the increase in knowledge and doubts on the validity of many requirements. There has just been an increase and this has been reflected in the time-lag between starting a research project and making a new medicine generally available on prescription. An analysis of over 200 medicines showed that the average time between first publication and marketing has increased from six years in 1965 to 10 years today. This is probably a very conservative estimate, as the first publication takes place well after the start of a project and the calculation ignores the many early compounds in a project which never reach the market. Bearing this in mind, an extrapolation of the current trend means that new medicines will have exceeded their 20-year patent life before reaching the UK market by the early 1990s.

However, it must not be assumed that regulatory requirements are the only factors influencing pharmaceutical innovation. Almost every regulation, legislation, or proposed legislation such as price controls, reduced promotional allowances, WHO essential drug lists, postmarketing surveillance, strict or no-fault liability and compensation, "good clinical practice," and information to patients adds to the disincentives for pharmaceutical research. Many of these appear to be sensible when considered in isolation, but each one affects others and the total package could have a catastrophic impact. The result of these regulatory and non-regulatory influences is not difficult to envisage.

An analysis of some of the largest research-based pharmaceutical companies in the world demonstrates that a rapidly increasing percentage of their research budgets is devoted to non-innovative work. An extrapolation of this trend suggests that innovative pharmaceutical research will cease completely by 1990. Observers of the pharmaceutical industry today look at the few new medicines coming on to the market and discount prophecies of gloom, but these people forget that the new medicines of today are the fruit of projects started 10 or more years ago, when conditions were very different.

This time-lag between starting projects and having new medicines available effectively hides the state of today's innovative pharmaceutical research, but any complacency is misplaced and today's clear and observable trend points to an end of improved medicines from innovative research within 20 or so years if current conditions are allowed to continue.

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Cimetidine for ulcers recurring after surgery

SIR,—We have read with interest the recent reports on the use of cimetidine in the treatment of ulcers which have recurred after gastric surgery by Mr Terence Kennedy and Dr Anne Spencer (13 May, p 1242) and Dr A M Hoare and his colleagues (20 May, p 1325). We would like to record our experience of the use of cimetidine in this context.

In a study designed to test the efficacy of cimetidine in preventing the recurrence of duodenal and stomal ulcers 100 patients have been treated with full doses of cimetidine (1 g/day) for up to 12 months and subsequently

followed up after stopping the treatment. Thirteen of these patients had had previous gastric surgery (eight vagotomy plus pyloroplasty; one vagotomy plus gastrojejunostomy; four Polya gastrectomy). Eight of the post-operative recurrences were therefore duodenal ulcers and five were stomal ulcers. The mean gastric acid and pepsin responses to an intravenous infusion of pentagastrin (2 µg/kg/h) were high: acid 28.8 mmol/h (range 8.7–44.6 mmol/h) and pepsin 210 KU/h (range 95–418 KU/h). All patients were assessed endoscopically initially and monthly until the ulcer had healed. The endoscopic examination was repeated at the end of the course of treatment with cimetidine or when symptoms recurred during the course of treatment.

Ten of the 13 ulcers had healed after treatment for one month and two other ulcers had healed after three months' therapy (one duodenal ulcer after vagotomy plus pyloroplasty; one stomal ulcer after vagotomy plus gastrojejunostomy). These latter two patients did, however, have rapid symptomatic relief. One patient with a stomal ulcer after Polya gastrectomy healed only when the dosage of cimetidine was increased to 1.6 g/day. Three ulcers (two duodenal and one stomal) recurred during treatment with cimetidine (two asymptotically). Three patients remained well more than seven months after stopping treatment.

In this study cimetidine has been shown to heal postoperative recurrent ulcers at a rate similar to that in unoperated patients. The pattern of recurrence of the ulcers after healing, during and after long-term treatment, is proportionately similar to that observed in our unoperated patients. We therefore conclude that cimetidine in conventional dosage will satisfactorily heal postoperative recurrent ulcers and, in addition, that maintenance treatment with cimetidine may be of use in preventing further ulcer recurrence in these patients.

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Maintenance treatment of duodenal ulcer with cimetidine

SIR,—Drs K G Wormsley and N R Peden (20 May, p 1351) state that radiological signs of duodenal ulcer disease in patients with epigastric pain do not constitute a proper indication for cimetidine treatment and they recommend the routine use of duodenoscopy for confirming or disproving the diagnosis. We feel that it is unwise to recommend the routine use of a diagnostic method if its benefit to the patient has not been proved, and we are aware of no evidence to this effect in the case of routine duodenoscopy. We have conducted both a therapeutic trial¹ and a maintenance trial (29 April, p 1095) of the effect of cimetidine in patients with radiologically diagnosed duodenal ulcer, and the results were similar to those obtained by others in cases of duodenal ulcer diagnosed by endoscopy. Thus radiological and endoscopic diagnostic criteria seem equally valid for predicting a therapeutic response. Duodenal ulcer disease has many clinical facets and we do not believe that it is justified to maintain that the result of a single endoscopic examination

represents the ultimate diagnostic truth. Cimetidine trials, for instance, have shown that there is only a poor correlation between relief of symptoms and ulcer healing in duodenal ulcer patients. Cimetidine treatment is expensive, but some of the expense may be compensated for if more duodenal ulcer patients are treated in general practice. Recommendations to refer duodenal ulcer patients for duodenoscopy and outpatient treatment will only place an unnecessary extra burden on the hospital sector.

