difficult cases. Nevertheless, recent guide-lines based on a national survey amongst thoracic physicians should provide a powerful incentive to change. Formal intercostal tube drainage is probably not necessary in up to 80% of cases—either observation or simple needle aspiration will suffice as management. It is not possible to determine in advance those cases which will resolve by aspiration alone although the average volume aspirated in successful procedures was ~1·6 litres. It is therefore suggested that aspiration should be abandoned if significant re-expansion has not been achieved after 2 litres air has been withdrawn.

Thoracoscopic surgery

Thoracoscopic surgery may now be employed in the biopsy of intra-pulmonary lesions, assessment of malignant disease, the definitive treatment of pneumothorax and the resection of any lobe or even an entire lung. In uncomplicated cases it employs a simple 3-port technique with chest drains inserted through the ports at the end of the procedure. Operative blood loss and hospital stay are all significantly less with the thoracoscopic approach and post-thoracotomy syndrome is completely abolished. These advantages more than compensate for the slightly longer primary procedure when compared to the open approach. Two caveats must be remembered when assessing what seems such a major surgical advance however; the operator must always be able to convert to an open technique and therefore needs to be fully trained in 'conventional' thoracic surgery, and the *internal* physiological insult from thoracoscopic resection remains unchanged despite the less aggressive approach. Those patients with insufficient pulmonary reserve to tolerate loss of lung tissue by open resection will therefore be similarly unable to tolerate thoracoscopic resection, although the marked improvement in post-operative morbidity will benefit all others.

Cystic fibrosis: screening and gene therapy

To enable genetic counselling for cystic fibrosis (CF) at the earliest appropriate stage, it would be necessary to screen all young adults through primary care. Such an approach has been attempted and demonstrated a 60–70% take up following a personal invitation but a very poor response to a standard written invitation. The resource implications for this sort of approach are large and not practicable. Most studies have therefore concentrated on the ante-natal population with the partner screened only if the mother is found to be a carrier. If both parties are heterozygous pre-natal diagnosis is offered and almost three-quarters of affected cases can be detected. Several studies have shown at least 70% take up by this approach which, theoretically, could reduce the CF population by 50%.

Gene therapy offers hope to CF sufferers in the foreseeable future. A number of problems relating to the appropriate DNA, vector systems and stability of integration have been overcome and there are large on-going studies in both the UK using a liposome vector and the USA, largely using an adenovirus vector. Initial results show a variable and somewhat unpredictable insertion of DNA in the target organ but there is good reason to expect this will improve and that some form of gene therapy for CF will be available by the end of the decade.

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LESSONS FROM A SYMPOSIUM ON HYPERTENSION HELD IN THE COLLEGE ON 8 FEBRUARY 1995★

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WHO SHOULD BE GIVEN ANTI-HYPERTENSIVE DRUGS?

Systemic blood pressure (BP) is a continuously distributed variable in the population with an approximately normal distribution. The incidence of cardiovascular disease rises with increasing BP across a wide range including those values which we conventionally think of as within normal limits. For example, the risk of stroke in someone with a diastolic BP of 85 mmHg is higher than that in one whose diastolic BP is 80 mmHg. Any definition of hypertension is therefore arbitrary; it is a trait rather than a disease, a quantitative rather than a qualitative difference between individuals. In a research programme, it is easy to divide and compare subjects who are hypertensive or normotensive. However, in clinical practice the threshold of BP above which an individual should be treated with drugs and the action required for those whose BP oscillates around that threshold, remain contentious.

During the last 30 years, a series of intervention studies have consistently demonstrated the benefits of anti-hypertensive therapy (with thiazide diuretics and/or β-blockers) in reducing the incidence of stroke. These benefits accrue even in groups with diastolic BP as low as 90 mmHg (MRC Mild Hypertension Trial, 1985), and importantly also in elderly patients with diastolic BP $<$ 90 mmHg but systolic BP $\geqq$ 160 mmHg (Systolic Hypertension in the Elderly Programme, 1992). However, because the benefits are in a fixed proportion (30–40%) of the incidence, they are greatest in those whose absolute risk of stroke is greatest. Thus, extrapolating from the above trials one would have to treat 566 young but 286 elderly patients with bendrofluazide for one year to prevent one stroke. It is clear that treatment should be limited to those likely to gain most.

