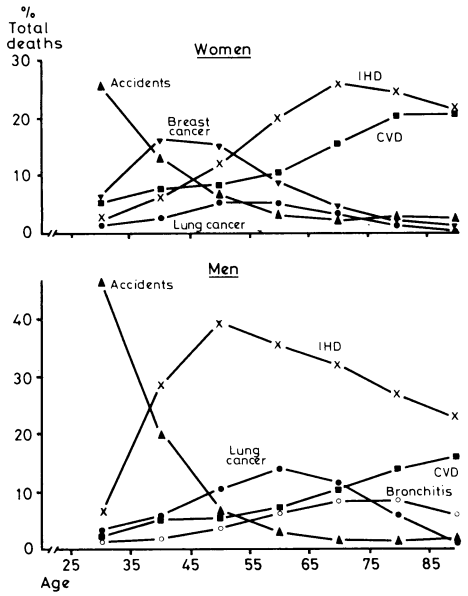

Percentage of total deaths attributed to selected causes by Age and Sex (England and Wales 1973)

For women the gap between IHD and the next leading cause is much narrower than it is for men, and IHD becomes the leading cause of death only after the age of 55 because accidents, breast cancer, and cerebrovascular disease (CVD) are of relatively greater importance at the younger ages in women.

Male sex hormones have existed since the beginning of mankind, but IHD is a characteristic of modern developed countries predominantly linked with our life style. If loss of sex hormone were to protect men from IHD disease it is difficult to understand why IHD continues to be the leading cause of death even in the over-85s. It will be difficult to evaluate the independent role of male sex hormones, if they have any role at all, in the aetiology of IHD except by a follow-up study of subjects for whom hormones, lipids, blood pressure, behaviour type, smoking habits, and age have been ascertained.

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SIR,—Examination of the Registrar General's data for 1970-74 led Drs R F Heller and H S Jacobs (25 February, p 472) to conclude that male sex hormones may be risk factors for coronary heart disease (CHD), rather than female hormones being protective.

During the years 1950-72, the CHD mortality rate increased in men, particularly in the younger age groups, whereas female mortality did not alter significantly.[1] If male sex hormones are risk factors for CHD at least part of this increase may be explicable on this basis. For at least the last 120 years the mean age of puberty in both sexes has been getting earlier, advancing by about five months every decade.[2] If male sex hormones are a risk factor for CHD this secular trend would lead to an increasing incidence of CHD in men but not in women. Earlier puberty would either potentiate the rate of increase of CHD with age, causing the curve to rise more steeply, or would just cause a left shift of the curve.

The trend to earlier puberty is largely due to improved nutrition in childhood and has been subject to fluctuation. In the years 1939-42 the nutritional status of 12-year-olds fell, at least in some parts of England,[3] reversing for a brief period the general trend. Between 1965 and 1968 there was a marked drop in CHD mortality confined to men aged 35-40.[1] Most men in this age group would have been approaching puberty in the early war years.

Male sex hormones may thus explain at least part of the rising CHD mortality affecting males as well as the male/female difference at risk.

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[1] Clayton, D G, Taylor, D, and Shaper, A G, *Health Trends*, 1977, **9**, 1.
[2] Tanner, J M, in *Endocrine and Genetic Diseases of Childhood*, ed L I Gardner. Philadelphia, Saunders, 1969.
[3] Daley, A, *Medical Officer*, 1948, **79**, 242.

SIR,—Dr R F Heller and Dr H S Jacobs (25 February, p 472) suggest that testosterone may be implicated in the aetiology of coronary heart disease (CHD). We would like to point out an observation concerning the effect of testosterone on vascular responses to thromboxane A_2 (TxA_2), an agent which may be involved in platelet and vascular changes in CHD.[1]

TxA_2 is a potent vasoconstrictor and its contractile effect upon isolated strips of rabbit aorta or mesenteric artery is used to bioassay TxA_2 activity.[1] When using rabbit tissues for this purpose we found that, from a total of 84 rabbits, vascular tissue from only 54 animals (63·5%) responded to TxA_2. Prior treatment of the rabbits with testosterone, however, elevated the response level to 85·0% (34 out of 40 rabbits). This difference is significant at the $P=0·02$ level. Testosterone treatment consisted of three single injections on successive days of 10 mg, 10 mg, and 5 mg, subcutaneously, of testosterone phenylpropionate *BP* to adult male New Zealand white rabbits. The animals were used in bioassay studies on the day following the third administration of testosterone.

