became a professor of medicine at Jefferson and later in New York.

* * *

Two hundred years later we should perhaps spare a thought for Dr James Thacher, "the young country boy untrained in narration,"³⁰ who left us such a vivid picture of his times. The doctors of 1776 do not seem far away when one remembers that the great-great-grandson of Paul Revere, son of Sir William Osler, died on the Ypres salient in 1917, while successive generations of Warrens have served to this day on the staff of the Massachusetts General Hospital in Boston and the Harvard Medical School.

References

- ¹ Chidsey, D B, *July 4, 1776*, p 53. New York, Crown Publishers, 1958.
- ² Toner, J M, *Medical Men of the Revolution*. Philadelphia, Collins, 1876.
- ³ Hawke, D, *A Transaction of Free Men*, p 5. New York, C Scribners, 1964.
- ⁴ Thacher, J, *American Medical Biography*, Boston, Richardson and Lord, 1828.
- ⁵ Beck, J B, *An Historical Sketch of the State of Medicine in the Period of the American Revolution*, 1850. Republished with foreword by C F Fishback. Albuquerque, New Mexico, Horn and Wallace, 1966.
- ⁶ Mumford, J G, *A Narrative of Medicine in America*, p 136. Philadelphia, Lippincott, 1903.
- ⁷ Garrison, F H, *An Introduction to the History of Medicine*, 4th edn. Philadelphia, Saunders, 1929.
- ⁸ Packard, F R, *History of Medicine in the United States*. New York, Hoeber, 1931.
- ⁹ Goodman, N G, *Benjamin Rush; Physician and Citizen*. Philadelphia, University of Pennsylvania Press, 1934.
- ¹⁰ Flexner, J, *Doctors on Horseback*. New York, Garden City Publications, 1939.
- ¹¹ *Autobiography of Benjamin Rush*, ed G W Corner. Princeton, Harvard University Press, 1948.
- ¹² Riedman, S R, and Green, C C, *Benjamin Rush; Physician, Patriot, Founding Father*. New York, Abelard-Schuman, 1964.
- ¹³ Binger, C, *Revolutionary Doctor—Benjamin Rush; 1746-1813*. New York, Norton, 1966.
- ¹⁴ Hawke, D F, *Benjamin Rush; Revolutionary Gadfly*. Indianapolis, Bobbs-Merrill, 1971.
- ¹⁵ Bell, W J, *The Colonial Physician*, pp 31, 44, 69. New York, Neale Watson Academic, 1975.
- ¹⁶ Shryock, R L, *Bulletin of the History of Medicine*, 1970, **45**, 507.
- ¹⁷ Rothstein, W G, *American Physicians in the Nineteenth Century; from Sects to Science*, pp 42, 54. Baltimore, Johns Hopkins Press, 1972.
- ¹⁸ Brierley, G H, *Medical America in the Nineteenth Century; Readings from the Literature*, p 90. Baltimore, Johns Hopkins Press, 1972.
- ¹⁹ Norwood, W F, *International Record of Medicine*, 1958, **171**, 391.
- ²⁰ Shryock, R H, *Development of Modern Medicine*, p 3. New York, A A Knopf, 1947.
- ²¹ Carlson, E T, and Simpson, M M, *American Journal of Psychiatry*, 1964, **121**, 209.
- ²² Hammond, W A, *A Treatise on Insanity and its Medical Relations*. New York, D Appleton and Company, 1883.
- ²³ Tuke, D H, quoted by DeJong, D E, *Annals of Medical History*, 1940, **2**, 195.
- ²⁴ Cash, P, *Medical Men at the Siege of Boston, April 1775-April 1776*, p 17. Philadelphia, American Philosophical Society, 1973.
- ²⁵ Hume, E E, *Bulletin of the History of Medicine*, 1943, **13**, 10.
- ²⁶ Charles, S T, *Bulletin of the History of Medicine*, 1965, **39**, 435.
- ²⁷ Billings, J S, *A Century of American Medicine; 1776-1876*, p 293. Brinklow, Maryland, Old Hickory Bookshop, 1962.
- ²⁸ Forbes, E, *Paul Revere and the World he lived in*, pp 244, 302. Boston, Houghton-Mifflin, 1942.
- ²⁹ Truax, R, *The Doctors Warren of Boston, First Family of Surgery*. Boston, Houghton-Mifflin, 1968.
- ³⁰ Viets, H R, *Virginia Medical Monthly*, 1949, **76**, 384.

