as infections, infestations, or other factors related to bird keeping in different countries.

Another potential explanation for the discrepancy is that neither of the two new studies has looked specifically at pigeon keeping, which was the only significant association with lung cancer in the study from Scotland.[5] In Britain at least there is likely to be a substantial difference in the number of birds kept, and consequent degree of exposure, between those keeping pigeons for racing and those who keep one or two birds as indoor domestic pets. It is perhaps still possible that the previously reported associations relate to an underlying effect that is specific to pigeon keeping.

To resolve these uncertainties it would be necessary to repeat these studies yet again in the populations that gave rise to the original observations of an association, taking particular care to deal with confounding effects. However, these two new studies seem to be conclusive in two respects. First, they provide further evidence that, irrespective of any perceived misconception,[13] cigarette smoking remains by far the single strongest and most commonly encountered avoidable cause of lung cancer. Secondly, and importantly for vast numbers of people, they show that keeping domestic pet birds such as budgerigars, canaries, and parrots does not seem to be associated with an increased risk of lung cancer. The question of whether heavier exposure to pigeons carries an increased risk remains unresolved.

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1 Holst PAJ, Brand R, De sigaret en de huisvogel. Verslag van een aantal aspecten van een 10-jarige praktijksurvey naar relaties tussen rookgewoontes, huisierbezit en morbiditeit. *T Soc Gezondheidsz* 1986;**64**:491-7.
2 Holst PAJ. *Gezondheidsrisico's van huisvogels*. Delft: Eburon, 1987.
3 Holst PA, Kromhout D, Brand R. For debate: pet birds as an independent risk factor for lung cancer. *BMJ* 1988;**297**:1319-21.
4 Kohlmeier L, Arminger G, Bartolomeycik S, Bellach B, Rehm J, Thamm M. Pet birds as an independent risk factor for lung cancer: case control study. *BMJ* 1992;**305**:986-9.
5 Gardiner AJS, Forey BA, Lee PN. Avian exposure and bronchogenic carcinoma. *BMJ* 1992;**305**:989-92.
6 Britton JR, Lewis S. Pet birds and lung cancer [editorial]. *BMJ* 1992;**305**:970-1.
7 Kohlmeier L, Bellach B, Thamm M. Pet birds and lung cancer [letter]. *BMJ* 1993;**306**:60.
8 Gardiner A, Lee P. Pet birds and lung cancer [letter]. *BMJ* 1993;**306**:60.
9 Morabia A. Pet birds and lung cancer [letter]. *BMJ* 1993;**306**:61.
10 Rampen FHJ. Pet birds and lung cancer [letter]. *BMJ* 1993;**306**:61.
11 Alavanja MCR, Brownson RC, Berger E, Lubin J, Modigh C. Avian exposure and risk of lung cancer in women in Missouri: population based case-control study. *BMJ* 1996;**313**: 1233-5.
12 Modigh C, Axelsson G, Alavanja M, Andersson L, Rylander R. Pet birds and risk of lung cancer in Sweden: a case control study. *BMJ* 1996;**313**:1236-8.
13 Coggon D. Pet birds and lung cancer [letter]. *BMJ* 1993;**306**:61.

Non-compliance with oral chemotherapy in childhood leukaemia

An overlooked and costly cause of late relapse

In childhood acute lymphoblastic leukaemia, complete remission is usually followed by relapse unless patients receive prolonged outpatient "maintenance" treatment based on daily oral 6-mercaptopurine and weekly methotrexate.[1] When patients relapse unexpectedly some months or years after completing their planned schedule of treatment (as still occurs in 20-30% of patients in Britain), the maintenance component of treatment has probably failed for some reason.

One contributory factor used to be insufficient doses of antimetabolites. Before 1980, four year disease free survival in Britain was less than 50%. Then a more rigid and detailed national protocol was introduced, where maintenance was more aggressively applied and attenuation of the drug dose was not left up to the individual physician. The result was an increase in toxicity accompanied by a 15-20% improvement in long term survival.[2] This experience has persuaded paediatric oncologists in Britain to prescribe the maximum tolerated dose of antimetabolites and to avoid interruptions to treatment wherever possible.

So far, so good. But the story does not end there. It is now becoming increasingly apparent that some children simply do not take the drugs they are prescribed. Based on experience with asthma,[3] tuberculosis,[4] cystic fibrosis,[5] diabetes,[6] and penicillin prophylaxis for sickle cell disease,[7] we know that children often fail to follow important diets or treatment schedules. It is therefore illogical to assume that, just because they have a life threatening disease, young patients with leukaemia will all reliably take pills every day without fail for two years when they (mostly) are in normal health. But despite warnings[8] that is precisely what has been assumed until recently.