Increasing age is not the only factor associated with a higher risk of cardiovascular disease at any given BP. The risk is magnified by the presence of other factors (smoking, diabetes mellitus, male sex, hypercholesterolaemia, obesity, positive family history and previous evidence of atheromatous disease). For example, the presence of non-insulin dependent diabetes approximately doubles the risk. The management of hypertension is now moving towards a clearer stratification of the risks of cardiovascular disease for the individual patient which should facilitate recognition of the level of BP at which treatment should begin. This strategy is reflected in the most recent guidelines of the British Hypertension Society (*Br Med J*, 1993; 306: 983–7). The principal recommendation is that all patients below the age of 80 years who have sustained BP of $\geqq$ 160 mmHg systolic or $\geqq$ 100 mmHg diastolic should receive anti-hypertensive drugs. In addition the large cohort of the population with a diastolic BP between 90–99 mmHg should receive drugs if any of the above cardiovascular risk factors is present, or if they have evidence of damage to the heart, retinae or kidneys, or if they are older than 60 years.

★A list of speakers and the titles of their papers presented at this symposium is recorded in *Proceedings* Vol. 25 p. 354.

However, this strategy of targeting anti-hypertensive therapy to those in whom hypertension is not the only cardiovascular risk factor has not been tested experimentally. While there is evidence that elderly patients have more to gain than the young, other risk factors may impair the efficacy of anti-hypertensive agents. For example in a much-quoted but statistically dubious male sub-group of the MRC Mild Hypertension trial, smoking reduced the benefit from propranolol of stroke reduction. If this were confirmed it would make much more sense to encourage men to stop smoking rather than to treat them with anti-hypertensive drugs when their diastolic BP crept above 90 mmHg. This strategy was the basis of the Multiple Risk Factor Intervention Trial, which failed to show any impact on coronary heart disease largely because the placebo group enjoyed healthier diets and had stopped smoking. As we can no longer ethically deliver placebo therapy to individuals at high cardiovascular risk, there will probably never be a trial which examines the relative merits of treating different cardiovascular risk factors simultaneously.

Another approach to more rational prescribing of anti-hypertensive agents is to ensure that patients being treated really do have BP above the agreed threshold. Dr Paul Padfield reported that 40% of those classified as hypertensive at the start of a study (on the basis of diastolic BP > 90 mmHg sustained for 3 months) were normotensive by the same criterion 6 months later. Others have shown that up to 20% of patients with a high BP in a hospital clinic have normal BP on ambulatory blood pressure monitoring. Such individuals may have 'white-coat' hypertension, and probably are not at increased cardiovascular risk. Many now argue that ambulatory monitoring should be routine in the assessment of newly discovered hypertension. It eliminates 'white-coat' hypertensives and, being more reproducible, the need for multiple recordings over several months. It also correlates best with damage to target organs (e.g. left ventricular hypertrophy lacunar infarcts in the brain, microalbuminuria, and fundal changes). In 80% of subjects ambulatory BP is lower than clinic BP, so the threshold for anti-hypertensive treatment would be lower. Since a mean day-time ambulatory BP < 135/85 mmHg is not associated with left ventricular hypertrophy, this level could be a cut-off for the use of anti-hypertensive drugs. Also as mean day-time BP of $\geqq$145/95 mmHg corresponds with clinic BPs of $\geqq$160/100 mmHg this is an absolute indication for treatment. In between these levels assessment of cardiovascular risk and of target organ damage should determine treatment. Critics of ambulatory blood pressure monitoring argue that it is expensive, unlikely to be available to all patients and has never been tested in an intervention trial.

WHO IS BEING GIVEN ANTI-HYPERTENSIVE DRUGS?

