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New Drugs

Non-steroidal analgesic and anti-inflammatory agents

GEORGE NUKI

Population studies suggest that more than 20 million people in the United Kingdom experience some form of "rheumatic complaint" in the course of a year. Eight million consult a general practitioner every year, accounting for 15% of all patients on each practitioner's list and 23% of all consultations. Rightly or (often) wrongly, non-steroidal analgesic anti-inflammatory drugs are prescribed for many of these patients and millions of aspirins, paracetamol, and proprietary compound analgesics are bought over the counter to alleviate headaches, dental pain, and symptoms of all types.

Thirty years ago aspirin and simple analgesics were the only agents available. Today doctors are faced with a bewildering choice of old and new non-steroidal analgesic anti-inflammatory drugs. In the past decade these agents have been developed and marketed faster than any other group of drugs, and the flow of new compounds shows no sign of diminishing. Sadly, the increase in quantity of new preparations available has not been matched by qualitative advances in treatment for patients with rheumatic diseases or by successful radical new approaches to the pharmacological control of pain and inflammation. The proliferation of new agents largely reflects the fact that none is ideal and that the market for new products is large and lucrative. In the main, the newer agents are "me too" molecular variants of older aspirin like drugs. None is appreciably more effective than aspirin in controlling symptoms in patients with inflammatory joint disease, although some are better tolerated and more convenient to take. Rational and clinically useful classification of the newer agents is difficult. Historically, aspirin, phenylbutazone, and indomethacin comprised the first generation of agents, combining moderate efficacy with a high incidence of adverse side effects. During the 1970s a new wave of second generation carboxylic acid

derivatives appeared, which were generally better tolerated but often intrinsically less effective anti-inflammatory agents. In the past three years emphasis has been placed on the added *convenience* and improved *compliance* associated with a third generation of agents with longer duration of action, requiring only daily or twice daily dosing.

To a greater or lesser extent all these agents have analgesic, anti-inflammatory, and antipyretic activity. Among a wide range of direct and indirect effects on cellular metabolism they all inhibit the synthesis of prostaglandins at one or more points in the endoperoxide biosynthetic pathways and desensitise blood vessels to the permeability effects of other mediators of inflammation. This inhibition of prostaglandin synthesis is believed to be the basis of both the anti-inflammatory action of these agents and their common propensity to cause gastrointestinal irritation by inhibiting the cytoprotective effect of prostacyclin on gastric mucosa. Recent research has focused on the possibility that some agents may exert their anti-inflammatory effects by inhibiting leucotriene rather than prostaglandin synthesis. Unfortunately, hopes that these would form a fourth generation of safer more effective agents with fewer gastrointestinal side effects have proved to be premature. Indeed, the withdrawal of benoxaprofen after several cases of fatal cholestatic jaundice has emphasised the potential dangers of many drugs with prolonged half lives in elderly patients with impaired renal function. It has also underlined the need for caution in prescribing any new non-steroidal anti-inflammatory drug.

Chemically these agents are carboxylic acid or enolic acid derivatives of several different classes (table). As a group they are weakly acidic, highly protein bound drugs; in general those with a higher pKa have a longer duration of action.

Salicyclic acids

Aspirin is the oldest and cheapest non-steroidal anti-inflammatory drug. In low doses (300-600 mg) it is an effective analgesic and remains the drug of choice for many sorts of pain.

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At the high doses (3.6-4.2 g/day) required to achieve a clinical anti-inflammatory effect in rheumatoid arthritis up to 50% of patients will not tolerate simple soluble aspirin over prolonged periods because of dyspepsia (nausea, vomiting, and epigastric pain), occult blood loss, or side effects of the central nervous system (tinnitus). Serious gastrointestinal haemorrhage, hepatotoxicity, and aspirin hypersensitivity are more remote risks. Patients with severe allergy to aspirin (urticaria, rhinorrhoea, asthma, or anaphylaxis) may also react to other agents. Children with juvenile chronic arthritis tolerate aspirin (80-100 mg/kg) better than adults, but it is important to watch out for signs of hyperventilation and occasionally to monitor plasma salicylate concentrations (therapeutic range 250-300 mg/l (25-30 mg/100 ml)) if serious metabolic acidosis is to be avoided, as young children do not normally complain of tinnitus.

