All infants jaundiced after 2 weeks of age must have their urine tested for bilirubin and their total and direct bilirubin measured.

If conjugated bilirubin is present the infant should be referred to a paediatrician for urgent investigation.

The doctor should see the stool to determine whether it is yellow or green; if it lacks pigment the infant should be referred to a specialist centre to exclude or treat biliary atresia.

Introducing systematic screening for hepatobiliary disorders has been suggested, as has reducing the age of well baby reviews from 6 to 4 weeks of age. It would allow the identification of infants with hepatobiliary disorders and other conditions that may benefit from earlier diagnosis.

Physiological jaundice almost always clears by 14 days of age except in a very few breast fed infants. In Japan, parents receive written advice on the serious implications of yellow stained urine, pale stools, and jaundice in early infancy. Posters in infant welfare clinics and general practitioners' surgeries reinforce this message. In Japan well baby review is carried out at 4 weeks; other countries should adopt similar measures.

The "Yellow Alert" National Awareness Campaign launched this week is the first serious attempt to tackle the problem in Britain. As well as targeting parents it is aimed at ensuring that all doctors dealing with babies are fully aware of liver disease, its signs, and the need for early intervention.

GORDON A MACKINLAY
Consultant paediatric surgeon

Royal Hospital for Sick Children,
Edinburgh EH9 1LF

1 McClement JW, Howard ER, Mowat AP. Results of surgical treatment for extrahepatic biliary atresia in United Kingdom 1980-2. *BMJ* 1985;290:345-7.
2 Mieli-Vergani G, Howard ER, Portman B, Mowat AP. Late referral for biliary atresia—missed opportunities for effective surgery. *Lancet* 1989;i:421-3.
3 Thomson J. On congenital obliteration of the bile ducts. *Edinburgh Med J* 1891;37:523-31.
4 Kasai M, Suzuki S. A new operation for "non correctable" biliary atresia; hepatic porto-enterostomy. *Shujitsu* 1959;13:733-9.
5 Sokal EM, Veyckemans F, de Ville de Goyet J, Moulin D, van Hoorebeek N, Alberti D, *et al.* Liver transplantation in children less than 1 year of age. *J Pediatr* 1990;117:205-10.
6 De Conti RW, Craver RD, Willis GW, Hill CB, Hayes DH, Arensman RM. Extrahepatic biliary atresia: from diagnosis to liver transplantation. *Paediatr Surg Int* 1992;7:337-40.
7 Ohya T, Miyano T, Kimura K. Indication for portoenterostomy based on 102 patients with Suruga II modication. *J Pediatr Surg* 1990;25:801-4.
8 Hussein M, Howard ER, Mieli-vergani G, Mowat AP. Jaundice at 14 days of age: exclude biliary atresia. *Arch Dis Child* 1991;66:1177-9.

Clozapine: progress in treating refractory schizophrenia

Side effects, but a cost-benefit analysis supports treatment

The rediscovery of the unique properties of clozapine mark an advance in the treatment of acute and chronic schizophrenia. Unlike typical neuroleptics, the relief of symptoms with clozapine is not tightly coupled with unpleasant extrapyramidal side effects and 30% to 50% of patients with symptoms unresponsive to typical neuroleptics improve on clozapine.

Clozapine was synthesised in 1958, and a clinical trial in 1962 found that it was highly effective in chronic schizophrenia.[1] Results from further clinical trials led to its licensing for treatment in over 30 countries. In 1975, however, granulocytopenia occurred in 16 patients in Finland; agranulocytosis developed in 13 of these patients, of whom eight died. Many countries then withdrew clozapine from use.

Its reintroduction, particularly in the United Kingdom and the United States, followed a large trial by Kane and colleagues, which showed that clozapine was more effective than chlorpromazine—both in patients with chronic delusions and hallucinations not fully responsive to standard treatment and in patients with thought disorder and negative symptoms of schizophrenia such as emotional withdrawal, psychomotor retardation, and disorders of affect.[2] The patients had been selected for this trial if they were refractory to high doses of haloperidol. Over six weeks 30% of the patients treated with clozapine improved compared with only 4% of the patients treated with chlorpromazine. Longer trials suggested that up to a half of patients improve after six months' treatment with clozapine.[3] Some patients whose refractory schizophrenia had kept them in hospital for many months responded to clozapine.[3,4] Social functioning also improved in patients who responded to the drug.[5]