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¹ Gudmand-Hoyer, E, *et al*, *Scandinavian Journal of Gastroenterology*, 1977, **12**, 611.

SIR,—Drs K G Wormsley and N R Peden (20 May, p 1351) are correct in their assertion that the radiological demonstration of a deformed duodenal cap is not sufficient justification for the use of cimetidine in clinical practice if the barium meal has been performed by the conventional method. However, when the barium meal is performed using a double-contrast technique not only does this allow an accurate prediction as to whether or not the duodenum is abnormal but in particular whether the abnormality is due to scarring or active ulceration.

There is no reason, in the UK, why patients with suspected duodenal ulcers cannot have the benefit of having their diagnosis confirmed by a double-contrast barium meal, which is safe, quick, easy to perform, and exceptionally well tolerated by the patient. Endoscopy can then be reserved for the small percentage of patients in whom diagnostic doubt still remains.

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SIR,—Cimetidine (3 June, p 1435) is to ulcer as truss to hernia. Any enterprising and otherwise healthy person would gamble on a good surgeon rather than stuff their guts in all day or swallow pills, even those greased with glamour.

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Side effects of nifedipine

SIR,—The paper by Drs A G Jariwalla and E G Anderson (6 May, p 1181) interested us; we too have a patient in whom nifedipine (Adalat) apparently provoked ischaemic cardiac pain. Our experience suggests that this side effect can develop during treatment and that it is not only patients starting therapy who need to be warned of it.

A man aged 46 with a three-year history of effort angina was changed from oxprenolol 120 mg daily to nifedipine 10 mg thrice daily. Angina decreased in frequency, and in an attempt to abolish it the dose of nifedipine was increased after six weeks to 20 mg thrice daily. Within the next week the patient had his first protracted episode of central chest pain at rest; it occurred about 15 min after a dose of nifedipine, lasted over

an hour, and was accompanied by agitation and sweating but not by palpitation or dyspnoea. Similar symptoms followed most subsequent doses of nifedipine; they ceased as soon as the drug was discontinued two weeks later. An electrocardiogram recorded since was normal.

Our patient also complained of a fine tremor involving particularly the upper limbs. It occurred within 30 min of a dose of nifedipine and lasted up to two hours. It developed after he had been on nifedipine 30 mg daily for a month, was unchanged on 60 mg daily, and resolved immediately the drug was stopped. This possible side effect of nifedipine has not apparently been reported previously.

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SI, moles, and drugs

SIR,—We wholeheartedly support the plea made by Dr P Crome and others (13 May, p 1277) for the preservation of mass units for the expression of drug concentrations. As they point out, the use of several different units is a particular hazard in clinical toxicology and we could provide many examples such as those quoted in their letter. We too have experienced major problems with inquiries to the Scottish Poisons Information Bureau and our toxicology laboratory when the units used by different hospitals differ. The caller is usually unaware of the units used locally.

The introduction of molar SI units for a few drugs has exacerbated a pre-existing problem with units. Barbiturate, salicylate, and paracetamol concentrations have previously been reported in different mass units, generally $\mu\text{g/ml}$ or $\text{mg}/100\text{ ml}$, and now and again mistakes in interpretation have occurred because of this. The addition of molar units in the east of Scotland has now resulted in the use of both $\mu\text{mol/l}$ and mmol/l for paracetamol. Other laboratories and the National Quality Control Scheme for this drug continue to use mass units. With such commonly encountered drugs confusion over units remains a problem despite assurances that increasing familiarity with the new units would obviate the need for conversion.

In the case of less commonly measured drugs there are no reference values for molar units and no comprehensive list of conversion factors is available. In order to interpret a drug concentration quoted in a poisoning inquiry it is necessary to find a reference book containing the chemical formula or the molecular weight before the conversion can be calculated. This may not be too difficult for laboratory staff, but it is asking a lot of the secretaries, doctors, and nurses who staff our poisons information bureau. The dangers are well illustrated by the serious mistakes recently made by both your editorial office (18 March, p 716) and Dr S G Ball (8 April, p 920) in attempting to convert chlormethiazole concentrations.