Today's Treatment

Diseases of the cardiovascular system

Drugs affecting the cardiovascular system: pharmacological basis of treatment

JOHN C GILBERT

British Medical Journal, 1976, **2**, 31-33

The functioning of the heart and blood vessels can be influenced by many drugs, and a wide variety of mechanisms is implicated in the drugs' actions. This account will be heavily restricted, but will cover many drugs used clinically.

Cardiac glycosides

The cardiac glycosides slow the heart in atrial fibrillation and also increase the force of contraction of the heart by increasing the rate at which tension is developed. This increases the cardiac output and increases blood flow to other organs, including the kidneys—where water excretion is enhanced. Observations in animals and man indicate that digitalis acts directly on contractility. If the heart is of normal size the net

cardiac output need not be increased. If the heart is failing, however, its efficiency is depressed and by its positive inotropic effect digitalis restores this and increases the output.

The increased contractility and cardiac output induce a response in baroreceptor activity, and this results in increased vagal activity and slowing of the heart. This contributes to the beneficial effect of digitalis in atrial fibrillation. Other events are also implicated, however, particularly a direct action on the atrioventricular node so that the effective or functional refractory period is prolonged; this reduces the frequency of ventricular contraction. But these effects of digitalis may also underlie some of its toxic manifestations, which include extrasystoles, usually arising in the ventricles; atrial and ventricular tachycardias; and heart block.

Speculation concerning the mechanism of the positive inotropic action of digitalis has centred mainly on the role of adenosine triphosphatase (ATPase), which is activated by sodium and potassium ions together (Na,K-ATPase) in the presence of magnesium ions. This enzyme is present in the membrane of the heart cell, and its function is to mediate the pumping of sodium ions out of the cell and potassium ions into the cell against concentration gradients, the energy for these processes

Heriot-Watt University, Edinburgh

JOHN C GILBERT, PHD, professor of pharmacology

being supplied by the splitting of adenosine triphosphate. Some 20 years ago it was shown that this enzyme is strongly inhibited by cardiac glycosides. Such inhibition interferes with the coupled sodium-potassium pump, and sodium ions accumulate in the heart muscle cell.

Much evidence suggests that glycosides which do not inhibit the enzyme do not exert a positive inotropic effect on the heart: digitalis does not exert this effect in species where it fails to inhibit ATPase.

These observations support the hypothesis that the effect of digitalis on heart contractility is mediated through inhibition of the ATPase. Some studies, however, have thrown doubt on this relationship and on the fundamental concept that this enzyme is the receptor for the drug in the heart. For instance, while some experiments have shown a direct relation between wash-out of the pharmacological action of digitalis in the isolated animal heart and the dissociation of the drug from Na,K-ATPase preparations, others have suggested that inhibition of the enzyme may persist after the decay of the positive inotropic effect. The problem is complicated by the roles of ions, such as calcium, other than sodium and potassium in the heart cell. When the muscle cell membrane depolarises, calcium ions enter the cell. Moreover, calcium is released from bound forms within the cell so that the contractile mechanism is activated. In relaxation the released calcium is taken up again by membrane systems and also calcium moves out of the cell. There is evidence that links the inward movement of calcium, which initiates the contractile process, with the inward movement of sodium ions.

Putting these ideas together one can postulate that cardiac glycosides inhibit the Na,K-ATPase, causing sodium to enter the cell. This triggers the entry of calcium ions (which may, however, be independent of sodium ion entry) and increases the availability of this ion to the contractile machinery. Despite evidence to the contrary, therefore—and despite a hypothesis suggesting that digitalis in low concentrations mediates its effects on the heart by actually stimulating the ATPase—the positive inotropic action so vital for alleviating congestive heart failure may result from ATPase inhibition.

Whatever the mechanism of the therapeutic action of digitalis, one is on firmer ground in proposing that the toxic manifestations of drug treatment result from inhibition of ATPase. Digitalis and potassium ions compete for a site on the outside of the membrane where potassium normally increases enzymic activity, and this results in enzyme inhibition. Because the process includes competition the effect of the drug may be increased by decreasing the serum potassium concentration. Hence diuretics which cause hypokalaemia have to be used carefully. Nevertheless, recent work suggests that some potassium-sparing diuretics may raise the threshold of digoxin toxicity by a direct action on the heart rather than on the kidney. This action could result if the drugs directly inhibit the loss of potassium from the heart muscle cell.

