unless we fail an MAG III renogram was indicated; (n=22) in whom it was 5–10 mm and the mic-

those infants in whom persisting renal pelvis

the diagnosis of “idiopathic dilatation” only

approach is now adopted in cases of pelvi-

generally treated medically, was the most

surveillance.

were discharged from further follow up, as we

surviving cystogram were normal, the infants

resolved and, more importantly, no renal scar-

The answer to this question is not yet known

The nub of the matter is whether

EDITOR,—Dr Nicholl raises some pertinent

points in his letter regarding our paper.7 The rub of the matter is whether

the radiological techniques used may have

our findings were significant.

We accept that in a review of the published

findings, from which Bailey acquired his data,

common finding, and a more conservative

were discharged from further follow up, as we

With regard to the specific points raised by

Nicholl around 50% of the babies with VUR in

their studies, have now under-gone further imaging at the age of 3 years. Their reflux had resolved and,

more importantly, no renal scar-

had been incurred. In those babies where both postnatal ultrasonography and the mic-

caturating cystogram was normal, the infants

were discharged from further follow up, as we

saw no further indication for continuing their surveillance.

The fact that only one baby required surgi-

cal intervention reflects that VUR, which is
generally treated medically, was the most
common finding, and a more conservative

approach is now adopted in cases of pelvi-

ureteric junction obstruction.

In table 1 of our study we included, under

the diagnosis of “idiopathic dilatation” only

those infants in whom persisting renal pelvis
dilatation was > 10 mm, because in those (n=22) in whom it was 5–10 mm and the mic-

caturating cystogram was normal, we did not

feel an MAG III renogram was indicated; therefore, they did not strictly fulfil our criteria for this diagnostic label.

This is not an area where more money is needed for research. More than 200 papers have already been published on this topic over the past decade. There is no commercial pres-
sure on the manufacturer to modify the data sheet: they are generic products unprotected by patents. Nor does the Medicines Control Agency believe that it should take the initiative over this, although it would be very willing to review the case for voluntary modification with manufacturers if an appropriate and responsible professional body. Why, then, does the Royal College of Paediatrics and Child Health not do this?

For most of the drugs listed by Conroy, there is no need for further discussion as papers stating that drug data sheets are out of step with current practice. Nor do “they” need to tighten the prescribing rules and restrict what “we” can do. What is needed is sensible, sustained, and constructive dialogue between the profession, the licensing authorities, and the manufacturers, to get drug sheets revised at regular intervals, so that they reflect all the additional information that becomes available in the years after the product gets on the market. My message is, that it is up to the profession to start the ball rolling.

Dr Conroy et al respond: We welcome the opportunity to clarify our “take home” message. This is actually very simple: drugs used in children should be tested scientifically to ensure that age depend-

ent changes in pharmacokinetics and pharma-
codynamics are known, the likely side effects are anticipated, and that the minimum effective
dose can be given.

We expect the Medicines Control Agency to ensure that neonates receive drugs that are as carefully evaluated for efficacy, safety, and quality as the drugs given to adults. We also expect the pharmaceutical industry to provide drugs that are appropriate for use in neonates and children as well as in adults. We accept that health professionals involved in the care of neonates have a responsibility to contribute to this process. It requires a joint effort between healthcare staff caring for children, the indus-

ty, and the government. Dr Hey states that data sheet information is “advocacy”, but this is the only information that the pharmaceutical manufacturer will take responsibility for, any-
thing else is on the head of the prescriber.

There may be few published reports of renal or any few reports of the use of certain drugs in neonates, as it is difficult to definitely attribute such problems to the drug. However, this does not mean that gentamicin does not cause such problems. We note that renal insufficiency is not uncommon in all preterm infants and that long term hearing problems occur in babies who have been through neonatal intensive care. We do not know how many of these problems are associ-

ated with gentamicin use because the babies

Unlicensed and off label drug use in neonates

Editor,—Most papers in this journal have a commendable clear “take home” message, but this was not really true of the recent paper by Conroy et al.1 They described a 13 week, one unit study in Derby as finding that two thirds of all neonatal gentamicin prescriptions (for 4 out of 455) involved the use of a drug in a way that the manufacturers had no license to recommend. The authors do not say what should be done about it.

They note that 84 prescriptions for vitamins and 77 for penicillin or an aminoglycoside used a dose other than the one mentioned in the drug data sheet. But they must be aware, surely, that all doctors often use medicines in a way that is not relevant to the drug’s registration. Second, an immense amount of information has been published on these issues since the drug sheets were first prepared. Thirdly, many UK college and American academ单位 treated medically, was the most

Until this matter is resolved, however, we feel it appropriate to look for VUR when there has been antenatal renal pelvis dilatation, and treat accordingly. As stated in our study,7 this judgement is partly based on the fact that the prevalence of asymptomatic VUR is around 1%, as described by Bailey, in contrast to an incidence of 20% in our study, implying that our findings were significant.