The problem of dyspepsia may be reduced in adults by giving *aloxiprin* or *glycinated* or *enteric coated* preparations, but only *heavily buffered* preparations such as *Alka-Seltzer* (Miles) are associated with reduced faecal blood loss and these are rapidly excreted by the kidney. *Benorylate* is a paracetamol ester of aspirin that is cleaved to its active constituents in the liver. It is associated with less dyspepsia and blood loss than simple aspirin and may be given in liquid form and in twice daily dosage. *Choline magnesium trisalicylate* is a long acting non-acetylated salicylate that may be better tolerated than aspirin, and *salsalate* is a slowly hydrolysed aspirin ester that is long acting and absorbed only after transit to the small intestine. *Diffunisal* is a non-acetylated, difluorinated salicylate that is marketed as a

simple analgesic but that also has anti-inflammatory effects. There is some evidence to suggest that it has greater potency and better tolerance as well as a longer duration of action than aspirin.

Propionic acids

Although propionic acids are generally weaker anti-inflammatory agents than aspirin, they are widely regarded as the drugs of first choice in the management of patients with inflammatory joint disease because they are the class of non-steroidal anti-inflammatory drugs with the lowest incidence of side effects. Comparative trials of *ibuprofen*, *ketoprofen*, *fenoprofen*, and *naproxen* have shown naproxen to be marginally superior, but individual and unpredictable patient preference for one or another propionic acid is more apparent than consistent differences between the drugs. *Indoprofen* and *tiaprofenic acid* are two recently introduced propionic agents with a similar profile of anti-inflammatory action and side effects. Neither appears to have any special advantages. *Flurbiprofen* is more effective than ibuprofen, but its use in the recommended doses is associated with a higher incidence of gastrointestinal side effects. Ibuprofen is more effective but also causes more gastric irritation when the dose is increased from 1200 mg to 2400 mg daily. *Fenbufen* is a so called prodrug with no anti-inflammatory activity of its own and a low incidence of gastrointestinal side effects. After absorption it is converted in the liver to its active

Comparison of established and newer non-steroidal anti-inflammatory drugs for the treatment of inflammatory joint disease

