathectomized ear. In this animal vasodilatation can be seen to occur after administration of reserpine in the ear with intact nerve supply, whereas it fails to appear in the denervated ear (McQueen, Doyle and Smirk, 1955). Additionally, at least in rats and rabbits and possibly in man, there is a peripheral effect causing dilatation in vessels, the tone of which is being maintained either by nervous or by humoral means (McQueen, Doyle and Smirk, 1955; McQueen and Blackman, 1955). These actions, including the capacity to decrease reflex pressor responses, are also possessed by rescinnamine and canescine. In experiments with isolated organs, rescinnamine and canescine have a shorter period of action than reserpine. The differences may be due to their relatively greater solubility.

In man a hypotensive effect of reserpine can be observed with large doses orally within a few hours (Doyle and Smirk, 1954), but even when given intravenously there is a time lag of, on the average, about one to two hours (Hughes *et al.*, 1955) before the minimum pressure is reached, and in therapeutic doses given by mouth, a month may elapse before the full extent of the fall becomes apparent. In general, when reserpine is given alone, blood pressure falls are of relatively small order, but in a few patients they may be very considerable, well beyond the range resulting from full sedation. Of still more practical importance is the enhancement by reserpine of the hypotensive effect of other agents, particularly the methonium compounds. As a result of this enhancement, much smaller doses of pentolinium (Ansolsen) suffice to maintain a good control over the blood pressure, and thereby side effects are lessened. The daily fluctuations of blood pressure are much less on the combination of reserpine and pentolinium than on pentolinium alone (Doyle, McQueen and Smirk, 1955).

Side effects from reserpine consist in flushing of the face, nasal obstruction, feelings of coldness, shivering, diurnal lassitude, disturbed sleep with nightmares, and, in about 10 to 15 per cent. of the cases treated on reserpine in this clinic, a significant degree of mental depression such as to make its abandonment seem advisable. In a few

psychiatric treatment has been necessary. In the very severe cases depression has lasted some months after all Rauwolfia drugs were discontinued. In several of the patients developing the more severe manifestations there had been previous episodes of endogenous depression. Now, we avoid the use of reserpine in such patients.

There is a tendency towards retention of salt in patients on reserpine and congestive cardiac failure may be aggravated by it. Patients gain weight, both probably from this cause and from increased appetite.

Rescinnamine

Rescinnamine appears to have a hypotensive effect which in man is a little less than that of reserpine, but in some patients a higher dose can be tolerated without important side effects, so that the blood pressure lowering effect which can be achieved may be even greater than with reserpine. Rescinnamine appears to have a lesser tendency to induce depression, and lassitude and diurnal somnolence are considerably less marked. An appreciable number of patients in whom depression has occurred on reserpine have relief on changing to rescinnamine, with maintenance of an equal degree of blood pressure control (Smirk and McQueen, 1955). We have, however, encountered patients who have developed depression on rescinnamine. Some patients complain of anorexia, abdominal discomfort and insomnia, and may lose weight. As with reserpine, rescinnamine is of most value when used in conjunction with pentolinium.

Canescine

Preliminary trial of canescine (recanescine) has indicated that it too has a hypotensive action, though of a less powerful order than that of reserpine or rescinnamine. Side effects appear to be somewhat similar to those of rescinnamine. Some patients who had had moderate mental depression on reserpine lost this symptom when transferred to canescine.

Detail of Management

Preliminary Investigations

In addition to a routine clinical investigation, attention is directed to some investigations which are of particular value in prognosis and in determining a therapeutic régime. The Keith, Wagener and Barker grading of the optic fundi should be determined. The basal blood pressure, that is, the lowest pressure recorded under conditions of physical, emotional and metabolic rest, should be estimated. The method involves sedation, preparation as for basal metabolic rate and certain

other procedures, including repeated measurement of the blood pressure at half-minute intervals for 15 minutes or more, in order to desensitize the patient to the emotional stimulus provided by the observer and his sphygmomanometer.

A chest X-ray, electrocardiogram, a blood urea or non-protein nitrogen and a urea concentration test should also be performed. Indications for other tests may be provided by the clinical findings, as for instance pyelography, tests for pheochromocytoma, Cushing's syndrome, etc.