These results support the observation of Uzunova *et al*,[2] which showed that testosterone potentiated, in mice, thrombosis produced by the TxA_2 precursor arachidonic acid. Our observation suggests that testosterone is working at the "TxA_2 receptor" level rather than altering TxA_2 synthesis.

Potentiation of the biological effects of TxA_2 is a possible mechanism through which testosterone may raise the risk level for CHD in man. Of immediate value to the pharmacologist, however, is that testosterone can assist in overcoming the problems of biological assay of TxA_2.

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[1] Needleman, P, *et al*, *Nature*, 1976, **261**, 558.
[2] Uzunova, A D, *et al*, *Prostaglandins*, 1977, **13**, 995.

Who discovered the circulation of the blood?

SIR,—Confronted with the above question, doubtless most physicians and physiologists would reply, "William Harvey, in 1628." His classic treatise[1] was entitled *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, Guilielmi Harvei Angli, Medici Regii et Professoris Anatomiae in Collegio Medicorum Londinensi. Today the use of the term "Angli" (Englishman) would be thought jingoistic, but I prefer to believe that it revealed an unexaggerated pride in his mother country, or was it a custom of that era?

I have always firmly believed that it was Harvey who discovered the circulation of the blood. Thus I was surprised recently when reading the late Professor Cecilia Mettler's *History of Medicine*[2] and the *Encyclopaedia Britannica*[3] to learn that the Alexandrian physicians Erasistratus and Herophilus conjectured, albeit by faulty reasoning, that the veins and arteries were inosculated. They taught that the veins carried blood to the members while the arteries (air pipes) carried a subtle form of air or "spirit." Later Galen discovered that the arteries contained blood as well as "vital spirit," but he claimed that the cardiac septum was pervious to blood. According to Professor Mettler, whose reputation as a historian, linguist, and scholar must surely be acknowledged to be outstanding by all medical historians, the events were as follows.

In 1571 Caesalpinus[4] postulated, without supporting evidence, the "circulation of the blood," but he believed, as did Galen, that the cardiac septum was pervious to blood. His ideas were investigated by the famous anatomists and surgeons Casserius and Fabricius (Fabrizio d'Acquapendente), who served as mentors to Harvey when in 1602 he visited Padua, where he worked for and received his doctorate of medicine. Berengarius, Canano, Estienne, Vesalius, and Fabricius[5] supported in essence Caesalpinus's and Galen's theories, although they were fully aware of the existence but not the function of the non-return valves in the veins. Vesalius, an over-modest man, ascertained that the cardiac septum was impervious to blood, but unfortunately he was reluctant to refute the claim of the redoubtable Galen that it was not. Michael Servetus, in his *Christianisma Restitutio* (1553), went somewhat further, and from the anatomical facts of the intact cardiac septum and the large size of the major arteries he concluded that there was a communication in the lungs by which blood passes from the pulmonary artery to the pulmonary vein. (It will be recalled that the pulmonary arteries and veins carry venous and arterial blood respectively.) It must be emphasised that the Italian anatomists relied heavily on physicists in their work.

Fabricius communicated these findings and theories to Harvey, who, on returning to England, converted most of his fellow physicians, who had been ignorant of or loath to accept the Italians' theories. After much painstaking experimentation he taught that the purpose of respiration was to convert venous to arterial blood. His calculation that at the normal pulse rate of 70 beats a minute the heart pumped more than 50 gallons of blood an hour converted the last of the sceptics. In particular he emphasised the vital function of the venous valves, but not surprisingly he was unable to demonstrate the capillary circulation. It was left to Malpighi, four years after Harvey's death, actually to demonstrate, with the aid of magnifying lenses, an anastomosis between the arteries and veins. Although Malpighi conveyed his discovery only in a personal letter to his close friend Borellius, the letter was later published.[6]

I do not wish to be thought iconoclastic or

to belittle Harvey's great contributions to the discovery of the circulation of the blood, but is it not time that we in Britain stopped perpetuating what at least is an oversimplified claim, that it was Harvey and Harvey alone who made this great discovery?