Approved name	Proprietary name	Dose	Half life (h)	Side effects	Cost (£/28 days)
Carboxylic acids					
Salicylic acids:					
Soluble aspirin	Solprin	600 mg × 6 daily	15 min	Tinnitus, deafness, dyspepsia, gastrointestinal haemorrhage	1.48
Enteric coated aspirin	Disprin				
Slow release aspirin	Nu-Seals	900 mg × 4 daily			5.62
	Levius	1000 mg × 4 daily			2.37
Aloxiprin	Palaprin Forte	1200 mg × 4 daily	9		5.33
Benorylate	Benoral	10 ml (4 g) × 2 daily	1	Better gastrointestinal tolerance	16.78
Diffunisal	Dolobid	500 mg × 2 daily	12		10.10
Salsalate	Disalcid	1.5 g × 2 daily	8		11.52
Choline magnesium trisalicylate	Trilisate	1.5 g × 2 daily	18		13.38
Propionic acids:					
Fenbufen	Lederfen	300 mg in morning 600 mg at night	10	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	13.64
Fenoprofen	Fenopron	600 mg × 4 daily	3	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	16.27
Flurbiprofen	Froben	100 mg × 3 daily	4	Dyspepsia, gastrointestinal haemorrhage, occasional rashes	13.15
Ibuprofen	Brufen	4-800 mg × 4 daily	2	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	6.34-12.68
Indoprofen	Flosint	200 mg × 3 daily	3	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	2.60
Ketoprofen	Alrheumat	100 mg × 2 or × 3 daily	2	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	7.03-10.55
	Orudis	100 mg × 2 or × 3 daily	2		
	Oruvail	100 mg × 2 daily			
Naproxen	Naprosyn	500 mg × 2 daily	12	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	10.96
Tiaprofenic acid	Surgam	200 mg × 3 daily	2	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	13.23
Acetic acids:					
Diclofenac	Voltarol	50 mg × 2 or × 3 daily	2	Dyspepsia, gastrointestinal haemorrhage, headache, dizziness	10.39-15.58
Fenclofenac	Flenac	600 mg × 2 daily	21	Occasional dyspepsia and gastrointestinal haemorrhage; rashes common (25%)	16.21
Indomethacin	Indocid	25-50 mg × 3 daily		Dyspepsia, gastrointestinal ulceration, and haemorrhage	4.84-9.72
	Indocid R	75 mg × 2 daily	4	Dyspepsia, gastrointestinal ulceration, haemorrhage, headache, and dizziness	13.91
	Osmosin	1 tablet × 2 daily			20.16
Sulindac	Clinoril	200 mg × 2 daily	7 (sulphide 18)	Occasional dyspepsia and gastrointestinal haemorrhage, headache, and dizziness	11.5
Tolmetin	Tolectin	400 mg × 4 daily	5	Dyspepsia and gastrointestinal haemorrhage, headache, dizziness	19.30
Fenamates:					
Mefenamic acid	Ponstan Forte	500 mg × 3 daily	4	Diarrhoea, occasional dyspepsia, gastrointestinal haemorrhage, and rashes	7.23
Flufenamic acid	Meralen	200 mg × 3 daily	9		9.24
Enolic acids					
Pyrazolones:					
Azapropazone	Rheumox	600 mg × 2 daily	20	Dyspepsia and gastrointestinal haemorrhage	11.22
Feprazone	Methrazone	200 mg × 3 daily	3	Dyspepsia and gastrointestinal haemorrhage	10.81
Oxyphenbutazone	Tanderil	100 mg × 3 daily	50-100		
				Dyspepsia, gastrointestinal haemorrhage, fluid retention, stomatitis, and bone marrow suppression	2.32
Phenylbutazone	Butazolidin	100 mg × 3 daily	50-100		1.12
	Butacote	100 mg × 3 daily			1.63
Oxicams:					
Piroxicam	Feldene	20 mg daily	38	Occasional dyspepsia, gastrointestinal haemorrhage, and rashes	8.40

metabolite (4-biphenylacetic acid), which has a plasma half life of 10 hours. Although this allows the convenience of daily or twice daily dosing, special care must be taken in patients with renal insufficiency and rashes are more common than with other propionics.

Acetic acids

Indomethacin, *sulindac*, and *tolmetin* are chemically related cyclic acetic acid derivatives. Indomethacin is one of the more effective agents but has a high incidence of gastrointestinal side effects including bleeding and ulceration as well as causing headaches, confusion, or vertigo in about 15% of cases. The side effects involving the central nervous system are dose related, so it is always wise to begin with a small dose (25 mg twice daily) increasing gradually to 25 mg four times daily or 50 mg three times daily. A 50 mg capsule or a 100 mg suppository at night is often helpful in overcoming early morning stiffness in patients with rheumatoid arthritis, while others prefer to use the 75 mg slow release preparation. Most recently, sodium indomethacin trihydrate has been formulated as a controlled release tablet with an osmotically sensitive semipermeable membrane penetrated by a single laser hole. Although there is pharmacokinetic evidence that this results in a more sustained and non-fluctuating drug release profile with a single tablet over 10 hours, improved efficacy and reduction in side effects is still to be proved.

Sulindac is an indene sulphoxide derivative of indomethacin. It is a prodrug that becomes active only after conversion to a sulphone metabolite in the liver. It is much less effective than indomethacin but has good gastric tolerance.

Tolmetin is a pyrolealkanoic acid with a short half life and a profile of side effects that resembles that of indomethacin. In a dose of 400 mg four times daily it is one of the more expensive non-steroidal anti-inflammatory drugs, and it has no special advantages. *Zomepirac sodium* (temporarily withdrawn) is a chemical analogue of tolmetin with notable analgesic potency. Doses of 50 mg are superior to 600 mg aspirin, and a 100 mg dose compares in analgesic effect with 8 mg morphine intramuscularly.