Selection of Patients

The existence of complications arising directly from the height of the blood pressure constitutes an indication for treatment. Grade IV or grade III retinal changes, congestive cardiac failure of hypertensive origin, or hypertensive encephalopathy, call for an immediate and effective control of the blood pressure, which almost always involves the use of methonium compounds. The discovery of a high blood pressure on a single occasion does not necessarily indicate that treatment should be instituted, although the occurrence of very high readings of the casual blood pressure (systolic greater than 230, diastolic greater than 130) usually means that treatment is necessary. The association with high casual readings of a high basal blood pressure, 160 to 110 or more, strengthens the indication, and evidence of cardiac enlargement or a left ventricular strain pattern in the electrocardiogram would be confirmatory. Age and sex are also important; high casual, and especially basal, levels in the younger age groups, particularly in males, have a poor outlook in the untreated case.

Renal disease with impaired excretion does not contraindicate treatment but calls for particular care in supervision, as delayed excretion of methonium compounds may lead to excessive action unless the dosage is suitably adjusted. Ischaemic heart disease with angina in hypertensive patients is frequently benefited symptomatically by reduction of blood pressure, presumably by decreasing the cardiac overload (Doyle and Kilpatrick, 1954). Excessive falls of blood pressure, however, are likely to induce anginal pain and should be avoided. One may aim at a pressure of say 140 over 90 in the trough of the blood pressure fall with the patient in the standing posture. In hypertensive patients with a history of recent cerebral vascular accident undue lowering of the blood pressure should likewise be avoided. With increasing experience we find some patients of over 70 with definite hypertensive manifestations derive benefit from treatment. The initial doses of hypotensive drugs should be half of the usual amount and this should

be increased by small increments to an effective level.

Detail of Treatment

Patients with malignant hypertension or hypertensive heart failure should be admitted to hospital so that an effective blood pressure reduction may be secured without delay. Methonium compounds are pre-eminently valuable, and where there is urgency, parenteral administration may be used to institute treatment. In most cases the 'retard' preparation is satisfactory from the outset. The major doses should be given in the early morning and at night with a supplementary dose in the early afternoon. In almost all severe cases a change may be made later to oral therapy with pentolinium (but not with hexamethonium). In the less severe cases oral pentolinium can be used from the outset. Initial doses and increments are shown in the table in which also the duration of effect is shown.

In all cases it should be the aim to adjust dosage so that the blood pressure at the trough of the blood pressure fall reaches levels in the region of 120 over 85 (standing). It is only by achieving falls to fully normal levels that adequate duration of effect is likely to be achieved. In ambulant patients the effects of individual doses must be measured in the erect posture, as well as sitting and lying, and the regulation of the dosage level is based on the standing blood pressure, otherwise faintness may be experienced at the time of maximum action of the drug.

Accurate recording of the time-course of drug action requires frequent blood pressure estimations. This is best performed by technicians specially trained for the task, who also carry on the observations at a special clinic as often as it may be indicated after the discharge of the patient.

The importance of posture in the satisfactory control of the blood pressure requires particular emphasis in the patient confined to bed. Such patients are best nursed on a 'cardiac' bed in which the trunk can be propped up at an angle of 45° from the horizontal. It is only when patients are nursed in this posture that full use is made of the hypotensive properties of the methonium compounds. After discharge from hospital it is still necessary for patients to continue sleeping in a similar posture, propped up with pillows at an angle of 45°, or with blocks 1 ft. 4 in. high beneath the head of the bed.

Tolerance develops rapidly to the methonium compounds. It may be demonstrated on the day after the first effective doses of methonium compounds have been administered. To maintain adequate blood pressure falls, doses must be raised daily at first and later every few days.

After two or three months the dose is comparatively stable, although minor fluctuations may occur. Toleration is lost if the methonium compound is suspended for more than a few days, and when dosage is resumed, it must be at a lower level.

The dose of pentolinium required to achieve adequate blood pressure reduction varies considerably. The final dosage of parenteral pentolinium ('retard') may be anything from 5 to 50 mg., and of oral pentolinium anything from 60 to 600 mg. two or three times daily. Equivalence of oral and parenteral doses is shown in the table.

Relief of Acute Clinical Manifestations

With fully adequate control over the blood pressure level papilloedema should invariably diminish within three weeks and have disappeared within three to six months. Soft exudates clear rapidly and haemorrhages also soon disappear. Hard exudates with star-shaped macular figures seldom disappear with less than six months' effective treatment, and may take 12 months to disperse. The manifestations of hypertensive heart disease are rapidly brought under control. After even the first day of effective blood pressure control, paroxysmal nocturnal dyspnoea no longer occurs, and exertional dyspnoea rapidly diminishes in severity. Pulmonary oedema is seen by X-rays to diminish rapidly in degree and disappear within a few days. These results are achieved in most cases having a fully adequate régime of blood pressure control without recourse to digitalis, mersalyl or salt-free diet. Manifestations of right-sided failure usually disappear more slowly, and in a number of these maintenance treatment with digitalis is necessary (Hamilton *et al.*, 1955).

