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Heritability of blood pressure

Ever since Morgagni[1] commented on the familial occurrence of apoplexy investigators have been trying to determine whether cardiovascular risk factors are inherited. Soon after measurement of the arterial blood pressure became a common procedure Stocks[2] showed that there was a stronger correlation between the blood-pressure levels of monozygotic than of dizygotic twins. Kahler and Weber[3] confirmed these observations, finding that the difference in pressure between monozygotic twins was 6·3 mm Hg but between dizygotic twins 11·4 mm Hg; while Feinleib *et al*[4] found a correlation coefficient of 0·55 for male monozygotic twins but only 0·25 for dizygotic pairs.

In all these studies it was difficult to separate the effect of common genes from that of shared environment. In theory, studies on the blood-pressure correlation between husbands and wives should answer this question, since they share their environment but not their genetic material. The results of such investigations have been less clear-cut than those of twin studies,[5] but the correlation coefficient seems in general much lower for spouse pairs than for genetically related members of the same family. Adopted children also show a very low correlation coefficient,[6] but their blood pressure does begin to resemble that of their adoptive family with the passage of time. Thus both genetic and environmental factors must be at work; what is still in doubt is the relative size of each component. Feinleib[4] has suggested that 82% of systolic and 64% of diastolic pressure differences are genetically determined; whereas Miall and Oldham[5] believe that only 30% of the systolic correlation is genetic, leaving 70% to be accounted for by environmental factors. Forewarned by the difficulties of interpretation found in these earlier studies, workers in Detroit are carrying out a major project[7] that may allow the relative contributions of nature and nurture to be assessed.

Although the genetic contribution to arterial pressure was identified as early as 1930, fierce debate about the mode of inheritance continued unabated until the 1950s. Galton[8] had shown that the distribution of a characteristic in the first-degree relatives of index cases can be used to differentiate single-gene from polygenic inheritance. In single-gene transmission some of the relatives have the characteristic while others do not, and when the distribution of the characteristic is plotted the pattern is bimodal—a graph with two humps. On the other hand, with a feature such as height that is inherited polygenically a normal distribution—a single, symmetrical curve—results. According to Galton's principles, determining the blood pressure distribution of the relatives of patients with hypertension should show whether inheritance is single-gene or polygenic. Unhappily, blood pressure is not so simple to measure as height: firstly, height can be recorded accurately, while there is substantial variability in blood pressure measurement between observers and even with a single observer; secondly, unlike height, blood pressure varies from minute to minute; and, thirdly, while no preconceived boundaries have ever been drawn been "normostature" and "hyperstature," many doctors believed that there was a disease called hypertension whose victims were qualitatively as well as quantitatively different from "normotensives." This arbitrary division introduced bias into measurements of blood pressure, since observers showed marked digit preferences and avoided values on or near to the imagined cut-off point.

The great contribution of Pickering[9] was to emphasise that arterial blood pressure is a continuously distributed variable with no logical sharp boundary between "normal" and "abnormal" values. The St Mary's group[10] went on to show that the blood pressures of first-degree relatives of patients above and below an arbitrary normotension/hypertension line were normally distributed. Although the distribution curve for the relatives of patients with high blood pressure was shifted towards the higher values, there was no trace of the bimodality that would have pointed to a single-gene effect. They concluded that "arterial pressure is inherited as a graded character through the ranges hitherto described as normal blood pressure and hypertension." Subsequent studies have amply confirmed this conclusion, and a recent review states[7] that "virtually all epidemiologic studies based on large samples have confirmed the existence of unimodal, continuous distributions of blood pressure in populations." Pickering's concept was, however, challenged by Platt,[11] who produced distribution curves that he considered bimodal. In the spirited controversy that followed in the 1950s and early 1960s it became clear that digit preference and boundary avoidance were bound to give irregular curves with small series. No acceptable evidence of true bimodality could be marshalled by Platt, and now[12] "most investigators accept that variability in blood pressure is multigenic in origin."

This means, then, that an unknown proportion (30-80%) of the variability in blood pressure found in different people is an inherited characteristic and that, like height, this genetic

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component appears to be polygenic. What is not inherited, it appears, is the rate of rise of blood pressure with advancing years—though this rise does not seem to alter the ranking order for height of pressure in groups observed at intervals. Kass and his colleagues[13] studied this "tracking" phenomenon and found that blood pressure ranking was relatively stable in groups of children studied over an eight-year period. The crucial question may well be how early in life we can detect the combination of an inherited blood pressure level and a "tracking" pattern that will expose an individual to unacceptable cardiovascular risk in later life. De Swiet *et al*[14] have suggested that an infant's blood pressure at four to six days correlates significantly with its pressure at five to seven weeks, while Kass and his colleagues[13] have shown that "sibling to sibling aggregation of blood pressure . . . probably begins during the first few months of life and mother-child aggregation seems to be present from the first days of life." Clearly the best precaution a newborn baby can take over its arterial blood pressure and therefore its cardiovascular risk in later life is to choose its parents carefully.

