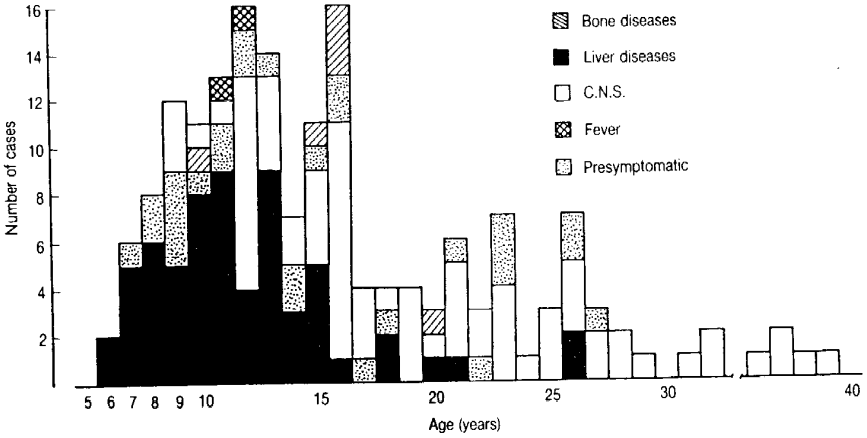

Fig. 1 Distribution by age and presenting symptoms for 172 patients with Wilson's disease.

cytopenia with gangrene of the toes some four years before the onset of tremor.

The picture of the hepatic illness is in no way diagnostic of Wilson's disease; it can be acute, subacute or chronic and is often apparently symptomless almost until the stage of terminal liver failure. Occasionally the illness can be very acute and if there is associated haemolysis the patient may die within a week of the first symptoms. The diagnosis should be considered in any child with unexplained liver disease or with symptomless hepatomegaly or splenomegaly.

The neurological illness, like the hepatic illness, can show a quite remarkable range of signs and symptoms. Occasionally the first symptoms may be a change in personality, attempted suicide or an even more severe psychiatric disturbance. There is a real case for screening all new admissions to psychiatric hospitals in the relevant age group. Perhaps the commonest neurological presentation is slurring of speech with drooling but often there is a subtle deterioration in school performance in an otherwise promising pupil. School teachers seem unable to detect that such a child is in need of help and has not become, in the way one child was described, as being 'surly, untidy, and unco-operative'. The tremor of Wilson's disease is characteristically described as 'batswing' and indeed it may be very wild involving one or more limbs and often being asymmetrical. But Parkinsonian tremor or cerebellar ataxia (pseudosclerosis) are also seen; some patients develop bradykinesia or may even become virtually akinetic and anarthric. Others develop dystonic postures, choreic or ballistic movements or even severe torsion spasms which may be intensely painful. Again the diagnosis of Wilson's disease should be considered in any adolescent or young adult with a neurological syndrome which spares the sensory nervous system. But it must be added it is rare for speech and lip or tongue movements not to be involved in the face of an otherwise advanced neurological lesion.

Probably the best known of the diagnostic markers for Wilson's disease is the Kayser Fleischer corneal ring. This is a granular deposit of copper (probably as copper proteinate) in the deep layer of Descemet's membrane. The usual colour is brown but rarely a very heavy pigment deposit when seen over a brown iris, may appear grey. The pigment is *always* densest (and often only present) in the top crescent of the cornea from 10 to 2 o'clock. It then appears in the lower crescent and these two crescents extend laterally to join and form complete rings which are, therefore, a rather late manifestation of the disease. Corneal pigment is invariably present in the neurological stage and it may be present, but is not always so, in the hepatic or even the presymptomatic stages of the illness. A practised observer can almost always identify the pigment with a hand lens and a well-directed beam of light shone on the cornea obliquely from above. When doubt exists an experienced ophthalmologist should always be asked to conf refute the presence of granular pigment in the cornea wit lamp. Another, less common, occular manifestation is t flower cataract, due to copper deposits in the lenses; it dc impair vision. Though seldom obvious to naked eye insp lens changes can be seen in 5 to 10 per cent of cases under sl examination.

Laboratory diagnosis

In the final resort the diagnosis of Wilson's disease, h strong the clinical evidence, must rest on the identificatio abnormality of copper transport and storage. Unfortunatel atories which do not do such determinations routinely oft duce unreliable or inaccurate results. This is particularly urine copper estimations when there are so many chances tamination of the specimen during collection and handlin false high results are a common finding. The issue is furth plicated by the wide range of biological overlap which i between patients and heterozygotes and between hetero and normals and even, at extremes, between patients and r (Fig. 2).

In view of the difficulty of accurate collection of unc nated 24-hour urine specimens it is advisable first to detern serum copper and caeruloplasmin concentrations. The serum copper ranges from 80 to 135 μg/dl (13 to 21 μmo the caeruloplasmin from 25 to 45 mg/dl. It must be reme that caeruloplasmin is 0.3 per cent copper so that there ca be more 'caeruloplasmin copper' than total plasma copper. many laboratories appear to be unaware of this. In the no total serum copper is usually slightly higher (perhaps 1 than the caeruloplasmin copper and this is the so-called 'f per' presumably bound to albumin and small molecular compounds; ionic copper never exists in the plasma. In disease this accurate relationship between the two copp tions breaks down so that there is always a dispropc amount of 'free copper'. Total copper is thus only mo depressed whilst the caeruloplasmin is usually very low but does, occasionally overlap into the normal range parti there is a clinical picture of chronic active or aggressive h To confuse the issue further other forms of severe liver di not infrequently associated with a true or an apparently lo loplasmin concentration. Caeruloplasmin is most comm mated by its ability to oxidize *p*-phenylene diamine activity) and this oxidase reaction can be inhibited by co accumulating in the plasma of patients with severe live thus giving a low oxidase activity in the presence of a n near normal protein concentration. Alternatively, protei sis may fail in terminal liver disease giving a true low