It would be most interesting, especially to me, to learn the views of professional medical historians—British, Italian, and Dutch.

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[1] Harvey, W, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*. Frankfort, 1628.
[2] Mettler, C C, *History of Medicine*. Toronto, Blackiston, 1947.
[3] *Encyclopaedia Britannica*, 1963, vol 11, p 236.
[4] Caesalpinus, *Quaestionum Perpeticarum*, libro V. Florence, 1571.
[5] Fabricius (Fabrizio d'Acquapendente), *Tractatus de Respiratione ejus Instrumentis*, libro II. Padua, 1615.
[6] Malpighi, M, *De Pulmonibus, Epistolae II, ad Borellium*. Bologna, 1661.

Erosive duodenitis during cimetidine treatment

SIR,—We were interested to read the case report by Dr J Webster and others (7 January, p 20) in which erosive gastritis and duodenitis were ascribed to a side effect of cimetidine treatment. We too have observed a case of erosive duodenitis occurring during cimetidine treatment.

A 46-year-old man presented with a history of epigastric pain for one month with no previous history. Endoscopy showed an ulcer on the posterior wall of the duodenal bulb with no evidence of duodenitis or duodenal deformity. Cimetidine treatment was started at 1 g/day and three days later the pain disappeared. During treatment he took a normal diet with no alcohol or coffee and he stopped smoking. No other drug was given. One month after starting treatment the patient was still free of symptoms and further endoscopy showed the duodenal ulcer to be healing; nevertheless, the duodenal mucosa showed intensive and widespread hyperaemia and oedema with several areas of punctate erosion. The appearance of the oesophagus and stomach was normal. Renal (blood urea, serum creatinine, and creatinine and urea clearance) and hepatic (serum transaminases, serum bilirubin, and bromsulphalein excretion) function was normal before and after the 30 days' treatment. Basal acid output and maximum acid output (pentagastrin test) before treatment were 12·7 mmol/h and 44·8 mmol/h and two days after stopping treatment they were 13·2 mmol/h and 49·1 mmol/h respectively. Cimetidine treatment was not resumed. A month later endoscopy showed a slight improvement in the punctate erosive duodenitis, but without the healing. A third pentagastrin test showed no significant variation from the previous ones. We have followed up 32 other patients with duodenal ulcer treated with cimetidine (1 g/day for one month and then 400 mg/day for six months) and also 18 patients with duodenal ulcer treated with an antacid (Maalox) in high dosage for one month followed after healing by small doses at night. All these patients were included in a randomised controlled trial carried out by our unit and we did not observe any further cases of widespread punctate erosive duodenitis.

The report by Dr Webster and his colleagues, together with ours, might suggest that the appearance of punctate erosive duodenitis or gastritis during cimetidine treatment is due to side effect of the drug. Nevertheless, it is not clear why, once the treatment is stopped, no significant improvement of the erosive duodenitis occurs even after as long as four months' suspension of treatment.

Since we deem it very important to determine the true incidence of this possible side effect we would appreciate any further observations.

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SI, moles, and drugs

SIR,—I was interested, but somewhat disturbed, by your leading article under this title (18 March, p 668), which seems to have been inspired, at least in part, by your experience in converting drug concentrations from mass concentrations to substance concentrations. Having recently been involved in the conversion to SI units (at University College Hospital, London) I can confirm that the conversion of drug concentrations did provide some problems. However, your leading article does little to clarify the matter and indeed may cause further confusion. The mathematics of conversion is not the main difficulty (though care is needed); nor is failure to understand the exact nature of the substance being measured (though it may be of some importance). The most important source of error is failure to identify the primary standard used in the assay.