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Choosing an antidepressant

Apart from the monoamine oxidase inhibitors, 18 tricyclic and related antidepressants are available for NHS prescription. These are amitriptyline, butriptyline, clomipramine, desipramine, dibenzepin, dothiepin, doxepin, imipramine, iprindole, maprotiline, mianserin, nomifensine, nortriptyline, opipramol, protriptyline, tofenacin, trimipramine, and viloxazine. Many were marketed after 1970, and the practitioner's choice is not simplified by the enthusiastic and sometimes contradictory pronouncements of the manufacturers claiming a novel chemical structure, a different mode of biochemical action, pharmacokinetic advantages, greater and more rapid efficacy, or fewer and less severe unwanted effects—and sometimes several of these features. Are these claims justified?

The first compounds of this class, such as imipramine and amitriptyline, were tricyclic derivatives of dibenzepin or dibenzocycloheptene; but some recent introductions have been tetracyclic (maprotiline, mianserin), bicyclic (viloxazine), and even monocyclic (tofenacin). However much a novel structure may fascinate the medicinal chemist it is irrelevant to the prescribing clinician, especially while the relation of structure to activity remains obscure. Nor is the claim of a different biochemical action of much clinical significance. The changes in biogenic amine concentrations in the brain induced by the tricyclic compounds are believed to follow interference with the reuptake mechanism by which amines in the synaptic cleft are actively taken back into the presynaptic neurones so that their action is terminated.[1 2] Compounds such as amitriptyline and chlorimipramine, chemically tertiary amines, tend to affect serotonin uptake more than noradrenaline uptake; secondary amines like nortriptyline and desipramine have more effect on noradrenaline mechanisms. Nevertheless, there is scant evidence linking these biochemical actions to clinical effects. Indeed, some apparently clinically effective drugs have hardly any effect on amine uptake mechanisms: iprindole is an example. Moreover, powerful inhibitors of amine reuptake such as cocaine are not useful antidepressants.

Several of the newer antidepressants are recommended for use in once-daily doses, usually given at night. Such a schedule is easier for depressive patients to remember. The sedative effects of many of these drugs may be helpful to insomniac patients who would otherwise require sleeping tablets. Unwanted effects such as dry mouth and postural hypotension, a problem during the day, are not troublesome during sleep. Many of the older compounds also have plasma half lives of a day or more and have been widely used in nightly dosage to good effect.[3] Sustained-release preparations are sometimes less well tolerated by patients—high plasma concentrations may be delayed beyond the time of wakening and be associated with sleepiness and autonomic side effects.

None of the newer antidepressants is consistently superior to amitriptyline or imipramine in terms either of the proportion of patients responding or of the average improvement shown.[4] Nor are claims of a more rapid onset of action tenable when differences in dosage regimens are taken into account.

Unwanted and toxic effects limit the usefulness of the tricyclic antidepressants. In particular, the anticholinergic effects leading to dry mouth, constipation, and blurring of vision may be a nuisance, and possible cardiotoxic effects may cause anxiety, particularly with amitriptyline. Several of the newer drugs, such as iprindole and mianserin, are claimed to have minimal anticholinergic activity and should be considered for patients intolerant of such effects. Cardiotoxicity seems least with doxepin[6] and maprotiline, which should be used for depressed patients with known cardiac abnormalities.

Apart from these considerations and apart from a few specialised types of case (such as depression in Parkinsonian patients, who will benefit from nomifensine[7] with its dopamine-agonist activity), the choice of tricyclic-type antidepressants is usually determined by their secondary psychotropic actions. These drugs are divisible into a group with sedative actions (amitriptyline, doxepin, dothiepin), neutral compounds (imipramine, dibenzepine), and stimulant drugs (nortriptyline, desipramine, and particularly protriptyline). Patients with agitation or anxiety usually respond best to a sedative antidepressant, whereas retarded and anergic patients often prefer a neutral or stimulant antidepressant. Most important of all, the practitioner (whether family doctor or psychiatrist) should familiarise himself with a few well-tried drugs rather than experiment with new antidepressants. Depression of a severity to require antidepressants is an illness to be taken seriously and treated with confidence, promptness, and vigour.

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