If we accept the current recommendations on prescribing, the next crucial question is whether we are delivering this therapy to a sufficient proportion of the 'at-risk' population to make it worthwhile in community terms. Here the 'rule of halves' remains depressingly true, even in recent studies described by Dr Gordon McInnes. Thus, in some areas at least, only half the hypertensive patients are diagnosed, only half of these receive treatment, and in only half of these is BP control adequate. This is probably explained by large differences between the 'best' and 'worst' care available in Scotland.

In this symposium a new system for audience voting was used for the first time in the Conference Centre which allows immediate analysis of responses by

the audience to clinical problems presented as case histories. This was entertaining, but the significance of such voting depends on the experience of members of the audience which ranged from undergraduates to consultants in cardiology. Many of the questions would have to be refined to avoid several equally valid answers to each one. Moreover, the audience was undoubtedly influenced by the British Hypertension Society's guidelines described in the previous session. However, the majority claimed to practise within these guidelines. For example, nearly 80% claimed to use a thiazide as first-line anti-hypertensive treatment. The absence of evidence of the 'rule of halves' in the audience responses illustrates the extent to which a specialty symposium is an arrangement for preaching to the converted, since those who have an interest in hypertension are more likely to attend. By contrast, analysis of prescribing habits in the community reveals that thiazides and β-blockers are no more frequently prescribed than are ACE inhibitors or calcium antagonists. The problem is the need to bridge the gap between the best and the poorest levels of detection and management of hypertension.

The written word does not seem to provide the answer. Recent evidence on the impact of published guidelines suggests that they are practically useless if published in a journal (e.g. British Hypertension Society Guidelines), and only of real use if the prescribers have participated in composing them. Solutions may lie in better liaison between hospital services and general practices through computerised schemes for shared-care, satellite clinics, joint development of local protocols, and in the training of practice nurses.

WHAT CAUSES HYPERTENSION, AND DOES IT MATTER?

Epidemiological data suggests that 20–60% of essential hypertension is inherited and that the remainder is acquired or environmental. The pattern of inheritance within families indicated that several genes exert an influence. Linkage studies, especially those using sib-pairs, have identified several genetic polymorphisms associated with hypertension, which might be expected to affect the synthesis of proteins which influence BP, such as angiotensinogen, glucocorticoid receptors and kallikrein. Rat models of hypertension suggest that these alleles may interact to produce hypertension. Other genes may influence the outcome of hypertension, even if they do not influence blood pressure. For example, a deletion mutant of the gene for angiotensin converting enzyme is highly predictive of coronary heart disease.

One of the ways to determine the candidate genes for linkage analyses is to identify the abnormalities underlying rare congenital causes of hypertension. Recent examples include the chimaeric aldosterone synthase/11β-hydroxylase gene which causes glucocorticoid-suppressible hyperaldosteronism, and polymorphism in the β-subunit of the amiloride-sensitive distal tubular sodium channel which is associated with Liddle's syndrome.

An older approach to understanding the aetiology of both genetic and environmental hypertension has been to characterise putative intermediate phenotypes which are predicted to increase blood pressure. Many of these are modelled on rare secondary causes of hypertension, which in their classical forms account for fewer than 2% of all cases of hypertension. The trouble with this approach is that, unlike the genotype, these intermediate phenotypes may be altered as a consequence of hypertension. Examples include the possible roles of insulin, endothelin, and cortisol.

Target organ resistance to the action of insulin in non-insulin dependent diabetes mellitus may result in hyperinsulinaemia, which can promote atherogenesis, vascular and cardiac smooth muscle mitogenesis, and sodium retention. Essential hypertension and glucose intolerance occur together more often than is expected by chance (when occurring with a third feature, obesity, this comprises Reaven's syndrome, also known as Syndrome X), but a causative link is not established.