Diclofenac and *fenclofenac* are phenylacetic acid derivatives. *Diclofenac* resembles the propionic acids in its profile of efficacy and gastrointestinal side effects but is currently one of the more expensive agents and has no special advantages. *Fenclofenac* is an effective short acting agent with a low incidence of gastrointestinal side effects but a high incidence (25%) of rashes. Preliminary trials have also shown that response to fenclofenac in patients with rheumatoid arthritis is associated with sustained falls in the erythrocyte sedimentation rate and acute phase proteins, suggesting that it may have a slow acting antirheumatic action as well as conventional short acting non-steroidal anti-inflammatory activity. Further studies are in progress to assess whether this really represents a slowing of disease progression of the type seen with remission inducing drugs such as gold or penicillamine.

Fenamates

Mefenamic and *flufenamic acid* are relatively mild anti-inflammatory drugs with plasma half lives of four and nine hours respectively. Diarrhoea is a special problem with these agents, and renal insufficiency has been reported in elderly people who have become dehydrated as a result of the diarrhoea.

Pyrazalones

Phenylbutazone and *oxyphenbutazone*, which is one of its major metabolites, are two of the oldest and most potent non-steroidal anti-inflammatory drugs but also two of the

potentially most toxic. In addition to dyspepsia, gastric ulceration, and haemorrhage, renal and hepatic damage have been reported and mouth ulcers and skin reactions are not uncommon, ranging from mild erythematous rashes to rare but serious exfoliative dermatitis and toxic epidermal necrolysis. Salt and water retention may be pronounced and should preclude the use of these drugs in the elderly or those with heart disease. Bone marrow suppression is the most serious potential adverse effect of these compounds. Agranulocytosis may be part of a hypersensitivity reaction, usually in the first three months of treatment. Aplastic anaemia usually occurs after more prolonged treatment, is dose related, and is more likely to occur in the elderly. Although bone marrow suppression is rare—occurring only about once in every 3000 patient years of treatment—half of all cases are fatal and these drugs are responsible for more than a third of all drug induced blood dyscrasias in the United Kingdom and from 25 to 50 deaths a year. With so many safer agents available, phenylbutazone and oxyphenbutazone should be used only when symptoms cannot be controlled with other agents.

Azapropazone is free from the risk of bone marrow suppression. Like phenylbutazone it is, however, uricosuric, potentiates the action of warfarin, and gives rise to salt and water retention. In other respects its profile of moderate efficacy and mild gastrointestinal irritation resembles that of the propionic acids.

Feprozone is a non-steroidal anti-inflammatory drug in which a terpene side chain has been added to the basic pyrazolone molecule in the hope that this would invest the drug with antiulcer potential. In practice it is a moderately effective agent with about the usual propensity to cause dyspepsia and gastrointestinal blood loss. It is uricosuric like phenylbutazone but less likely to cause salt and water retention and does not cause bone marrow suppression.

Oxicams

Piroxicam is now the most widely used non-steroidal anti-inflammatory drug world wide. It is a potent anti-inflammatory agent with a plasma half life of about 40 hours, permitting the convenience of daily dosing. The drug is extensively metabolised in the liver and excreted in the urine as glucuronides. Pharmacokinetic studies in the elderly and patients with renal impairment show no evidence of drug accumulation. Gastrointestinal irritation and occasional rashes are the main adverse effects.

Simple analgesics

Analgesics without appreciable anti-inflammatory action include peripherally acting agents such as paracetamol and centrally acting narcotic analgesics such as *dextropropoxyphene*, *dihydrocodeine*, *buprenorphine*, and *pentazocine*. Pentazocine, and combination drugs such as Distalgic (paracetamol and dextropropoxyphene (Dista), are widely and effectively used to manage pain of many kinds, but centrally acting narcotic analgesics are generally ineffective in musculoskeletal pain of all types and are strongly contraindicated as additional analgesics in patients with chronic rheumatic diseases. Non-steroidal anti-inflammatory drugs with analgesic activity are often used as simple analgesics for the relief of headaches, dental pain, dysmenorrhoea, and bone pain as well as musculoskeletal complaints. Examples include *aspirin* (600 mg), *azapropazone* (600 mg), *diflunisal* (500 mg), *fenoprofen* (200-300 mg), *ibuprofen* (400 mg), *indoprofen* (200 mg), *mefenamic acid* (500 mg), *naproxen sodium* (275 mg), and *zomepirac* (100 mg) (temporarily withdrawn). None is appreciably more effective as a simple analgesic, and all the new agents are more expensive than aspirin. As a general principle an agent with a short plasma half life should be chosen for this purpose and those with

especially long duration of action such as fenbufen, piroxicam, and phenylbutazone avoided for use as "on demand" analgesics.

