counts, or of measuring dementia, from individual variation in respect of threshold for mean plaque count beyond which dementia becomes manifest, or more than one of these factors. It seems unlikely that the accumulation of plaques in large numbers could have been a preterminal phenomenon since several cases dying of carcinomatous metastases had very low plaque counts.

The following tentative conclusions may be drawn from the findings:

(1) Far from plaques being irrelevant for the pathology of old-age mental disorder, the density of plaque formation in the brain proves to be highly correlated with quantitative measures of intellectual and personality deterioration in aged subjects.

(2) The establishment of a valid measure of cerebral damage in one group of organic psychoses opens up the possibility of defining and measuring the psychological defects that show the best correlation with measures of cerebral damage.

(3) Senile dements have a markedly reduced expectation of life[8]. As the brain is an organ with a fixed cell population and such organs have long been known to be particularly liable to the changes of senescence, the facts suggest that senile plaque formation and related processes may also deserve investigation with the aid of more precise techniques than those employed in this study, for their possible relevance to the problems of ageing in man.

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PSYCHOLOGY

Tranquillizers in Pregnancy and Behavioural Effects on the Offspring

In 1963 we published the third[1] in a series of reports[2,3] concerned with the administration of tranquillizers to gravid rats and their postnatal effects on the offspring. The data of this last report[1] indicated that meprobamate and not reserpine or chlorpromazine resulted in significant deficits in learning a Lashley III maze. This report generated much editorial comment[4,5] and additional experimental findings[6,7].

I wish to comment on these last two reports[6,7], not because they failed to replicate our findings but rather because their alterations in procedure implicate important and significant methodological questions concerning this area of research. Kletzkin *et al.*[6] administered meprobamate at a dosage of 20 mg/kg as compared to 60 mg/kg/day reported by Werboff and Kesner[1]. Furthermore, they[6] stated that the drug was injected for four days of gestation on days 5–9, 10–14, or 14–1 (these represent five days). Thus, the total dosage of meprobamate administered was 240 mg/kg in Werboff and Kesner's[1] experiment and either 80 or 100 mg/kg in the report by Kletzkin *et al.*[6]. Their inability to find differences between meprobamate-treated and control offspring in either bodyweight, activity on the inclined plane, activity and emotionality on the open-field, and learning ability on the Lashley III maze could readily be explained by these differences in levels of dosage administered. These discrepancies then suggest the need for more detailed analysis of the dose-response characteristics of pregnant animals to meprobamate administration.

Hoffeld and Webster[7], in a more complete replication, compared the effects of meprobamate, reserpine, chlorpromazine, or water on body-weight, learning a Lashley III maze and a conditioned avoidance problem. The major contention of these authors is that our previous report failed to demonstrate effects related to the stage of pregnancy in which the drugs were administered. Stage-dependent results were found only in neonatal mortality[3]. The fact that no consistent stage-dependent results occurred on several unrelated measures[1-3] of maturation and behaviour requires that a more critical evaluation be made of the methodology of the Hoffeld and Webster[7] report. Two factors are immediately apparent. These authors purchased their animals already pregnant and thus such animals probably experienced severe stress from shipping in the early stages of pregnancy; secondly, the offspring were colony-housed from weaning at 21–80 days of age. During this time, they experienced whatever stresses are concomitant to a populated colony cage, and they did not experience the handling and testing on the battery of behavioural measures used by Werboff *et al.*[2,3]. Thus, the Hoffeld and Webster[7] animals had a variety of other prenatal and postnatal conditions which could easily have masked and altered the effects of the particular drugs administered in pregnancy on the behaviour of the offspring.

Hoffeld and Webster[7] deal specifically and critically with the Lashley III data from the Werboff and Kesner[1] report. It should be pointed out that Hoffeld and Webster[7] misquote these findings[1]: only meprobamate and not reserpine was found to produce learning deficits. Furthermore, Hoffeld and Webster[7] state that a comparison of the absolute values of the trials to criterion measure of control groups in various reports are of special interest. Werboff and Kesner[1] reported that the control group required 9·5 trials to criterion as compared to Hoffeld and Webster's[7] 14·2 trials to criterion. These authors then refer to a previous report of Werboff, Havlena and Sikov[8] in which prenatal irradiation was administered with a combined control group requiring 13·1 trials to criterion. The fact that the data from the control group of this investigation[8] are more in keeping with the data of Hoffeld and Webster[7] is noteworthy. The pregnant animals in this work[8] had to be carted several blocks to be irradiated under a variety of weather conditions. Thus, they may have experienced the same kind of 'shipping' stress received by the Hoffeld and Webster[7] animals, which may explain the differences and similarities between the scores of the various control groups on the Lashley III maze.

In spite of the fact that it is difficult to replicate conditions exactly from one experiment to another, certain important methodological variables have been suggested that may explain the discrepancies noted and that require further experimental elaboration. These are the questions of dose-response characteristics of pregnant animals to various drugs, and the effects of compounding additional prenatal and postnatal stresses on subsequent behavioural development. If these discrepancies lead us to uncover new data and new relations between critical variables, then our efforts would be rewarded.

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