The best data on non-compliance come from studies where drug or drug metabolite concentrations have been measured. Several years ago an American study looking at urinary excretion of 17-ketogenic steroid in children supposedly taking prednisone for leukaemia showed that their excretion increased when they were supervised as inpatients.[9] More recently, a study in South Africa measuring urinary excretion of 6-mercaptopurine the morning after a supposed evening dose showed that some patients had no trace of the drug.[10] In Britain we have noted wide variations in the levels of slowly cycling intracellular metabolites of 6-mercaptopurine in some children who are supposedly taking a constant dose.[11] These and other reports[12 13] suggest that 10-30% children fail to take a substantial amount of their prescribed chemotherapy.

It would seem that non-compliance forms a continuum from the occasional lapse to total refusal. The patients most likely to fail are adolescents,[9 11 12] though the problem is by no means confined to this age group. Other risk factors seem to be family size (the smaller the better) and time on treatment (compliance can drift over time).[12] Educational, cultural, and socioeconomic factors are also important.[13]

The evidence that poor compliance matters in terms of disease free survival is circumstantial but persuasive. Firstly, there are widely different outcomes of similar treatment for acute lymphoblastic leukaemia in different countries and communities. Even allowing for possible variations in the incidence of disease subtypes or risk groups, there is a substantial shortfall in the proportion of children achieving long term disease free survival where there is poverty, malnutrition, poor communication between parents and doctors, or low standards of parental education.[14 15] Remission rates may be broadly comparable, but relapse rates are much higher. Many patients default on outpatient care. Persuading some ethnic groups that maintenance treatment is important when the child appears to be "cured" is difficult, and in some countries, 25 to 45% of families fail to attend clinic at all during this phase of treatment.[14]

Then there is other more subtle evidence, even where children are regular clinic attenders and solicitously collect their drugs. Unexpected relapses arise more often in children who tolerate full doses of oral antimetabolites than in those who

develop cytopenias.[16]. Children who receive additional pulses of parenteral vincristine and steroids or "intensive" multiagent inpatient treatment during maintenance are less likely to relapse.[17] Also, children on maintenance treatment who have lower than average concentrations of intracellular metabolites of 6-mercaptopurine and methotrexate are at greater risk of relapse, independently of other prognostic variables.[18]

Non-compliance is not, of course, the only explanation for low metabolite concentrations in regular clinic attenders. Even under controlled conditions there is considerable variability between individuals in accumulation of intracellular metabolites of both mercaptopurine and methotrexate, and this may be genetically determined.[19] So for some children oral antimetabolite treatment will be insufficient because of their constitution. Also the bioavailability of the native drugs depends on, among other things, timing and whether drugs are taken fasting or with food.[20] If, however, antimetabolite doses are gently and systematically titrated to the point where cytopenias occur, physicians' timidity and patients' idiosyncratic constitutional resistance should cease to be powerful influences. Patient compliance then becomes the major consideration. Arguably this is the point we have reached for most patients in Britain.

So how can non-compliance be eliminated? One way is to avoid oral treatment completely and give all drugs parenterally under medical supervision. Though this may have theoretical advantages, the practical and logistical aspects of such a policy make it almost impossible to achieve. Nor does delegating parenteral treatment to the patient or the parents overcome the potential for poor compliance. The only other way is to educate and inform parents and children about the importance of oral treatment and carefully to monitor progress, such as by regular and conspicuous measurement of drug metabolite concentrations.

We don't know how big the problem of non-compliance with maintenance treatment will prove to be, and it will vary in different communities. We believe it probably contributes to a substantial proportion of unexplained late relapses of "standard risk" childhood acute lymphoblastic leukaemia even in developed countries. If so, and if it could be circumvented, maybe long term disease free survival would increase by 10% even where rates of 75% are already being achieved. On this basis, late relapse might be avoided in around 30-40 children each year in Britain alone, and the figure would be much larger in some other countries.

Apart from being a desirable goal at any price, such an achievement would be economically attractive. Outpatient antimetabolite treatment is inexpensive whereas salvage treatment for relapsed acute lymphoblastic leukaemia, still unsuccessful in most patients, is extremely costly. The inexorable trend to more intensive, toxic, and expensive first line treatment protocols might also be slowed down. And on a worldwide scale, anything that simplifies and reduces the cost of treatment will eventually lead to more children receiving potentially curative treatment.