Rheumatoid arthritis

Although the proper use of rest, physiotherapy, local corticosteroid injections, suppressive antirheumatic drugs, aids, appliances, and surgery must be carefully and repeatedly considered in all patients, non-steroidal anti-inflammatory drugs are the mainstay for relieving symptoms in patients with inflammatory arthritis of all types. Few patients fail to derive some relief from pain, stiffness, and swelling, with consequent improvement in joint function, in the active phases of the disease or to a lesser extent in the later stages when inflammation is not obviously apparent. This is despite the modest anti-inflammatory activity of these drugs, their considerable toxic potential, and their inability to alter the fundamental course of the disease.

In formulating guidelines for choosing which agent to use it must be borne in mind that there is no obvious drug of choice for patients with rheumatoid arthritis. Since the variation in response to non-steroidal anti-inflammatory drugs is on the whole greater between patients than between drugs it is often necessary to try several agents before finding one that suits a particular patient best. In doing so it is logical to start with an agent with a low incidence of side effects, such as a propionic acid derivative, and to try one or two of these in succession before moving on to the stronger and potentially more toxic agents. A two week trial is sufficient to assess the efficacy of any of these agents, but it is important to check that the dose and regimen for any individual drug are optimum before moving on to another. In this respect it is probably best for doctors to familiarise themselves with the use of a small selection of agents from different chemical classes. Addition of an evening capsule or suppository of indomethacin to an optimum regimen of a propionic acid may help to overcome the problem of early morning stiffness, but in general combinations of agents are not helpful, tending to augment side effects without any appreciable increase in efficacy. In principle it is better to begin with longer established preparations, for which even the rare adverse effects have been established. In most instances these are also the cheapest.

Suppressive antirheumatic drug treatment with slow acting remission inducing drugs such as gold, penicillamine, or anti-malarials should be considered in patients with rheumatoid arthritis with persistently active symptomatic disease despite three to four months of optimum treatment with non-steroidal anti-inflammatory drugs, particularly if there is evidence of progression of erosions, deformities, or restriction of joint movements.

Gout

Non-steroidal anti-inflammatory agents are the drugs of choice for the treatment of acute gout. Unlike rheumatoid arthritis, acute gout will respond well to any agent if given in adequate dosage early in the course of the attack. Azapropazone, diclofenac, fepazone, indomethacin, ketoprofen, naproxen, phenylbutazone, piroxicam, and sulindac have all been shown to be effective. Non-steroidal anti-inflammatory agents may also be used prophylactically to prevent the development of "break-through" attacks of acute gout during the first few months of hypouricaemic drug treatment with allopurinol, but small doses of colchicine (0.5 mg twice daily) are probably preferable in this instance. Patients with gout should be warned to avoid taking aspirin containing compounds, which in low doses will raise the plasma urate concentration even though they are uricosuric in larger doses. It has recently been established that azapropazone

(600 mg twice daily), which has uricosuric as well as anti-inflammatory properties, may be used as a single agent in treating patients with chronic gouty arthritis provided that renal function is normal.

Osteoarthritis and non-articular rheumatic symptoms

Inflammatory changes are usually mild and secondary, and non-steroidal anti-inflammatory agents are generally less effective than in rheumatoid arthritis or gout. Nevertheless, these agents may be of symptomatic value when pain relief with simple analgesics such as paracetamol is inadequate. Short acting drugs that may be used intermittently on demand are preferable to drugs with a long duration of action, and this is particularly the case in elderly patients with impaired cardiac or renal function. Whenever possible, specific soft tissue lesions such as tennis elbow or supraspinatus tendonitis should be treated with local corticosteroid injection rather than a non-steroidal anti-inflammatory drug.

