Huxley *et al.*[1], although not necessarily of the same categories as proposed by the latter authors. If, for example, the difference were found in repeated investigations to hold only for the daughters, and not the sons, of the schizophrenic parents, a search for possible physiological advantages would have to take into account sex-related properties. The sex of the affected parent was not found to have a bearing on the survival data either for male or for female offspring.

These data are offered as a tentative, rather than a firm, clue to the problem of selection and schizophrenia. It should be noted that there are possible biases in method of data collection and that carefully selected cohort controls, rather than general population cohorts, are needed. Mortality data on the children of schizophrenic parents in three earlier studies[12,14,15] do not give evidence of a survival advantage—Sobel's data[15] demonstrate a sharply contradictory trend, but they refer only to children ($n = 222$) born to schizophrenic women in mental hospitals presumably during an acute phase of the mother's illness. In the study discussed here, the 213 children born within 3 yr of the parent's first hospitalization had higher death rates than the remainder of the children with earlier and later birth in the parental history.

Recently, it has been argued that discussion of selection, evolution and schizophrenia is premature until the specific genetic aetiology is better understood[5,6]. Admittedly it is awkward to attempt to discuss the problems of selection in an eclectic framework; admittedly, also, it is premature to attempt elegant mathematical formulations in response to negative and positive fitness differentials or to venture beyond the crudest statements with respect to the possible population dynamics of schizophrenia. Nevertheless, selection works in only two ways, and there are a fairly large number of research approaches that are capable not only of testing hypotheses about the selective balance in the recent past but also of contributing to a clearer assessment of the genetic mechanisms and the pathways of gene action in schizophrenia. Further exploration of possible differences in childhood survival between offspring of schizophrenic parents (also siblings of schizophrenic patients) and the non-carriers, for example, could provide the opportunity not only for successful evaluation of the hypothesis of a physiological advantage as a selective force in evolutionary history of schizophrenia, but for the possible clarification of pleiotropic action of the genes involved in schizophrenia. Many of the hypotheses advanced in speculations about selection and schizophrenia have testable bases—the physiological advantage hypothesis certainly does—and there is no reason why argumentation should not give way to research.

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Behavioural Effects of Some 4-Substituted Amphetamines

In previous studies, Smythies *et al.*[1] have developed a behavioural test for animals, predictive of psychotomimetic activity in man. This test is based on a Sidman avoidance schedule and the results are presented in the form of a modified Bovet-Gatti profile. Using this test, Smythies *et al.*[2] tested a series of tri, di and mono-methoxy phenylisopropylamines (amphetamines). Their results indicated that the essential feature of the "hallucinogenic" molecule in the series of compounds tested was the *para*-methoxy group. All compounds lacking this were inactive and compounds with additional groups were variously weaker. *Para*-methoxy amphetamine (PMA) proved to be the most potent hallucinogen tested. With a low dose a typical "low dose hallucinogenic" profile was obtained. With double this dose, bizarre behaviour was induced in both rats tested, and both rats died within a week of being injected with PMA.

Two hypotheses were suggested for the severe prolonged disruption of behaviour produced by PMA: (1) the irreversible inhibition of an enzyme—possible catechol *o*-methyl transferase, and (2) because amphetamine is normally *para*-hydroxylated in the rat, the presence of the *para*-methoxy group may have interfered with this reaction.

In the investigation reported here we examined the effects of three other *para* substituted amphetamines on behaviour: *para*-chloro, *para*-fluoro and *para*-methyl amphetamine. Each compound was tested twice on two animals, once in a concentration of 5 mg/kg and once in a concentration of 10 mg/kg. The animals were highly trained on the discriminated Sidman avoidance schedule used previously[1] (for full details of the parameters of this schedule see this ref.). The compounds were dissolved in isotonic saline and injected intraperitoneally in a volume of 0·5 ml. All drug days were preceded and followed by a control day, on which 0·5 ml. of saline was injected. Each treatment was separated by 14 days of normal training.

Of the three compounds tested the *para*-methyl amphetamine was the least active. In a concentration of 5·0 mg/kg a "low dose stimulant" profile was obtained. With this dose of the other two compounds a "high dose stimulant" profile was obtained. In a concentration of 10·0 mg/kg, *para*-methyl amphetamine gave a "high dose stimulant" profile, while with the chloro and fluoro-amphetamines bar pressing was completely disrupted. Although the animals were able to walk around the experimental chamber quite normally, they did not press the lever. Approximately 10 min after the compounds were administered the animals began taking continuous shocks and had to be removed. When returned to their home cages the animals walked round and round their cages and gave exaggerated startle responses in the absence of external stimuli. All animals injected with 10 mg/kg of either the *para*-chloro or the *para*-fluoro-amphetamine died between 6 and 20 h after being injected. During this period no animal was observed to eat or drink, and no faeces were found in the sawdust under the home cage.

Para-methoxy-amphetamine gives a purely hallucinogenic profile, and so the methyl group alone cannot substitute for the methoxy group. Snyder *et al.*[3] have shown that DOM (2,5 dimethoxy-4-methyl-amphetamine) has properties more akin to amphetamine at low

dosage and properties more akin to a hallucinogen at high dosage. Using the Sidman schedule, we have obtained similar results in rats (our unpublished results). This suggests that the effect of the 4-methyl group can be modified by the 2 and 5-methoxy groups.

The toxicity of the 4-chloro and 4-fluoro derivatives in the rat may be connected with the predominance of the 4-hydroxylation pathway in this species.