The relief of cardiac asthma may be immediate, and the other manifestations of congestive cardiac failure usually disappear rapidly with a fully adequate régime without recourse to digitalis, mersalyl or salt-free diet.

Failure to achieve such results has been, in our experience, the result in almost all cases of inexperience or insufficient attention to detail on the part of the physician. It is seldom that one cannot obtain a degree of control over the blood pressure levels sufficient to achieve the kind of result referred to above.

Side Effects of Methonium Compounds

The parasympathetic side effects of pentolinium are seldom altogether absent with effective doses, but may be relieved by various parasympathomimetic drugs. Dryness of the mouth may be benefited by pilocarpine, 1/32 or 1/64 gr. given by mouth before meals. Blurring of vision

may be helped by eserine or physostigmine drops, 1/32 per cent., but is often best managed by the prescription of extra lenses for use during the period of impaired accommodation. Constipation is the most inconvenient side effect, and is particularly troublesome with oral treatment when it may cause marked irregularity in absorption of the pentolinium. Prolonged constipation may be succeeded by bouts of diarrhoea with an increase of the hypotensive action. In the most severe cases paralytic ileus may occur and the risk of this dangerous complication makes oral administration risky when the single oral dose necessary to produce adequate hypotensive effect rises to more than 600 mg. Constipation can, in most cases, be avoided by a paraffin emulsion-phenolphthalein mixture and the laxatives to which the patient is accustomed. Prostigmine, 15 mg. tablets, at times give relief when the usual purgatives have failed. In males impotence is frequent, particularly amongst the older men, although younger men may not be severely affected. Dysuria is not a frequent complaint except when some organic obstruction exists, most frequently prostatomegaly. Patients in whom methonium compounds have regularly induced retention before prostatectomy may be able to tolerate them without difficulty later.

Pentolinium in Combination with Reserpine or Rescinnamine

Management of methonium side effects has been rendered much more satisfactory by the use of Rauwolfia alkaloids in combination with pentolinium. On the addition of reserpine in doses of 0.25 to 0.5 mg. per day the dose of pentolinium needed to produce the same blood pressure lowering effect begins to diminish after two or three days and continues to diminish over several weeks. Eventually as little as half of the original dose of pentolinium may be necessary and methonium side effects are thereby reduced. There is also an important lessening of the daily fluctuations of blood pressure, with abolition of the high and potentially dangerous peaks which occur even with the best régimes employing methonium compounds alone. There is, however, a danger which will be referred to in the next section.

Reserpine Alone

Reserpine has been widely used for the treatment of milder cases. It is probable that many of these are cases of labile hypertension in which the blood pressure is raised above normal levels only intermittently. In such patients, particularly the blood pressure may be maintained at fully normal levels. Even severe hypertensives occasionally exhibit considerable falls of blood

pressure and these are regularly greater than those produced by simple sedation or placebos.

Unfortunately in addition to the relatively minor side effects occurring early on, such as nasal obstruction, looseness of the bowels, diurnal lassitude or disturbed sleep at night with nightmares, mental depression may occur. This may come on after anything from a few weeks to more than 12 months of successful therapy. Among 200 patients treated with Rauwolfia alkaloids, mostly reserpine, we have encountered minor or major degrees of depression in about 40 patients. Our impression has been that reserpine is rather more liable to cause depression than rescinnamine. While many of these patients have improved rapidly following cessation of this form of treatment, the severity and prolonged duration of others has been a source of considerable anxiety. Five patients required psychiatric treatment including in some patients shock therapy. One of our cases committed suicide and we know of other suicides and attempted suicides in New Zealand. Most of the depressions occurred in patients taking 1 to 1.5 mg. of reserpine daily. We now use 0.25 to 0.5 mg. daily in the hope that there will be a lower incidence of depression.

While the degree of improvement in the condition of severe hypertensives seems to us to warrant the continued use of this substance, usually as an adjunct to methonium compounds, we have formed the impression that its routine use in mild hypertensives is unjustified.