Clozapine's actions probably differ from those of typical antipsychotic drugs because of its different effects on central neurotransmitters. The much lower incidence of acute extrapyramidal side effects with clozapine is likely to result from its relatively weak antagonism of striatal dopamine D_2 receptors. Importantly, the side effect of tardive dyskinesia does not seem to occur, even with long term use. This may be explained by the failure of chronic long term clozapine treatment to suppress the release of striatal dopamine, but clozapine's relatively strong blocking effect on serotonin S_2 receptors may be equally important.[6] Patients with low ratios of homovanillic acid to 5-hydroxyindoleacetic acid in their cerebrospinal fluid respond better to clozapine,[7] which is consistent with the hypothesis that what is important for the therapeutic actions of the drug is the balance between dopaminergic and serotoninergic neurotransmitter systems. In particular, compared with typical antipsychotic drugs, clozapine causes a greater antagonism of serotonin S_2 receptors relative to D_2 receptors[6]; the standard neuroleptic drugs are thought to act through blocking D_2 receptors. Clozapine also has a high affinity for D_4 receptors and a relatively high affinity for D_1.[6,8,9] The selective interaction with these different receptors is thought to account for its profile of clinical actions.

Schizophrenic patients most likely to benefit from clozapine are those who have not responded to other antipsychotic drugs and those beginning to show serious parkinsonian side effects or signs of tardive dyskinesia. Some patients respond well to low doses—for example, 50 mg a day.

Sandoz Pharmaceuticals was granted a product licence for clozapine (Clozaril) in Britain in 1989 for use in treatment resistant schizophrenia. Owing to the relatively high risk of blood dyscrasia, the licensing requirements included the stipulation that clozapine must be started only in inpatients and that its use should be restricted to patients registered with the Clozaril Patient Monitoring Service, which provides regular haematological screening to a defined standard. Patients' blood samples need to be sent to the monitoring service at the following times: before the start of treatment with clozapine, weekly during the first 18 weeks of treatment, and fortnightly thereafter. The monitoring service detects early falls in the neutrophil count, and prescriptions for clozapine cannot be issued until the monitoring service has cleared the haematological results. If neutropenia occurs prompt discontinuation of clozapine allows the neutrophil

count to return to an acceptable value, usually within a fortnight. In the first two years since the drug's introduction 2337 patients have received clozapine in Britain. Seventy four of the patients (3·2%) have developed neutropenia induced by clozapine. Of these 74 patients, 11 developed agranulocytosis, of whom one died—a patient who had received clozapine for eight weeks.

Although neutropenia is the most important side effect of clozapine, other clinically important side effects occur in over half of patients. These include sedation in up to one fifth of patients; hypersalivation, which can be severe in up to one fifth of cases; considerable weight gain; electroencephalographic changes in up to a quarter of patients; electrocardiographic changes; and seizures in one in seven patients treated with more than 600 mg a day.[3 10]

The need for regular blood sampling and the drug's side effects probably account in part for the considerable lack of compliance with treatment. (In our experience the rate of non-compliance is between 30% and 50%.) Careful selection of patients for treatment is therefore important.

Partly because of the expense of regularly monitoring blood samples, treatment with clozapine costs about £2000 a year in Britain, which is much higher than for typical antipsychotic drugs. Indeed, this figure may be an underestimate owing to the hidden costs of the time taken for blood tests and to supervise treatment.[11] A cost-benefit analysis has shown, however, that for patients with schizophrenia resistant to treatment clozapine would lead to a net gain of 5·87 years of life with no disability or only mild disability and that the direct costs of using clozapine are £91 less per year than for standard treatment with typical antipsychotic agents when the effects on all health care resources are taken into account.[12] Thus the cost of treatment with clozapine is similar to that of other neuroleptics.[13]

A new generation of neuroleptic drugs is being modelled on the pharmacological profile of clozapine—that is, stronger central serotonin S_2 activity and weaker dopamine D_2 activity than with typical neuroleptics. It is too soon to report on their efficacy in refractory patients.

