bloodstream in this group of patients but not in normal controls. This conclusion was also reached by I. Smith (Middlesex Hospital, London), who followed a parallel experimental approach. Once tyramine reaches the circulation, Sandler showed that it will liberate nor-adrenaline from its tissue storage sites; thus secondary amine release is likely to be essential in the train of events leading to migrainous headache, although there may be many triggers to initiate the attack. One such agent, which releases amines from their binding sites and will also precipitate migrainous headache in susceptible subjects, is reserpine, which was discussed by G. Curzon (National Hospital, London).

Reserpine liberates 5-hydroxytryptamine as well as catecholamines from their binding sites. It is therefore particularly relevant that the powerful 5-hydroxytryptamine antagonist, methysergide, is also one of the most potent anti-migraine drugs. J. W. Lance (Sydney) described the loss of platelet 5-hydroxytryptamine during an attack in affected subjects, which is accompanied by an enhanced urinary excretion of its major metabolite, 5-hydroxyindoleacetic acid.

Among other possible biochemical factors in the pathogenesis of migraine are the kinins and a strongly fancied outsider, the prostaglandins, which gives rise to a migraine-like headache when infused into normal subjects. The opinion was expressed that the answer to migraine may lie in the direction of an imbalance in the physiological interactions between the amines, kinins and prostaglandins.

TRANSPLANTS

Detecting Rejection

from a Correspondent

VARIOUS special tests have been advocated for the early detection of rejection of renal allotransplants, but many are non-specific, unsuitable for routine daily use or not readily available. It is hardly surprising that most transplantation units rely on quite simple standard laboratory determinations on blood and urine for early diagnosis. After analysing retrospectively several of these determinations, four members of the urological unit at Hammersmith Hospital and Royal Postgraduate Medical School have found that a decrease in the 24 hour urinary urea and osmolar excretion (which is a measure of solutes in the urine) provides the earliest and most reliable evidence of rejection.

Reporting their findings in the *Lancet* (i, 904; 1969), G. D. Chisholm, A. E. Kulatilake, M. Papadimitriou and R. Shackman describe how they studied—for at least 4 months after operation—twenty consecutive patients who had been given renal allotransplants. During that period, twelve were treated for twenty-three acute rejection episodes; immunosuppressive therapy with azathioprine and prednisone restored kidney function in twenty of the episodes. Laboratory determinations were carried out during six days before and after the first day of treatment of a rejection episode.

Changes in the 24 hour urinary urea and osmolar excretion provided the earliest evidence of a rejection episode and were noted in seventeen and sixteen episodes respectively. Both began to decrease three days before anti-rejection treatment was started, and reverted completely the sixth day after the start

of treatment. The decrease in the volume of urine was also significant (in thirteen out of twenty episodes); the volume returned to the previous level after treatment in ten cases. Although there was a rise of blood urea, an increase of the 24 hour urinary protein and a decrease in the platelet count in eleven of twenty episodes, these were not early features of rejection, and there was reversion of the changes after treatment in eight, nine and sixteen episodes respectively.

Because creatinine clearances were only estimated twice weekly, Chisholm *et al.* say it was not possible to equate the time of a rejection episode with a change in creatinine clearance unless they happened to coincide. In spite of this, in all but one rejection episode there was a significant decrease in creatinine clearance which returned to previous levels after treatment. They consider therefore that creatinine clearance is a reliable index of a rejection episode, and suggest that if the estimation were carried out often enough, a decreased 24 hour creatinine clearance could prove to be one of the earliest signs of rejection.

In addition to these functional changes, diagnosis of rejection can be based on histological findings after renal biopsy. But biopsy, Chisholm *et al.* say, is not usually carried out until functional changes have been observed, and the histological findings do not necessarily correlate with function. They add that whatever methods of detection are used "it seems inevitable that less precise changes will have to be accepted now that more effective methods for matching donor and recipient are being used".

LARGE NUMBERS

Last Exit to Epsilon

from our Mathematical Probability Correspondent

THE most unadorned case of the strong law of large numbers asserts that if (X_i) is a sequence of independent and identically distributed random variables with mean μ and finite variance σ^2 , then as $n \rightarrow \infty$, $Z_n = 1/n \{X_1 + X_2 + \dots + X_n\} \rightarrow \mu$, with probability one. The importance of this theorem is crucial: if it were not true, probability theory would not exist, and no doubt nature would be infinitely more incomprehensible than it already is. It has received such a vast amount of attention that one would have thought that any obvious question that could be asked about the process $\{Z_n\}$ had already been answered or shown to be extremely difficult. So that the reader of "The limiting distribution of the last time $Z_n \geq \epsilon$ ", by Robbins, Siegmund and Wendel (*Proc. US Nat. Acad. Sci.*, **61**; 1968), is likely to be a little surprised that it has not been done before. They give a very explicit solution to a fairly obvious question, and their method of proof, though sophisticated (and elegant), does not indicate that they experienced any difficulties in deriving their solution.

The law of large numbers asserts that for any strictly positive ϵ , no matter how small, the process (Z_n) will eventually enter the interval $(\mu - \epsilon, \mu + \epsilon)$ and thereafter stay inside this interval. Thus there is a positive integer-valued random variable $\tau^* < \infty$ such that $|Z_n - \mu| \geq \epsilon$ if $n = \tau^*$ and $|Z_n - \mu| < \tau^*$ for all $n > \tau^*$, and that, moreover, $Pr\{\tau^* < \infty\} = 1$. It is then an obvious question to ask for the distribution of τ^* —the last time that $|Z_n - \mu| \geq \epsilon$. Clearly this question is