Diuretics play a prominent part in treating heart failure not accompanied by fibrillation, and they are also added to the therapeutic regimen after digoxin treatment when fibrillation does occur.

Antiarrhythmic drugs

Quinidine was introduced as an antiarrhythmic agent after the observation that atrial fibrillation, in patients with malaria who were treated with quinine or quinidine, was considerably improved. Since then the antiarrhythmic action has been investigated fully and several factors are now known to be concerned in the actions of antiarrhythmics. The first of these is the suppression of the spontaneous depolarisation that may occur in tissue some distance from that normally responsible for pacemaker activity in the heart. Secondly, antiarrhythmics prolong the period in the cardiac cycle when an impulse cannot be propagated—the so-called effective refractory period. Quinidine itself increases the effective refractory period both by reducing the rate of depolarisation and by prolonging the repolarisation process so that it lengthens the time during which the heart cell cannot respond with an action potential. This

decreases the heart rate, and it appears to be the basis for the past use of both quinidine and procainamide in atrial fibrillation.

Phenytoin is not used in atrial fibrillation but it does counteract digitalis-induced tachycardia. It reduces the refractory period and so increases the conductivity and membrane responsiveness of the heart muscle cell. The outcome of these effects seems to be that abnormal spontaneous depolarisations that would otherwise have occurred in "ectopic foci" are prevented from intruding on the normal pacemaker activity.

Lignocaine is another commonly used antiarrhythmic, particularly for ventricular arrhythmias. It reduces the duration of the action potential, and as a result the effective refractory period:action potential ratio is increased in the Purkinje fibres and the muscle fibres so that the discharge at ectopic sites is opposed. Beta-adrenergic receptor antagonists such as practolol and propranolol have also been useful in treating arrhythmias. Whether the value of propranolol depends more on its quinidine-like action which results in membrane stabilisation or on its beta-adrenoceptor antagonist activity is difficult to say. While the beta-receptor antagonist activity is pronounced in the (–)-but not the (+)-isomer of propranolol, antiarrhythmic activity is pronounced in both, suggesting that membrane stabilisation is important. Even so, low doses of (–)-propranolol are said to be effective in treating paroxysmal tachycardias, and it is known that noradrenaline can induce depolarisation at ectopic foci and cause an arrhythmia.

Vasodilators

Since amyl nitrite was introduced in 1867 for treating angina several nitrites have been examined for pharmacological activity and they remain the most important vasodilators for this condition. They are effective because they cause quite non-specific relaxation of smooth muscle. The heart relies on a continuous supply of oxygen from the blood, and any impairment of the efficiency of the coronary circulation must be corrected quickly.

Glycerol trinitrate increases the coronary blood flow in normal vessels, but whether this is because of dilatation of the coronary vessels is not known. The response of diseased vessels is quite another matter. Possibly the larger coronary vessels become dilated but there is considerable doubt as to the response of smaller vessels. Moreover, possibly any decrease in coronary resistance is too short to account for the alleviation of angina. Probably the decreased venous return caused by nitrites and the resulting reduced diastolic volume of the ventricles are important actions because the work performed by the heart is reduced. Drugs such as theophylline and its ethylenediamine derivative aminophylline have pronounced coronary vasodilator action in normal vessels but they are toxic and so have not been used routinely in treating angina.

Antihypertensive drugs

The most commonly used drugs in treating hypertension are diuretics, particularly the thiazides. The direct effects of the drugs on vascular smooth muscle may well be concerned in their action.

VASCULAR SMOOTH-MUSCLE RELAXANTS

Drugs which relax vascular smooth muscle are gaining importance in treating hypertension because they decrease the resistance of the peripheral vascular bed. We still do not know how this relaxant activity occurs, though hydralazine, for example, appears to affect arterioles more than veins. Diazoxide is a potent antihypertensive drug that, though structurally similar to the thiazide diuretics, is not a diuretic. Diazoxide is particularly useful in the emergency treatment of hypertension: given intravenously, it has a direct effect on vascular smooth

muscle that results in vasodilatation and a rapid fall in blood pressure. Again, it affects the arterioles more than the veins but we do not know the precise mechanism. If it antagonises the effects of calcium ions, as has been suggested, then its powerful vasodilator action could result from interference with the role of calcium in generating action potentials or in the release of calcium ions during the initiation of muscle contraction.