STEVEN R HIRSCH
Professor of psychiatry
BASANT K PURI
Honorary lecturer

Department of Psychiatry,
Charing Cross and Westminster Medical School,
London W6 8RP

1 McKenna PJ, Bailey PE. The strange story of clozapine. *Br J Psychiatry* 1993;**162**:32-7.
2 Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;**45**:789-96.
3 Naber D, Hippius H. Drug treatment of schizophrenia: current concepts. *Atypical antipsychotics: clinical advantages*. Kyoto: Sandoz, 1990:3-4. (Symposium abstracts.).
4 Lindstrom LH. The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for up to 13 years. *Acta Psychiatr Scand* 1988;77:524-9.
5 Meltzer HY, Burnett S, Bastani B, Ramirez LF. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. *Hospital and Community Psychiatry* 1990;**41**: 892-7.
6 Meltzer HY, Gudelsky GA. Dopaminergic and serotonergic effects of clozapine: implications for a unique profile. *Arzneimittelforschung* 1992;**42**:268-72.
7 Pickar D, Owen RR, Litman RE, Konicki E, Gutierrez R, Rapaport MH. Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. *Arch Gen Psychiatry* 1992;**49**:345-53.
8 Fitton A, Heel RC. Clozapine: a review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs* 1990;**40**:722-47.
9 Meltzer HY. Clinical studies on the mechanism of action of clozapine: the dopamine-serotonin hypothesis of schizophrenia. *Psychopharmacology* 1989;**99**(suppl):S18-27.
10 Alphs LD, Meltzer HY, Bastani B, Ramirez LF. Side effects of clozapine and their management. *Atypical antipsychotics: clinical advantages*. Kyoto: Sandoz, 1990:7-8. (Symposium abstracts.)
11 Healy D. Psychopharmacology and the ethics of resource allocation. *Br J Psychiatry* 1993;**162**:23-9.
12 Davies LM, Drummond MF. Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. *Br J Psychiatry* 1993;**162**:38-42.
13 Bosanquet N, Zajdler A. Psychopharmacology and the ethics of resource allocation. *Br J Psychiatry* 1993;**162**:29-32.

What does London need from its ambulance service?

More thought about how best to improve clinical care

Last November South West Thames Regional Health Authority set up an inquiry into the failure of the London Ambulance Service's computer aided dispatch system and its wider implications for the management of the service.[1] Although the inquiry team's report criticised the pace and manner in which the untested system was implemented, the team was convinced that the service should continue to move towards the orderly introduction of a computer aided dispatch system.[2] Two months ago the London Ambulance Service's management board was dissolved and replaced by a more directly accountable arrangement.[3]

When a 999 call is made to the London Ambulance Service the public has a right to expect a quick response to the call and the quick dispatch of an ambulance. The service, however, deals with 500 000 such calls each year, and under current quality standards[4] no allowance is made for the urgency of the call. Two of the key blanket standards are that 95% of calls should have a response activated within three minutes and that in 95% of cases an ambulance should arrive within 14 minutes. In March the performance figures for the service were 47% and 67% respectively (London Ambulance Service, personal communication).

If we accept that some calls require a faster response than others then we must question these blanket standards. But how do we ensure that the best response is provided effectively and economically? Several possibilities exist.

Firstly, the London Ambulance Service must attempt to limit the number of calls placed on its resources. Although few data have been collected in London, studies in Chester and Birmingham suggest that up to a half of emergency calls are medically unwarranted.[5 6] As the largest emergency ambulance service in Britain, London's service would be ideally placed, with help from central government, to organise and evaluate a campaign to educate the public about the right use of the emergency service.

Secondly, the service should continue to move toward the design and implementation of a computer aided dispatch system that allows the response to be matched to the medical need. Computer technology should greatly enhance this process. After the caller has been reassured that help is on the way, an opportunity exists to provide first aid instructions over the telephone.[7] These elements form the basis of a medical priority dispatch system, which differs from criteria based dispatch systems by using algorithms rather than prompts. Such systems have been used for 15 years in metropolitan areas in the United States[8] and have the benefits of being more structured, requiring little training, being easy to audit, and minimising the stress to the controller. A key function of the system is to prioritise the allocation of ambulance resources to 999 calls for which the response time is crucial to the patient's survival.

The current strategy of the Department of Health is that there should be at least one trained paramedic in every emergency ambulance crew by the end of 1995.[9] Currently,