Dyspepsia and peptic ulceration

All non-steroidal anti-inflammatory drugs that are prostaglandin synthetase inhibitors are essentially contraindicated in patients with active peptic ulceration, but in some circumstances these agents cannot be withheld. In such patients it is wise to treat the ulcer with cimetidine or ranitidine before considering treatment with a prodrug—for example, sulindac or fenbufen, an enteric coated preparation—for example, diclofenac, a relatively weak prostaglandin synthetase inhibitor—for example, low dose ibuprofen, azapropazone, fenclofenac, or a non-steroidal anti-inflammatory drug in suppository form—for example, diclofenac, indomethacin, ketoprofen, naproxen. Dyspepsia and upper gastrointestinal bleeding may, however, follow treatment with such suppositories.

Drug treatment in the elderly

Several special precautions are required with non-steroidal anti-inflammatory drugs in the elderly. It is important to avoid drugs with a high incidence of side effects involving the central nervous system (high dosage aspirin, indomethacin), highly gastrototoxic drugs (high dosage aspirin, indomethacin, phenylbutazone), and drugs that cause fluid retention (high dosage aspirin, phenylbutazone, azopropazone, indomethacin). Although long acting agents improve patient compliance, plasma half lives of drugs excreted by the kidney may be greatly prolonged in elderly people. Piroxicam appears to be safe, and fenbufen may be used in the elderly if renal function is adequate.

Drug treatment in children

Although it is true that children tolerate aspirin at high dosage better than adults, toxic side effects may occur and the need to monitor drug concentrations in young children is a deterrent. Naproxen (5 mg/kg) is an excellent alternative that has the advantage of permitting twice daily dosing and is available as a syrup. Benorylate, ibuprofen, and tolmetin are other examples of newer agents that may be given safely to children.

Pregnancy and lactation

All non-steroidal anti-inflammatory drugs should be avoided throughout pregnancy if possible. There is inadequate information on the potential teratogenicity of the newer agents

during the first trimester and some evidence that prostaglandin synthetase inhibitors given later in pregnancy may be associated with prolongation of labour and premature narrowing of the infant's ductus arteriosus with pulmonary hypertension. Fortunately, pregnancy is commonly associated with disease remission in patients with rheumatoid arthritis, reducing the need for analgesic anti-inflammatory drugs. Aspirin is believed to be reasonably safe if it has to be given, but results of a Finnish study suggest that children born to mothers who received aspirin in the first trimester have an increased risk of oral clefts. Codeine, dextropropoxyphene, flufenamic acid, ibuprofen, ketoprofen, mefenamic acid, paracetamol, and pentazocine may be given safely to lactating mothers, but high dosage aspirin, indomethacin, and phenylbutazone should be avoided.

Drug interactions

Some non-steroidal anti-inflammatory drugs have important interactions with oral anticoagulants with the potential for displacing warfarin from its protein binding sites and inhibiting hepatic metabolism, the synthesis of clotting factors, and platelet aggregation. Aspirin at high dosage, azapropazone, fenoprofen, and phenylbutazone all interfere with coumarin anticoagulant control in practice, and it is wise to monitor the prothrombin time carefully in all patients receiving non-steroidal anti-inflammatory drugs and important to ensure that the drugs are taken regularly rather than intermittently. The acidic highly protein bound agents may also displace oral hypoglycaemics, anticonvulsants, and oral contraceptives from protein binding sites, but these are seldom the cause of serious problems in clinical practice.

To a greater or lesser extent all non-steroidal anti-inflammatory agents may cause some fluid retention, and it has recently been shown that they will antagonise the diuretic and hypotensive effects of thiazides and frusemide. Inhibition of prostaglandin synthesis may also be the cause of the renal medullary ischaemia that is thought to be the initial lesion in analgesic nephropathy and strongly suggests that all non-steroidal anti-inflammatory drugs are potentially capable of causing this important adverse effect.

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Can herpes simplex and herpes genitalis be spread via contact with inanimate objects such as plates, books, towels, and lavatory seats?

