breakfast may have been promoted, albeit in good faith, on little scientific evidence. The coronary disease prevention lobby that was all the rage with politicians in the past went through this dietary phase 30 years ago, but alas it did not stem the tide. This time it is the cancer prevention school who have taken up the banner, and it will be interesting to see how long its disciples will follow.

10 Hill, M. J., Digestion, 1974, 11, 289.

Drug Metabolism and Increasing Age

In many animals the liver microsomes of fetuses and neonates have little or no ability to metabolize drugs. Enzyme activity usually appears after birth and increases with age to reach a maximum in adulthood.1 In human infants the activity of drug metabolizing enzymes is lower than in adults,2 but recent reports suggest that the age-dependence of hepatic drug metabolizing enzymes which is found in animals may not apply in children. Indeed children in the age range 1-8 years appear to metabolize some drugs at almost twice the rate of adults. This has been reported for drugs such as antipyrine and phenylbutazone, which are metabolized primarily in the liver by the mixed function oxidase system dependent on cytochrome P450.3 An increased rate of metabolism has also been shown in children for diazoxide, phenobarbital, and clindamycin.4-6 One explanation may be that the ratio of the weight of the liver to the body in children may be 30-50% greater than in adults. In animals such as rats, on the other hand, the ratio of liver to body weight increases with age and reaches a maximum in the adult.1

Lengthening of the plasma half-lives of antipyrine and phenylbutazone has been noted in the elderly, and differences in their absorption or protein-binding have been suggested as possible explanations.7 With increasing age plasma albumin levels tend to fall,8 and a change in the degree of binding of drugs by plasma proteins could increase the concentration of free drugs available for action, for distribution to the tissues, and also for drug metabolism. In a group of elderly patients Hayes et al.9 have shown a decrease in the plasma binding capacity for warfarin. The decrease in binding correlated with a fall in the plasma albumin concentration. No change in the affinity of plasma albumin for the drug occurred. In a second paper the same authors reported a marked increase in the clearance of phenytoin in patients over 65 years of age compared with those under 45, whether phenytoin (which is metabolized by hepatic microsomal enzymes) was given orally or intravenously.10 The clearance correlated inversely both with the phenytoin-binding capacity of plasma and with the plasma albumin concentration, both of which were reduced in the elderly patients. These findings support the suggestion that a greater availability of the drug for metabolism and excretion would result from decreased binding to plasma albumin.

Drug metabolism is only one of many factors concerned in the response to drugs. Other variables which complicate the interpretation of clinical studies include absorption, distribution, excretion, route of administration, dosage, other drugs, disease states, nutrition, temperature, individual variation, and genetic factors.11 Studies on drug metabolism and protein-binding of drugs must, therefore, be interpreted with caution. Nevertheless, there are important implications for drug dosage regimens in the elderly, in whom an increased number of adverse reactions to drugs have been reported.12

3 Alvares, A. P., et al., Clinical Pharmacology and Therapeutics, 1975, 17, 179.
6 Keuffert, R. E., et al., Clinical Pharmacology and Therapeutics, 1972, 13, 704.
8 Woodford-Williams, E., et al., Gerontologia, 1964, 10, 86.

Shoulder Pain from Subluxation in the Hemiplegic

Shoulder pain is a fairly frequent complaint of patients with hemiplegia. It may be blamed on the shoulder-hand syndrome, sympathetic dystrophy, frozen shoulder, or the thalamic syndrome; but in fact these causes are rare, and by far the most frequent explanation is that of subluxation of the shoulder on the hemiplegic side. This more mundane cause, though well known to many practising clinicians, has been neglected in print—for example, receiving a mention neither in a recent monograph on cerebrovascular disease nor in a comprehensive textbook of geriatrics.

A recent paper from a Glasgow geriatric department2 provides a valuable and timely reminder, redirecting the attention of clinicians dealing with hemiplegic patients to this neglected but common complication. Radiological evidence of subluxation was found in 17% of an unselected group of hemiplegic patients. Earlier surveys3-4 have indeed shown far higher prevalences in hemiplegics of various age groups of 40-60%. These varying rates probably reflect differences between the series, subluxation being more likely where the paralysis is flaccid and accompanied by disuse oedema so as to increase the weight of the dependent paralysed arm,2 and occurring with far greater frequency where arm paralysis is more severe.

The mechanism of subluxation is simply failure of the normal muscular support to the shoulder, on which its stability principally depends. Thus subluxation is seen only on radiographs taken in the erect position,2 4-6 and absence of supporting muscle tone has been shown electromyographically.5
Physicians dealing with hemiplegic patients need to keep the possibility of this common complication well in mind. Patients with shoulder pain from this cause can be made more comfortable and their rehabilitation facilitated if the arm is supported by a sling when they are erect. Permanent damage to the shoulder capsule must be prevented, so nurses and others caring for hemiplegic patients should be taught to use correct lifting methods which support the weak shoulder; and the patient must never be pulled up by traction on the paralysed arm.