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1 Gale RP, Butturini A. Maintenance chemotherapy and cure of childhood acute lymphoblastic leukaemia. *Lancet* 1991;**338**:1315-8.
2 Eden OB, Lilleyman JS, Richards S, Shaw M, Peto J. Results of Medical Research Council childhood leukaemia trial UKALL VIII. *Br J Haematol* 1991;**78**:187-96.
3 Gibson NA, Ferguson AE, Aitchison TC, Paton JY. Compliance with inhaled asthma medication in preschool children. *Thorax* 1995;**50**:1274-9.
4 Beyers N, Gie RP, Schaaf HS, van Zyl S, Nel ED, Talent JM, *et al.* Delay in the diagnosis, notification and initiation of treatment and compliance in children with tuberculosis. *Tuber Lung Dis* 1994;**75**:260-5.
5 Patterson JM, Budd J, Goetz D, Warwick WJ. Family correlates of a 10-year pulmonary health trend in cystic fibrosis. *Pediatrics* 1993;**91**:383-9.
6 Schmidt LE, Klover RV, Arfken CL, Delamater AM, Hobson D. Compliance with dietary prescriptions in children and adolescents with insulin-dependent diabetes mellitus. *J Am Diet Assoc* 1992;**92**:567-70.
7 Cummins D, Heuschkel R, Davies SC. Penicillin prophylaxis in children with sickle cell disease in Brent. *BMJ* 1991;**302**:989-90.
8 Tebbi CK. Treatment compliance in childhood and adolescence. *Cancer* 1993;**71**:3441-9.
9 Smith SD, Rosen D, Trueworthy RC, Lowman JT. A reliable method for evaluating drug compliance in children with cancer. *Cancer* 1979;**43**:169-73.
10 MacDougall LG, McElligott SE, Ross E, Greeff MC, Poole JE. Pattern of 6-mercaptopurine urinary excretion in children with acute lymphoblastic leukemia: urinary assays as a measure of drug compliance. *Ther Drug Monit* 1992;**14**:371-5.
11 Davies HA, Lennard L, Lilleyman JS. Variable mercaptopurine metabolism in children with leukaemia: a problem of non-compliance? *BMJ* 1993;**306**:1239-40.
12 Tebbi CK, Cummings KM, Zevon MA, Smith L, Richards M, Mauon J. Compliance of pediatric and adolescent cancer patients. *Cancer* 1986;**58**:1179-84.
13 MacDougall LG, Wilson TD, Cohn R, Shuenyane EN, McElligott SE. Compliance with chemotherapy in childhood leukaemia in Africa. *S Afr Med J* 1989;**75**:481-4.
14 Hicsönmez G, Ozsoylu S, Yetgin S, Zamani V, Gurgey A. Poor prognosis of childhood acute lymphoblastic leukaemia. *BMJ* 1983;**286**:1437.
15 Viana MB, Murao M, Ramos G, Oliveira HM, de Carvalho RI, de Bastos M, Colosimo EA, Silvestrini WS. Malnutrition as a prognostic factor in lymphoblastic leukaemia: a multivariate analysis. *Arch Dis Child* 1994;**71**:304-10.
16 Dolan G, Lilleyman J S, Richards SM. Prognostic importance of myelosuppression during maintenance therapy of lymphoblastic leukaemia. *Arch Dis Child* 1989;**64**:1231-4.
17 Chessells JM, Bailey CC, Richards SM. Intensification of treatment and survival in children with lymphoblastic leukaemia: results of Medical Research Council Trial UKALL X. *Lancet* 1995;**345**:143-8.
18 Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet* 1994;**343**:1188-90.
19 Lennard L, Lilleyman JS, Van Loon J, Wienshilboum RM. Genetic variation in response to 6-mercaptopurine for childhood lymphoblastic leukaemia. *Lancet* 1990;**336**:225-9.
20 Pinkerton CR, Welshman SG, Glasgow JFT, Bridges JM. Can food influence the absorption of methotrexate in children with acute lymphoblastic leukaemia? *Lancet* 1980;**ii**:944-6.

Prehospital emergency care

A new faculty and journal are encouraging research and better services

Many of the people who die of trauma, heart attacks, or stroke die within the first hour. Many do not reach hospital. People have thus long recognised the need to improve the emergency services offered to patients before they reach hospital. But research on what happens at that critical time is hard to do. Many questions remain about who should offer the care and how it can best be offered. In an attempt to encourage research into prehospital emergency care and to develop the services offered, the Royal College of Surgeons of Edinburgh has established a multidisciplinary faculty of prehospital care. Now BASICS (British Association for Immediate Care) and the BMJ Publishing Group are launching a new journal—*Pre-hospital Emergency Care Journal.**

BASICS was begun by Ken Easton in 1966 after he had seen serious road accidents poorly managed. It now comprises 1700 doctors around Britain, most of them general practitioners, who are prepared to offer immediate care. Ambulance staff have meanwhile greatly improved their skills. Some ambulance services believe that prehospital care belongs to paramedics,[1] but there is evidence that results are better in a rural setting if a trained general practitioner is called.[2]

Arguments continue over who is the best person to provide care, and research is limited. Defibrillators undoubtedly improve the outcome from cardiac arrest,[3] and first aiders can be trained to use them.[4] The advantages of a paramedic (who can intubate and give drugs) over a technician (who can defi-