Enveloped viruses such as herpes simplex are readily inactivated by environmental factors—for example, exposure to sunlight and the range of ambient temperatures occurring in most households and wards. Although I am not aware of any work carried out to determine the infectivity of herpes simplex after contact with inanimate objects over a varying time interval, respiratory syncytial virus (a virus equally if not more labile than herpes simplex) has been shown to retain infectivity in freshly obtained infant secretions for a considerable time. Thus respiratory syncytial virus was recovered from Formica counter tops for up to six hours after contamination, from rubber gloves for up to one and a half hours, from cloth gowns and paper tissue for 30-45 minutes, and from the skin for up to 20 minutes. Infections could be transferred to the hands by contact with such contaminated surfaces, and in a children's ward there was evidence to suggest that staff were infected by autoinoculation in this way.¹ Herpes simplex virus, therefore, may also survive for sufficiently long to allow the transfer of infectious particles to hands (or other parts of the body) in contact with contaminated surfaces. Attention to such good "housekeeping" measures as disinfecting environmental surfaces—for example, with hypochlorite detergent solution—and ensuring that those caring for patients pay particular attention to good handwashing procedures (or wear gloves) is important in reducing the risks of hospital acquired infection through environmental contamination.—J E BANATVALA, professor of virology, London.

¹ Hall CB, Douglas G, Geiman JM. Possible transmission by fomites of respiratory syncytial virus. *J Infect Dis* 1980;141:98-102.

What are the effects on the fetus of oxygen deprivation during labour?

Because of the difficulty of research in women, much of our knowledge on this subject has been gained from animals. In most species (including the human) the fetus can withstand hypoxia for longer than the adult.¹ Hypoxia has pronounced effects on the fetal cardio-

vascular system, producing changes in the heart rate,² which (though not pathognomonic of hypoxia) form the basis of widely used clinical methods of fetal monitoring. Fetal hypoxia causes acidosis, a steady fall in blood pressure, and a progressive depletion of cardiac glycogen.¹ Shunting² occurs to maintain blood flow to essential organs such as the heart and the brain, and cerebral blood flow increases with preferential shunting to vital areas such as the brain stem.³ In the mature fetus the cerebral cortex is particularly at risk from hypoxia, but in the preterm fetus the periventricular area is the commonest site of hypoxic damage,⁴ owing to the inadequacy of its blood supply. Hypoxia produces metabolic changes in the brain and changes in the fetal electroencephalogram.⁴ Alterations in the composition of the blood have also been described; intrapartum hypoxia appears to stimulate erythropoiesis,⁵ and hypoxia near term alters the development of some clotting factors (including fibrinogen) in the early neonatal period.⁶ Fetuses vary in their susceptibility to hypoxia, and the fetus which has suffered repeated episodes of antepartum hypoxia is less able to withstand further oxygen deprivation during labour.³ Misconceptions about oxygen deprivation are common—for example, cerebral palsy is often attributed to intrapartum anoxia, which is seldom to blame.⁷ The popular belief that brief episodes of fetal hypoxia cause minor degrees of intellectual impairment is also unproved, and cerebral damage is probably an all or none phenomenon.⁷—JAMES OWEN DRIFE, senior lecturer in obstetrics and gynaecology, Leicester.

¹ Dorand RD. Neonatal asphyxia—an approach to physiology and management. *Pediatr Clin North Am* 1977;24:455-61.

² Gimovsky ML, Caritis SN. Diagnosis and management of hypoxic fetal heart rate patterns. *Clin Perinatol* 1982;9:313-24.

³ Ashwal S, Majcher JS, Longo LD. Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia: studies during the posthypoxic recovery period. *Am J Obstet Gynecol* 1981;133:365-72.

⁴ Viniker DA. The fetal EEG (detection of oxygen deprivation). *Br J Hosp Med* 1979;22:504-10.

⁵ D'Sousa SW, Black P, MacFarlane T, Jennison RF, Richards B. Haematological values in cord blood in relation to fetal hypoxia. *Br J Obstet Gynaecol* 1981;88:129-32.

⁶ Kisker CT, Robillard JE, Clarke WR. Blood coagulation changes following hypoxemia in the near-term fetal lamb. *Pediatr Res* 1982;16:732-9.

⁷ Niswander KR. The obstetrician, fetal asphyxia, and cerebral palsy. *Am J Obstet Gynecol* 1979;133:358-61.