5 Thorne, J. S., New York State Journal of Medicine, 1957, 57, 1377.

Antibiotics at Risk

In a striking and well-documented paper Anderson\(^1\) recently showed that transferable resistance to chloramphenicol is now common in the typhoid bacillus in Mexico and in some countries of south-east Asia. This serious observation demands both notice and action, because chloramphenicol is the drug of choice for the treatment of typhoid and because hopes were entertained\(^2\) by the Swann Committee that a sense of responsibility would impose enough self-restraint upon doctors, veterinarians, farmers, and the pharmaceutical industry to preserve the unique usefulness of chloramphenicol. Unfortunately these hopes have not been fulfilled; and Anderson's paper shows how readily and how widely the responsible transfer factors for chloramphenicol resistance and other resistances may be spread, for they are already to be found in many countries among various Gram-negative intestinal organisms such as Escherichia coli and Salmonella typhimurium.

It is not the widespread, protracted, and indiscriminate use of chloramphenicol alone, however, that has undermined the value of this precious drug; the misuse of other antibiotics just as readily leads to the transfer of multiple resistances, including that to chloramphenicol. The responsible plasmids are now abundant in the enterobacteria of man and livestock throughout the world, and it is now clear that the R factors in man and animals are drawn from a common pool.\(^3-^5\)

Resistance to antibiotics among bacteria may be caused by more than one mechanism, and the precise details of how and why tend to be fascinating only to microbiologists and not by any means to all of these. Nevertheless, it is reasonable to insist that both users and sellers of antibiotics should know enough microbiology and show enough sense of responsibility to realize the harm as well as the good they may do when they recommend use of an antibiotic. Certainly the laboratory resources of even developed countries and the methods available for assessing resistance both reliably and quickly are not such that therapy should be withheld pending the result of a sensitivity test. Reasonably enough, doctors prescribe the drugs they consider most likely to suit the needs of their individual patients; but they have a duty not to be palpably ignorant of what micro-organisms a particular drug will and will not act upon. For example, penicillin is not, never was, and never will be effective in brucellosis; and sulphonamides will effectively deal with a high proportion of the urinary infections seen in general practice.

By more often using their microbiological colleagues as consultants, and by submitting specimens taken before giving whatever drug is chosen, clinicians will build up for themselves a real knowledge of the main facts required to use most antibiotics wisely. This must be our guide, and not guesswork or over-optimistic claims for the newest and most expensive antibiotics. Many admirable and short texts are available—for example that of Garrod and O'Grady\(^4\)—and a recently published one by Lowbury and Ayliffe\(^5\) gives much interesting and sane guidance on controlling the emergence of antibiotic resistance. The clinician has a duty to give his patients the unquestionably great benefits of antibiotic therapy, but Lowbury and Ayliffe correctly insist that restriction of an antibiotic for use only in the treatment of certain severe infections is unlikely to endanger the lives of any patients and may help to preserve it for the treatment of diseases in which it is most useful. This applies especially in hospitals; and every hospital should have an antibiotic policy in which the selection of chemotherapy for different purposes is clearly laid down and revised at frequent intervals to meet altered sensitivity patterns of current hospital strains.

Certain antibiotics which are active against all or most strains should be reserved for restricted use. Whenever possible narrow-range antibiotics should be used in preference to broad-spectrum drugs. Systemic use of antibiotics for prophylaxis should be limited to situations in which their value is proved. Dosage must always be adequate, short courses with high dosage being best. Control of infection by isolation and by good aseptic and antisepsic discipline is essential; and maximum use should be made of antibiotics against which resistance rarely or never emerges. Combined chemotherapy and sensible rotations are generally sound, as are also any measures that may safely shorten patients' residence in hospital.

The recommendations of the Swann Committee\(^2\) restricting the antibiotics used for growth-promotion of livestock and the need for a general restraint in the use of antibiotics in animal husbandry must be kept in mind by those who can influence this complex and controversial situation. The importance of animal sources of R factors for man may be hard to assess with precision; but the enormous outbreak of chloramphenicol-resistant typhoid in Mexico, with more than 10 000 cases, is surely a stimulus to err on the side of caution. Indeed, in view of the recent excitement over laboratory and public safety in connection with R factors,\(^8-^9\) it is odd that there has not been equal concern about the excessive, uncritical use of antibiotics by doctors, veterinarians, and farmers. Perhaps, as Anderson\(^1\) suggests, the time has come when international co-operation at legislative and professional levels is needed to reverse the change in the ecology of the enterobacteria and other organisms caused by the indiscriminate use of antibacterial drugs.

1 Anderson, E. S., Journal of Hygiene, 1975, 74, 289.
8 British Medical Journal, 1974, 3, 483.
9 British Medical Journal, 1975, 1, 234.