Control of Blood Pressure in Outpatients

Except in the most severe cases, treatment is best instituted as an outpatient in a special clinic at which patients attend throughout the day, returning home at night. Patients attend daily at first and later at less frequent intervals. To this clinic are also referred the most severe patients after their discharge from hospital. Blood pressures are recorded half-hourly during the day by specially trained technicians. The blood pressure is measured in the sitting and standing positions and, if necessary, lying. Casual blood pressure readings at visits to ordinary outpatient clinics or to private practitioners, are likely to be misleading, although less so on the combination of reserpine and pentolinium than in those on pentolinium alone. A number of private practitioners in this country arrange for groups of their hypertensive patients to attend on certain days when a series of readings can be taken by their secretary or nurse.

In the absence of such methods of control considerable information can be gained by careful enquiry into the subjective manifestations experienced by the patients. Frequent faintness at the time of maximum drug action indicates excessive

effect and the oral dose of pentolinium required is 20 mg. below the level inducing faintness. Patients can tell when the régime is producing adequate falls by standing upright for one minute at the time of maximum methonium effect. If no sensation of faintness is experienced, the dose should be increased by the increments shown in the table until it just does produce faintness on standing still for this length of time.

There is no doubt, however, that a special clinic at which day tests can be arranged at short notice, and as often as necessary, provides the ideal facilities for the fully adequate blood pressure control by which only can the best results be achieved.

Summary

Appreciation of the fundamental importance of effective control of the blood pressure has been the major factor in the great improvement in prognosis of hypertension. However, meticulous attention to the detail of management is necessary to achieve the best possible results.

The most effective agent for control of blood pressure is pentolinium (pentapyrrolidinium, Ansolsen) which should be used for management of the most severe cases from the outset. The dose of pentolinium required is decreased by the addition of reserpine to the régime; hence side effects are reduced. The occurrence of significant depression on reserpine may be alleviated sometimes by a change to rescinnamine, but depression may occur also on rescinnamine. The incidence of mental depression is such that it is doubtful whether reserpine should be used in mild cases. It is our impression that its main use is in the combination with pentolinium for severe cases. Methods of control of treatment are outlined.

It is emphasized that only by the strictest attention to the detail of management can the excellent results of fully adequate blood pressure control be achieved.

It should now be accepted that failures to arrange an effective régime and to relieve reversible manifestations of hypertension are in almost all cases due to iatrotechnical deficiencies.

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low sodium diet, digitalis and injections of mersalyl will improve cardiac efficiency and make the operative and post-operative course smoother. If emergency surgery is essential and there is no time for adequate pre-operative treatment of heart failure the operative risk is increased although even then it is often surprising how well these patients do. Under these circumstances the patient should be digitalized rapidly, using digoxin 1.5 to 2 mg. in a single oral dose which will produce an effect in three to four hours. If greater speed of action is needed, 1 mg. of digoxin should be given slowly intravenously, but the intravenous route must be avoided if the patient has been receiving digitalis by mouth previously. These patients should be anaesthetized propped up, but may be placed flat when the laboured breathing of heart failure has been relieved by anaesthesia.

In the post-operative period they should be nursed propped up, digitalis should be continued and mercurial diuretics should be started early. Particular care should be taken to prevent chest infection and leg exercises should be started early to minimise the risk of thromboembolism.

The aetiology of the heart disease is in general less important than the pre-operative functional status of the patients in assessing the risk of anaesthesia and surgery. However, in certain types of heart disease, particularly aortic valvular disease or heart block, the risk of difficulties under anaesthesia is increased even though the patient has no symptoms. Patients with known coronary disease, with a history of angina pectoris or previous cardiac infarction are especially susceptible to hypotension or hypoxia but if these two factors can be avoided operation is usually well

tolerated. A history of recent cardiac infarction within the previous three months, or of increasing severity of anginal attacks, should cause all except emergency operations to be postponed. The particular risk in these patients is the occurrence of serious ventricular arrhythmias but if operation is essential the risk can be decreased by giving quinidine sulphate 5 gr. three times a day pre-operatively and continuing the drug during the early post-operative period.

Prostatectomy in the elderly patient with hypertension and arteriosclerotic heart disease carries a mortality nearly three times as high as in the patient with a normal heart⁷ and the increased risk should be taken into consideration when deciding the nature of the surgical treatment. Partial thyroidectomy for hyperthyroidism can be safely carried out in patients with heart disease as with adequate pre-operative treatment with thiouracil drugs the operation can be done when the patient is in the euthyroid state. If however, the heart disease is serious, treatment with radioactive iodine is preferable.

The use of local instead of general anaesthesia for cardiac patients has little to recommend it except for minor procedures such as dental extraction and a properly administered general anaesthetic is both safer and pleasanter for the patient.

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