quinidine depression. Consequently, depletion of catecholamines by reserpine would permit quinidine depression to develop more readily. It may also be argued that reserpine, like quinidine, is a cardiac depressant[7] and that against a background of reserpine-induced depression, the effect of quinidine would be enhanced. However, a direct depressant action by reserpine seems unlikely since the rate and stability of isolated reserpinized hearts did not differ from those of non-reserpinized preparations[8]. Furthermore, unlike quinidine, reserpine pretreatment does not affect the rate of rise or the overshoot of atrial action potentials[9].

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Tumour-inducing Effect of Hydrazine in Mice

AFTER the discovery of the experimental tumour-inducing effect of isonicotinic acid hydrazide[1] several later investigations verified that this compound showed carcinogenic effects in white mice of different inbred strains when administered intraperitoneally or orally over a long period[2–8]. According to Mori *et al.*[9], the carbamyl group is responsible for the cancerogenic effect of isonicotinic acid hydrazide. On the other hand, Biancifiori *et al.*[3] are of the opinion that the hydrazine radical[10] detached from the compound during the metabolic process plays a part in producing tumours. They found in their experiments that the frequency of tumours in mice of *BALB/c* strain caused by isonicotinic acid hydrazide or hydrazine sulphate was very high, while isonicotinic acid alone showed no carcinogenic effect.

In our own experiments we administered hydrazine to white mice having an average weight of 20 g. Hydrazine (NH_2–NH_2) is easily soluble in alcohol and water. It is a bivalent weak base; in a watery solution mono- or bivalent mono- or dihydrate develops. Each injection contained 0·5 mg hydrazine in a 0·5 ml. physiological saline solution. We treated thirty male and thirty female mice intraperitoneally, at the beginning of the experiment on each second day, and later on each third day. 16 injections were given in all over a period of 46 days. Altogether, 400 mg/kg body weight of hydrazine entered the organism of the experimental animals.

Treatment with hydrazine caused the development of focal liver necroses in some of the animals; twenty-six animals died as a result of severe liver damage in the first period of the experiment. The liver-damaging effect of drugs containing the hydrazine radical is a well-known clinical phenomenon[11–13]. Thirteen of the thirty-four mice surviving the treatment developed tumours and myeloid leukaemias between days 100 and 313 reckoned from the beginning of the experiment. The tumours appeared in the mediastinum and showed a local invasion, sometimes provoking metastases in the lungs, pleura and liver. Histologically the tumours proved to be reticular-cell sarcomata. In the cases of myeloid leukaemia, enlargement of the liver, spleen and lymph nodes was to be seen; histologically, there was infiltration of these organs as well as of the bone marrow by immature myeloid cells. As controls, we used sixty white mice of the same pedigree and age; there was only one case of spontaneous thymic lymphoma in them during a year's observation.

The hepatotoxic effect of hydrazine has been known for some time, but there were no communications on its cancerogenic effect. The investigations carried out with isonicotinic acid hydrazide directed attention to this property of hydrazine. The further examination of this compound, which has a very simple chemical structure, may reveal other valuable results. The question is of interest also from the point of view of human pathology, since many other drugs also contain hydrazine radicals, which may liberate hydrazine in the course of metabolism. Thus, a thorough investigation of hydrazine may also give us information about the important question of the cancerogenic effect of drugs.

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Effects of 3,4-Dimethoxyphenylethylamine in Man

FOUR laboratories have reported finding 3,4-dimethoxyphenylethylamine (DMPEA) in the urine of schizophrenic patients[1–4]. Evidence for its occurrence in some patients with this disorder seems well established despite a single negative report[5]. As the compound is quite closely related chemically to mescaline, the latter possessing an additional methoxy-group in the 5-position, it is conceivable that DMPEA might have similar activity in humans.

In initial attempts to determine activity in man, conservative oral doses of the free amine were used, beginning with 50 mg and increasing to a dose of 600 mg, without any appreciable clinical effects being noted. Because of the possibility that the free amine might not be absorbed, a bitartrate salt was prepared, and administered in similar fashion with similar lack of effect at doses up to 800 mg. A similar testing procedure was followed with the hydrochloride salt and then a formal investigation was contrived to compare DMPEA with mescaline and placebo under blind controlled conditions.

Thirteen volunteer subjects were studied. Twelve were recovered psychiatric patients, seven with previous diagnoses of schizophrenic reaction, three with depressive reactions and two with psychoneuroses; the other volunteer had no history of emotional disorder. Three trials were conducted at weekly intervals. In the first trial, DMPEA was given on each occasion, nine of the subjects receiving doses of 500 mg, the last three receiving doses of 1,000 mg. Mescaline and placebo were administered in random order over the next two trials; the dose of mescaline was based on 6 mg/kg, the actual ranges being 405–

635 mg. Clinical effects were assessed by observation, by self-report of patients on the Clyde Mood Scale prior to treatment and at two, four and six hours after, and by completion of a symptom-sign check-list after the effects of drugs had worn off. A 24-h urine sample was collected from each subject after each treatment.