Endothelin-1 is a potent vasoconstrictor peptide synthesised in the vascular endothelium and first described in 1988. Since then there has been rapid progress in developing potential anti-hypertensive drugs, such as endothelin receptor antagonists (e.g. RO47-0203) and endothelin converting enzyme antagonists (e.g. phosphoramidon). These tools have been employed to demonstrate the importance of endothelin-1 production in the physiological control of vascular tone. Patients with essential hypertension are more sensitive to endothelin-1.

In the rare syndrome of 'Apparent Mineralocorticoid Excess', renal mineralocorticoid receptors become unusually sensitive to cortisol because the enzyme 11β-hydroxysteroid dehydrogenase is defective and the conversion of cortisol to its inactive metabolite cortisone is impaired. There is preliminary evidence that more subtle defects in this enzyme occur in essential hypertension. However, in essential hypertension, rather than there being renal hypersensitivity to cortisol, it is suggested that there is either vascular smooth muscle hypersensitivity to cortisol, or that adults with essential hypertension were exposed to greater levels of maternal cortisol *in utero* as a result of impaired placental 11β-hydroxysteroid dehydrogenase. This latter hypothesis may explain the recent observations that adverse cardiovascular outcome and adult hypertension occur in individuals who had a low birth weight and high placental weight.

The search for the cause of essential hypertension has been long and frustrating. In recognising that it is multi-factorial, and in establishing means to assess the contributions of different mechanisms in different individuals, we may be able to target at-risk individuals more accurately and then tailor their therapy. The two themes of this symposium, improved management of hypertension and better understanding of its aetiology, are likely to remain closely related.

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WORKSHOP ON HEPATITIS C VIRUS

The six papers that follow are based on a workshop held in the College in 1993 but updated to 1995. They are a record of specialists talking to the specially interested, and general readers may find them difficult in places. But the effort of reading them is worthwhile as the viruses responsible for hepatitis are not only important clinically but present fascinating problems in biology. Older readers will remember that their textbooks in the 1930s contained a section on catarrhal jaundice which was distinguished from obstructive and haemolytic jaundice. The cause of the catarrh was unknown. The single diagnostic label was soon replaced by two, infectious hepatitis and serum jaundice, the latter being a common condition in patients being treated for syphilis with intravenous injections. When means were discovered for isolating and identifying viruses, these conditions were found to be due to separate viruses, hepatitis A and B (HAV and HBV). A third distinct virus with an affinity for the liver was yellow fever virus. Other identified viruses are hepatitis C virus (HCV), hepatitis D (HDV) and hepatitis E virus (HEV).

Yellow fever virus is spread by an arthropod vector from a pool of infection which still persists in some jungle primates. HAV and HEV infection is spread from case to case by the faecal-oral route. Infection by HBV is transmitted via intimate (usually sexual) contact or parenteral injection through a contaminated needle or transfusion fluid. HCV is rarely transmitted by sexual contact, occasionally by needle stick injury but usually by infusion fluid.

There is extreme variation in the clinical manifestations of infection with hepatic viruses. A self limiting attack of fever with jaundice is the common presentation with yellow fever and with HAV and HEV infections, but is often absent with HBV and HCV infection. A fulminating, usually fatal, hepatitis is common in yellow fever, very rare with HAV, HCV and HEV, a well known tragedy with HBV infection. A persistent inflammatory response, with or without the continuing presence of virus, leading to cirrhosis and carcinoma is the main clinical feature of HCV infection and common in HBV infection. It is rare, if it ever occurs, in yellow fever or in HAV infection. Hepatitis D virus is strongly related to intravenous drug use but has similar epidemiological and clinical features to HBV with which it is often associated in time. In the immunocompromised patient, as with AIDS, the liver may be affected by other viruses, in particular cytomegalovirus, herpes simplex virus, measles virus in adults and Coxsackie virus B, all of which may give rise to hepatitis in occasional individuals.

Do these marked variations in the clinical responses to infection arise from differences in the strains of infecting virus or in the nature of the immune response of individual patients? An understanding of these questions would help both in prevention of the infections and in the treatment of patients.

The Editors