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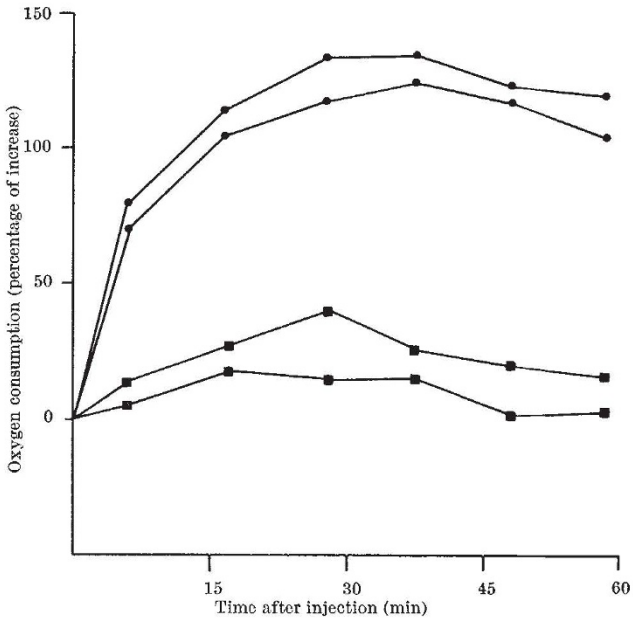

Fig. 1. Effect of noradrenaline (400 μg/kg, given subcutaneously) on the rate of oxygen consumption. ■, Two rats on HP diet; ●, two rats on LP diet.

Metabolic Origins of Thermogenesis induced by Diet

In this communication we discuss the possible origins of dietary induced thermogenesis and attempt to describe the role of energetically non-conservative metabolic pathways in energy homeostasis.

Miller and Payne[1] have demonstrated that rats and pigs possess the capacity to increase heat production in response to increased caloric intakes such that body energy content remains constant. More recently, Miller *et al.*[2,3] have shown that thermogenesis can be similarly induced in adult men. These findings lend support to and have revitalized the concept of "Luxuskonsumption"—the disposal of excess calories by increased heat production—originally proposed by Neumann[4]. The regulation of energy balance by dietary induction of thermogenesis is probably of greater importance in man than the control of intake, and the development of obesity is more likely to be due to a thermogenic defect than to aberrations in appetite[5]. Elucidation of the mechanisms involved in the production of thermic energy will therefore provide an insight into aspects of nutrition ranging from the efficiency of livestock production to the aetiology of obesity.

Thermogenesis induced by diet is similar to cold-induced thermogenesis—in both there is a decrease in feed efficiency caused by increased heat production. For this reason we have examined two systems that have been suggested to be responsible for heat production in cold adaptation. The first is the increased calorigenic response to catecholamines and the second is the increased activity of hepatic L-α-glycerophosphate oxidase.

Rats were maintained on diets similar to those used before[1]. One group was fed a normal stock diet (HP diet) in amounts sufficient to maintain weight, while the other group was fed the same stock diet but diluted with fat, sugar and starch (LP diet) such that the concentration of protein was small enough for the rats to maintain weight when fed freely. Several such experiments were set up at various times and the rats were kept on diets for 15–20 days. Table 1 summarizes the energy balances and body weight changes for one experiment.

The animals on the LP diet ate considerably more than their controls on the HP diet and they produced more heat (690 kcalories more). This amount of energy is equivalent to the total carcass energy content of the rats, and if thermogenesis had not been induced the animals would have been considerably heavier. In fact the weight of the rats remained constant (*S.D.* = 2·12 g). Rats on the other experiments behaved in a similar manner and confirm the findings of Miller and Payne[1].

Towards the end of the experiment the response of oxygen consumption to a standard dose of noradrenaline was measured in fasting animals and in those that were being fed. The results (Table 2) show that the sensitivity to noradrenaline was very much greater in rats in which thermogenesis had been induced. This difference is not the consequence of a delayed response to noradrenaline in those rats on the HP diet (Fig. 1).

At the end of the experiment L-α-glycerophosphate oxidase (EC 1.1.2.1) was assayed polarographically in 20 per cent sucrose homogenates of the liver with methylene blue (E_δ at *p*H 7·0 = 0·010 V) as an electron acceptor. The levels of this enzyme in the livers of the group fed on diet HP were barely detectable, 3·75 mμmoles/h/mg N, but were easily detected in the group fed on diet LP, 150 mμmoles/h/mg N. The assay conditions were essentially those used by Ringer and Singer[6].

Table 1. ENERGY BALANCE RESULTS FOR RATS MAINTAINED ON HP AND LP DIETS FOR 20 DAYS

	HP diet	LP diet
Intake (metabolizable energy)	1,340 kcalories	2,260 kcalories
Carcass energy	450 ,,	680 ,,
(1) Difference in intake	= 920 ,,	
(2) Difference in carcass energy	= 230 ,,	
(3) Difference in heat production (1–2)	= 690 ,,	

Average body weight during 20 days + *S.D.*

HP diet	LP diet
59·4 g ± 1·78	60·4 g ± 2·12

There were ten rats on each diet.

Table 2. EFFECT OF NORADRENALINE ON RATE OF OXYGEN CONSUMPTION*
Mean per cent increase (cf. baseline rate) + *S.E.*

	HP diet	LP diet
Fed	13·1 ± 8·3	62·8 ± 9·0
Fasting	27·5 ± 11·2	97·2 ± 8·6

Noradrenaline (400 μg/kg) was given subcutaneously.
Results represent the average increase measured during 30 min. There were four rats on each diet.
* Rats anaesthetized (30 mg/kg of 'Nembutal' given intraperitoneally).