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Laboratory testing for ototoxic effects of drugs

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D'Arcy and Griffin (1972) have highlighted the need for a laboratory test to screen new drugs for ototoxic side-effects, since at present patient deafness is often the first indication of the ototoxicity of a drug.

Simple techniques of possible application to the routine screening of new drugs for ototoxicity are being evaluated. The effect of noise on total body movement of mice and the startle response of mice to an intense sound stimulus have been investigated. The apparatus consisted of a Jiggle Cage (Brittain, 1961) connected through a strain gauge and pre-amplifier to a pen recorder. In initial studies the sound source was an electric bell (sound level 106db).

A score code was devised to quantify the measurements of gross body movement of mice (A2G strain) during a 60 s exposure to noise. This score was taken as an index of hearing. When exposed to noise in this way, at intervals over a period of 5 weeks, the response of a group of 12 mice did not change significantly. Results from 6 other groups of mice agreed.

In chronic tests, in which A2G mice received daily I.P. injections of kanamycin (200 mg/kg) for 8 weeks, there was a significant reduction ($P<0{\cdot}001$) in the response to noise stress with time. However, the response of control mice, receiving saline injections, was also significantly reduced ($P<0{\cdot}001$).

The response of mice receiving kanamycin (1,000 mg/kg) by daily subcutaneous injection fell after 7 weeks to 14% of the original score whereas control mice still showed 67% of their initial response.

In further experiments, the startle response to noise was used to assess hearing acuity after administration of selected drugs. In an acute study, "deafness" was detected in DBA strain mice after I.V. ethacrynic acid (100 mg/kg); the startle response was reduced after 10 min (62·5% of saline treated controls), was minimal at 30 min (27·3%), approached normal at 60 min (90%) and and had returned to control level by 2 h. In similar I.V. studies with frusemide (100 mg/kg), the response fell to 91% (10 min), 58% (30 min), and returned to 74% (60 min) and to a control level by 2 h.

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