It must also be noted that drug concentrations in most of the clinical toxicology and clinical pharmacology literature nationally and internationally are expressed in mass rather than molar units. A change is unlikely since drugs are manufactured, prescribed, and dispensed in mass units and the use of different units for dosage and concentrations in clinical pharmacokinetics is nonsensical.

If there were any practical advantages in using molar units the difficulties and hazards involved might be acceptable. But there are no obvious clinical advantages. In defence of SI it is sometimes claimed that the response to drugs is related more closely to molar than to mass concentrations at receptors. While this may be true in some circumstances it is largely irrelevant in clinical practice. For example, there may be up to a 500-fold range in mass (or molar) dosage of thiazide-type diuretics required to produce a similar clinical effect, which cannot be related to differences in plasma concentrations.

The present unacceptable situation has been brought about by those who devote only a small part of their total work load to drug analysis without consideration of the wider implications. The practical problems of clinical toxicologists, clinical pharmacologists, pharmacists, and those working in the pharmaceutical industry, all of whom are directly concerned with drugs, have not been taken into account. Unless some responsible body undertakes to secure general agreement on the use of mass or molar units for clinical drug concentrations the present muddle will continue indefinitely.

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Intravenous infusion of salbutamol in severe acute asthma

SIR,—The apologetic tone of the discussion at the end of the paper by Dr A J Johnson and his colleagues (22 April, p 1013) clearly betrays a lack of confidence both in the design of their study and in their rather lame conclusion that salbutamol given by intravenous infusion for 36 h does not "appear to have any advantages" over aminophylline administered in the same way.

It is, of course, true that there are ethical problems in conducting clinical trials on patients with severe acute asthma. One can, however, hardly imagine that patients who were already receiving a "standard supportive regimen comprising nebulised salbutamol (5 mg) given four times a day by intermittent positive-pressure breathing, corticosteroids, supplementary oxygen, and physiotherapy" combined with antibiotics when necessary (a generous therapeutic regimen by any standards) could have come to much harm, even if the initial response to this treatment was "unsatisfactory," as a result of the physician responsible for their care not knowing whether the supplementary (trial) treatment consisted of an intravenous infusion of salbutamol or one of aminophylline. Most hospital ethical committees would accept that view, provided the patients were all being expertly monitored, and permit both a double-blind allocation to the two types of infusion and the inclusion of a placebo infusion group.

In the way the study reported by Dr Johnson and his colleagues was, or perhaps had to be, conducted its results are virtually of no value. This is, in effect, conceded by the authors themselves when they admit (1) that "any possible additional bronchodilator effect from the intravenous administration of salbutamol may have been reduced by the large

regular doses of nebulised salbutamol causing saturation of the adrenoceptor sites"; (2) that "physician bias against the new infusion drug" (salbutamol) may have influenced the results; and (3) that "possibly, if a placebo infusion group had been included it would have yielded results similar to those of the bronchodilator infusion groups."

Indeed, the only conclusion a critical reader can draw from the paper is that patients varied in the rapidity of their response to the authors' "standard supportive treatment." They have certainly not proved, nor indeed have they claimed, that the prolonged intravenous infusion of either salbutamol or aminophylline had any significant effect on their patients' rate of recovery. In this connection the allusion at the end of the summary to a "rate [of recovery] that would occur *naturally*" (my italics) in the context of patients who were receiving what would usually be regarded as very intensive treatment for severe acute asthma seems a little strange.

If the article proves anything at all it is perhaps that some hospital ethical committees are less enlightened than others.

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SIR,—The paper by Dr A J Johnson and others (22 April, p 1013) concludes that in acute severe asthma not responding to an initial intensive regimen the intravenous infusion of salbutamol "has no particular advantage over aminophylline." In reaching this conclusion it seems that the authors place little weight on the fact that 6 out of 20 salbutamol patients were withdrawn because their response was "considered to be unsatisfactory" compared with 0 out of 19 in the aminophylline group ($P=0.02$, Fisher's exact test). Furthermore, two of the aminophylline group were removed late in the trial because their response was *satisfactory*.

The finding of an absence of significant differences between the lung function of the two groups at any time during the trial appears to be based on the data of those patients who were not withdrawn at any stage. If so, this has almost certainly biased the result against aminophylline since four of the salbutamol withdrawals had lung function values well below the mean response of their group. It appears that, although it may be correct to state that salbutamol has no particular advantage over aminophylline, it would be more correct to conclude that aminophylline may have some advantages over salbutamol.

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* * * We sent copies of these letters to Dr Johnson and his colleagues. A reply from two of them, sent with the concurrence of the others, is printed below.—Ed, *BMJ*.

SIR,—In response to Professor Grant's comments we must reiterate that the purpose of our study was to assess the effect of infusing the two bronchodilator drugs in asthmatics whose attacks were severe and had responded poorly to a standard initial regimen. This is a quite different situation from the previous