In practice most measurements are made by comparing the reaction of the test solution with that of a standard solution in an assay procedure. In drug measurements, as you point out, a number of related substances may be present and their reactivity may well vary. This is a fundamental problem in clinical chemistry, not merely in drug assays. It is unrelated to SI and cannot be fully eliminated. All that can be done is to define a standard and make the simplifying assumption that test and standard react equally in the assay.

Having defined a standard it is easy to convert results to SI units, using the molecular weight of the standard; and theoretically there is some justification for doing so. The activity of the reacting molecules is more likely to be related to their number than to their weight. The importance of identifying the primary standard was amply demonstrated by your experience with chlormethiazole, where both 513·5 mg of chlormethiazole edisylate and 161·65 mg of chlormethiazole base provide 10 mmol of chlormethiazole (as edisylate or base).

Only if the exact composition and molecular characteristics of the standard are uncertain or unknown is conversion unsafe or impossible. Total protein is a special case where the assay commonly employed quantifies peptide bonds and not protein itself.

While I do not readily defend SI, the problems thrown in its path are problems that it has not caused but merely drawn to our attention.

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Expression of complex symbols

SIR,—Your leading article "SI, moles, and drugs" (18 March, p 668) refers to the undesirability of using, for example, $mg \cdot kg^{-1} \cdot d^{-1}$ to avoid the ambiguity of mg/kg/d. Unfortunately ambiguity will always exist when the complex symbol is in a field of medical science outside one's own.

In a relatively simple expression such as the above negative indices are not essential and ambiguity may be avoided by using parentheses.[1] In mg/kg/d, if the numerical values are 12/4/2, then (mg/kg)/d or mg/(kg·d) equals 1·5 and mg/(kg/d) equals 6.

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[1] *Units, Symbols, and Abbreviations*, 3rd edn, ed D N Baron, pp 5-6, 41. London, Royal Society of Medicine.

**Surely in clinical medicine "mg/kg/d" is used as an expression of *daily* dosage, not of *total* dosage, so that the ambiguity to which Professor Baron refers does not arise.—ED, *BMJ*.

Typhoid and its serology

SIR,—Your leading article (18 February, p 389) on the use and limitations of serological tests in the diagnosis of typhoid fever is timely, especially as in the majority of cases reported in Britain the infection has been contracted abroad. Brodie[1] is to be congratulated on such painstaking and useful work in following up so many patients for so long after the outbreak of typhoid fever at Aberdeen in 1964. These serological tests have also been used for many years to "screen" waterworks staff and potential employees for possible carriage of *Salmonella typhi* and thus aid the detection and exclusion of typhoid carriers.[2] The limitations of typhoid serology for this purpose are also illustrated by Brodie's results.

The recent creation of water authorities with responsibility for water supply, sewerage, and river management—previously administered by separate bodies—has necessitated consideration of the multifunctional use of staff as well as the need to reassess the value of screening tests for them. The Public Health Laboratory Service Standing Committee on the Bacteriological Examination of Water Supplies has therefore recently reviewed the epidemiology of waterborne infectious disease in Britain since 1937—the year of the large outbreak at Croydon—as well as the role of serological screening tests.[3] The committee concludes, in view of the current low incidence and changes in the natural history of typhoid fever—quite apart from improvements in water treatment and examination since 1937—that the continued mass use of serological screening tests is no longer justified in Britain. Since typhoid fever is not the only potential hazard, however remote, the committee recommends that examination of waterworks staff and potential employees for carriage of agents of potentially waterborne disease should be done selectively by appropriate laboratory tests, preferably in consultation with medical microbiologists, and then only when indications for them are revealed by medical assessment. Indeed, this accords with advice issued by the Department of Health and Social Security[4] for employees in the food and catering services, where the potential microbiological hazards are probably very much greater than with water supplies. The role of codes of practice and of education in simple applied hygiene, previously mentioned in your columns,[5] cannot be too strongly