Several antihypertensive agents affect sympathetic nerves and adrenergic receptors. The constrictor action of noradrenaline, released from sympathetic nerves, on vascular smooth muscle can be antagonised by alpha-adrenergic antagonists such as phentolamine.

Pentolinium has an antihypertensive action by blocking transmission in sympathetic ganglia, but the drug is now seldom used. Adrenergic neurone-blocking drugs such as guanethidine, bethanidine, and debrisoquine are also used as antihypertensive agents. These act in a third way: after they are taken up into the adrenergic nerve terminal they prevent the release of noradrenaline.

BETA-ADRENERGIC ANTAGONISTS

Beta-adrenergic antagonists such as propranolol are of value for treating hypertension, and they may be given with vasodilators. The onset of the antihypertensive effect of propranolol is not immediate, and the mechanism of its action is still not clear, though its role in reducing the heart rate and the cardiac output is obviously important. Propranolol also affects the peripheral blood vessels, and lowers the plasma renin activity. The latter action would lower angiotensin levels, and since angiotensin contracts vascular smooth muscle, the result would be a reduction of the peripheral vascular resistance.

Two other possible mechanisms of propranolol are a change in the sensitivity of the baroreceptors of the carotid sinus and major arteries, so that their performance adjusts to the reduced cardiac output, and a direct effect on the central nervous system.

METHYLDOPA

Methyldopa also seems to have an antihypertensive effect by an action on the CNS. Methyldopa inhibits dopadecarboxylase, the enzyme which converts dopa (dihydroxyphenylalanine) to dopamine. This depresses the synthesis of dopamine, noradrenaline, and serotonin. The significance of this is being reconsidered, however, and a recent hypothesis is that methyldopa in the CNS is metabolised to alpha-methylnoradrenaline; this compound may exert an antihypertensive action through interaction with central alpha-adrenoceptors.

CLONIDINE

A drug often used in mild hypertension is clonidine, though initially it may increase the blood pressure. This may reflect the fact that clonidine, which is structurally similar to tolazoline, the alpha-adrenoceptor antagonist, has intrinsic alpha-adrenoceptor agonist activity so that a direct but transient peripheral vasoconstrictor action could occur. Its withdrawal may cause rebound hypertension.

The adrenoceptor agonist activity may be concerned also in its antihypertensive action if alpha-adrenoceptors in the CNS are activated so that the sympathetic nervous system is inhibited. This hypothesis is a difficult one to test but the action of clonidine does seem to result from effects in the CNS rather than at the periphery.

One cannot include here a discussion of the mechanisms of all the drugs that influence the activity of the cardiovascular system. Those which have been mentioned, however, do illustrate the extent to which the treatment of cardiovascular disorders has a sound pharmacological basis.

Statistics at Square One

VII—Statements of probability

T D V SWINSCOW

British Medical Journal, 1976, 2, 33-34

We have seen that when a set of observations have a "normal" distribution—as they commonly have in medicine and biology—multiples of the standard deviation mark certain limits on the scatter of the observations. For instance, 1.96 (or approximately 2) standard deviations above and 1.96 standard deviations below the mean ($\bar{x} \pm 1.96 \text{ SD}$) mark the points within which 95% of the observations lie.

Probability limits

We noted that Dr Green's 140 children had a mean urinary lead concentration of $2.18 \mu\text{mol}/24 \text{ h}$, with standard deviation 0.87. The 95% probability limits here are $2.18 \pm (1.96 \times 0.87)$, giving a range of 0.47 to 3.89. One of the children had a urinary lead concentration of just over $4.0 \mu\text{mol}/24 \text{ h}$. This observation is greater than 3.89 and so falls in the 5% beyond the 95% probability limits. We can say that the probability of each of such observations occurring is 5% or less. This probability is usually expressed as a fraction of 1 rather than of 100, and written $P < 0.05$.

Standard deviations (or standard errors, which behave in exactly the same way) thus set limits about which probability statements can be made. Some of these are set out in table 7.1. To use table 7.1 to estimate the probability that a certain observation, say a urinary lead concentration of $4.8 \mu\text{mol}/24 \text{ h}$, came

British Medical Journal

T D V SWINSCOW, MSC, MB, deputy editor