In each instance in which mescaline was administered, a rather typical clinical syndrome ensued, but neither DMPEA nor placebo produced any discernible effects. As judged by the symptom-sign check-list, mescaline evoked nausea, dizziness, blurred vision, tension, weakness, drowsiness, perceptual distortions, depersonalization, difficulty in thinking or expression, rapid flow of thoughts, poor memory, and a dream-like state. Only a few symptoms were reported from the DMPEA and placebo trials and these most commonly were weakness, drowsiness, and sadness, possibly attributable to the enforced inactivity of the testing situation. As reported on the Clyde Mood Scale, mescaline produced significant increases in friendliness, sleepiness, and dizziness, and a significant decrease in clear thinking, over several time-periods in each case. A sporadic significant increase in sleepiness was reported from DMPEA after four hours and an increase in aggressiveness from placebo at the same time. Due to the number of comparisons made, at least one significant change might have been expected to occur by chance from treatment. In addition, of the three treatments only mescaline produced pupillary dilation, increased deep tendon reflexes, unsteadiness and tremors, signs characteristic of increased sympathetic stimulation.

Table 1. RECOVERY OF METABOLITES FROM EIGHT OF THIRTEEN SUBJECTS ADMINISTERED DMPEA AND MESCALINE

	Mean percentage recovered per 24-h urine*		
	As DMPEA	As dimethoxyphenylacetic acid (DMPAA)	Total
After administration of DMPEA	0·37 (σ = 0·20)	77·1 (σ = 18·5)	77·5
	Percentage recovered as mescaline (TMPEA)	Percentage recovered as trimethoxyphenylacetic acid (TMPAA)	Total
After administration of mescaline	23·1 (σ = 8·4)	18·1 (σ = 13·2)	41·2

* Uncorrected for losses from the procedure. Approximate recovery of authentic material added to urine was: DMPEA 74 per cent, TMPEA 73 per cent, DMPAA 98 per cent, TMPAA 98 per cent.

It can be concluded that DMPEA administered orally in doses comparable to those used for mescaline exhibits none of the psychotomimetic effects of the latter drug. This is in contrast to findings from investigations carried out with lower mammals[6,7].

The difference in response of human subjects to mescaline and DMPEA may be related to the relatively complete conversion of DMPEA to its corresponding acid. Mescaline, in contrast, is, in significant amounts, excreted as the unmetabolized amine which is presumably the active form. This can be concluded from the data in Table 1. A detailed report of the metabolic aspect of this investigation is in preparation.

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PATHOLOGY

Teratogenic and Carcinogenic Effects in the Offspring after Single Injection of Ethylnitrosourea to Pregnant Rats

ALKYLNITROSOUREAS give the corresponding alkylating diazoalkanes on heterolysis, and are potent carcinogens, selectively producing malignant tumours in the brain[1] and peripheral nerves[2] of rats. As might be expected, methylnitrosourea is also mutagenic as in *Saccharomyces cerevisiae*[3] and is teratogenic in rats[4]. In teratogenesis investigations the embryos are generally killed and examined immediately after Caesarean delivery. If, however, only slight teratogenic effects are produced to allow the offspring to survive, cancer may also develop later on.

Ethylnitrosourea (ENU; melting point, 103° C) has been used in our experiments on rats of our inbred strain *BD* IX (*CPAH*, agouti). Using intravenous injection, the *L.D.* 50 is 240 mg/kg. At the fifteenth day of pregnancy, three rats were injected with 80 mg ENU/kg bodyweight. Twenty-one young rats were born. All showed malformations of the paws, as shown in Fig. 1. Two of these three litters were lost after 5 days due to agalacty of the mother rats. Five rats of the remaining litter survived and matured under artificial feeding. At the age of 160 days, three of them died with the symptoms of intracranial pressure. Autopsy revealed extensive tumours of the trigeminal nerve (Fig. 2), histologically classified as malignant neurinomata. Additional tumours were observed in two of these rats; one was a polymorphic cell glioma in the right frontal lobe, and the other was a very malignant neurinoma of the left brachial plexus. This was sucessfully transplanted to young *BD* IX rats.

The fourth animal developed paralysis of the left foreleg and the right hind limb. At the age of 165 days it

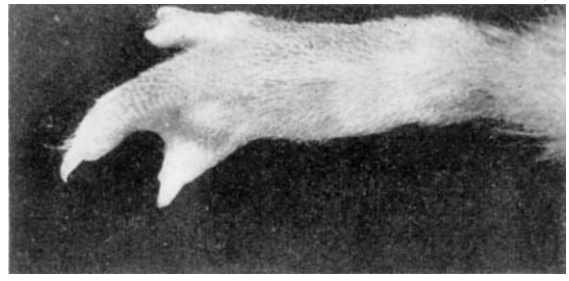

Fig. 1. Oligodactylia and syndactylia in a rat, induced by a single injection of 80 mg ethylnitrosourea per kg at the fifteenth day of pregnancy. (×2·5)

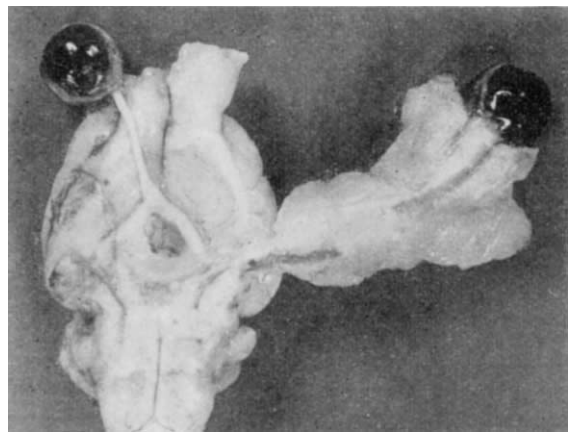

Fig. 2. Malignant neurinoma of the left trigeminal nerve with exophthalmia and rupture of the optic nerve. Ethylnitrosourea, 80 mg/kg, fifteenth day of pregnancy. (×2·5)