We accept that in a review of the published

findings, from which Bailey acquired his data,

radiological techniques used may have
differed from those currently in use, but as

can be imagined, it is not easy to acquire

information about the incidence of VUR in

healthy children, and Bailey’s work is, to our

knowledge, the currently accepted ref-

ence.7

With regard to the specific points raised by

Nicholl around 50% of the babies with VUR in

their studies, have now undergone further imaging at the age of 3 years. Their reflux had resolved and,

more importantly, no renal scar-

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have many other potentially contributory problems. Research is needed to establish the dose and frequency required to provide thera-
peutic, non-toxic serum concentrations of this drug for babies of all gestations.1

We were surprised by the media interest in our paper and responded to requests for inter-
views accordingly. Unfortunately, we cannot be held responsible for the headlines or tone of the published newspaper reports.

The extent of drug toxicity from unlicensed and off label drug use in neonates is unknown. We know that severe adverse drug reactions in children are more likely to occur with unlicensed and off label treatment than licensed drugs. The scientific study of drug treatment in neonates has been relatively neglected by both doctors and pharmacists in the UK and Europe. However, there are posi-
tive developments: the British Forum for the Use of Medicines in Children and the European Network for Drug Investigation in Children are trying to both encourage and coordinate clinical trials in this area.2

It is clear that many health professionals now accept the need for research in paediatric therapeutics. We are not simply bidding for money but trying to raise the profile of a neglected area of research. Historically, re-
search has been centred on disease in specific acute care areas such as cystic fibrosis, leukaemia, cardiac defects, etc. When seeking funding for research on the extent and risk of unlicensed and off label drug use in children3 we were told by a major children’s charity that they did not consider it an appropriate area for research and that they would not even consider an application for funding. We hope that the studies documenting the extent of unlicensed and offlabel prescribing4 and the conse-
quences of such prescribing5 will convince the Department of Health and the major charities that this is an important area of research, and that the use of drugs in the neonate should be evidence based.

1 de Hoog M, Mouton JW, van den Anker J. The use of aminoglycosides in newborn infants. Pau-
6 Kaddis E, Muenzen J, Tiller G, et al. Recombi-
nant α-iduronidase replacement therapy in mucopolysaccharidosis I. Results of a human clinical trial. J Hum Genet 1998;63(sup-
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7 Iwata S, Sukagawa K, Sasaki T, et al. Mass screening test for mucopolysaccharidosis using the 1,9-dimethylbicyclooctyl blue positive in-

Corrections

Please note that the authors of Gilbert et al (Role of Ureaplasma urealyticum in lung disease of prematurity: 1999;81:F162–7) have noted a discrepancy in the reference list for this article. Reference 2 should read:
2 Todd DA, Jane A, John E. Chronic oxygen dependency in infants born at 24–32 weeks’ gestation: the role of antenatal and neonatal factors. J Paediatr Child Health 1997;33:82–7. From there on all references should be renum-
bered accordingly.

Letters, Book reviews

Editors’ comments

We issue press releases on articles of public interest with the aim of helping journalists understand the material. The press releases are seen in advance by authors who have an opportu-
nity to make changes, and are issued with an embargo date, to avoid media publicity before the Journal’s publication date. However, we have no control over how the media choose to headline this information. The public and the media have access to articles in scientific journals once they are published and if we did not issue press releases we believe there would be every reason to be scope for misinterpretation.

Glycosaminoglycans in neonatal urine

Editor—Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by deficiency of the enzymes catalysing the stepwise degradation of glycosaminoglycans (GAG). Bone marrow transplantation can slow down or reverse some of the features of these diseases. Enzyme replacement (ERT) studies in several animal models of MPS disorders have shown promising results;1 clinical trials of ERT in MPS type I have only recently become possible.2 The clinical symptoms of MPS usually become evident only between the second and third years of life. This therefore argues for early therapeutic intervention before the develop-
ment of irreversible changes.

Quantitative measurement of urinary GAG (glycosaminoglycans) can be used to diagnose MPS. We investigated the change in urine excretion of GAG to use for early diagnosis.

Random urine samples were obtained from 570 neonates on days 2–6 of life. The samples were obtained from 320 boys and 250 girls with birthweights of mean 3137 (SD 374) g and gestational ages of 39.7 (1.1) weeks. Urine specimens were collected from 85 neonates on day 2, 254 on day 3; 92 on day 4; 65 on day 5; and 74 on day 6. The babies had been born after an uneventful pregnancy and delivery and were not known to have any specific clinical abnormalities. Urine samples were also obtained from 1328 infants aged between 1 and 2 months old who had no symptoms of MPS, and of whom 1256 (71.9%) had negative tests for MPS. Urine samples from five MPS patients: type II, 15 days of age, 978 mg GAG/g creatinine; type II, 26 days old, 940 mg GAG/g creatinine; type II, 1 month old, 1177 mg GAG/g creatinine; type III, 1 month old, 1180 mg GAG/g creatinine; type VII, 1 month old, 1205 mg GAG/g creatinine.

The GAG:creatinine ratio in MPS patients was much higher than in normal infants. We conclude that these results might be useful for the early diagnosis of MPS.

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4 Kaddis E, Muenzen J, Tiller G, et al. Recom-
binant α-iduronidase replacement therapy in mucopolysaccharidosis I. Results of a human clinical trial. J Hum Genet 1998;63(sup-
pub):A 23.

Figure 1 Urinary GAG: creatine excretion ratios for normal infants and MPS patients. Circles indicate means; bars SD.