SUSCEPTIBILITY TO METHYLPENTYNOL: PERSONALITY AND OTHER VARIABLES

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SUSCEPTIBILITY to drugs is a biological variable, and Clark (1933a) remarks that for organisms sufficiently large to permit measurement of individual dosage, the curves relating dose and incidence of effect are sigmoid and can be assumed to express the individual variation of the population. Some of the variables determining drug response include age, sex and body weight (Goodman and Gilman, 1955). Although a relation between personality and drug response has always been alleged, Kennedy (1957) alluded to the lack of work in this field.

Eysenck (1957a) cogitated this problem. He quotes McDougall (1929): "I have observed in a number of cases that the marked extraverted personality is very susceptible to the influence of alcohol. The introvert, on the other hand, is much more resistant to alcohol." This is casting the net wider, embracing the feasibility of subjective and objective changes to the drug response being determined by personality.

Methylpentynol ("Oblivon") is an unsaturated tertiary alcohol, and the phenomena found during adverse response to the substance have been portrayed (May and Ebaugh, 1953; Marley, 1955; Marley and Chambers, 1956). This paper analyses the significance of a number of factors, including personality, conceivably contributing to methylpentynol susceptibility.

METHODS

Fifty-four subjects were first investigated (24 males, 30 females) aged 18–60 years with a weight range of 47·3–126·4 Kg. (Group 1). Of these, 36 individuals (14 males, 22 females) suffered from neurotic or psychosomatic disorders. The remainder (10 males, 8 females) were volunteers with no psychiatric history. Patients with factors known to alter response to drugs (drug addiction, hepatic or renal impairment, previous brain injury) were excluded. Methylpentynol was incriminated as hepatotoxic by Schaffarzick and Brown (1952) but experience with methylpentynol carbamate (Bartholomew *et al.*, 1959), a drug 3–4 times more potent than methylpentynol, makes it evident that, for the five days methylpentynol was prescribed, no abnormality

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of liver function was likely. This is important, as the drug is excreted as a glucuronide (Perlman *et al.*, 1953) and impaired liver function might result in accumulation of the substance. The contribution of other factors likely to influence response to drugs, namely age, body weight and sex, are considered under Results. As anaemia prolongs the action of narcotics (Dundee, 1952) the possible relation between haemoglobin levels and susceptibility to methylpentynol was considered. Sedated basal metabolic rates were determined for a few individuals prior to commencing methylpentynol to exclude any connection between susceptibility to the drug and metabolic rate.

To tackle the problem of personality and drug susceptibility, use was made of tests elaborated by Eysenck (1953, 1956, 1957b). These included a questionnaire and apparatus to determine Kinaesthetic After-Effect and Reminiscence Effect, measurements alleged to objectify certain aspects of personality. Eysenck conceives of at least two personality dimensions, "Neuroticism-Normality" (N-N) and "Extraversion-Introversion" (E-I), each a continuum and orthogonal to one another.

The questionnaire, Maudsley Personality Inventory (MPI), has been developed by Eysenck from the Guilford questionnaires (Guilford and Guilford, 1934, 1936, 1939a, b) and from the Maudsley Medical Questionnaire. It consists of 80 items, 24 related to N-N, 24 to E-I and the remaining 32 being concerned with a lie scale or included as "spares". In this study only the 48 items related to the two personality dimensions were utilized. Three responses are possible. Prior to the present investigation Bartholomew (1955) tested 200 males and 200 females with this questionnaire, scoring an answer in conformity with the key as 1, that not in conformity as 0, and an answer expressing uncertainty as a $\frac{1}{2}$. He found the mean scores for the combined sexes on the N-N scale to be 9·12 (S.D. 5·16) and that for the E-I scale to be 11·26 (S.D. 4·64) with little discrepancy between the mean scores for the sexes. To be certain the questionnaire had predictive reliability, a test-retest correlation over a period of a year was determined and found to be satisfactory (Bartholomew and Marley, 1959).

The Kinaesthetic After-Effect (KAE), which is alleged to correlate with extraversion, was determined by the apparatus and method advocated by Eysenck (1955). From this test three scores (KAE 1, 2 and 3) were obtained.

The Pursuit Rotor has also been described by Eysenck (1956). The score derived with it is designated the Reminiscence Effect. This score is alleged to correlate with extraversion.

Each of the 54 individuals was prescribed 0·5 g. of methylpentynol q.d.s. for 5 days, a base line of individual reaction being obtained by the prior administration, for the same period, of an identical number of inert capsules, the tests being performed in the above order for all subjects during the control period. This was essential, as Franks and Laverty (1955) demonstrated that another central depressant (amylobarbitone sodium) increases extraversion scores measured on the Guilford R scale.

The clinical response to methylpentynol was graded into Nil, Minimal and Maximal toxic categories (Marley and Bartholomew, 1958). The prototypes of clinical response to methylpentynol are briefly portrayed. A maximal toxic reaction (Clinical Grading 3) was deemed present if it included a majority of the following: dilated pupils reacting sluggishly to all stimuli, sustained nystagmus on conjugate lateral gaze, diplopia, ptosis, loss of tone in the facial musculature, dysarthria and a fine tremor of the protruded tongue. A cerebellar type of ataxia might be found in the limbs or an admixture of this with posterior

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column type of ataxy and a positive Romberg sign. Alterations in the mental state included mood disturbance and impairment of attention, concentration and abstract thought. A minimal toxic reaction (Clinical Grading 2) was epitomized by little more than nystagmus on conjugate lateral gaze and perhaps slight unsteadiness of gait or drowsiness. Mood alterations were also evident. The designation of nil toxicity (Clinical Grading 1) is self explanatory.

Finally, one year after the completion of the main investigation, 15 of the original 54 subjects were retested for susceptibility to methylpentynol. At the same time, a further 40 subjects ("Normals" and patients with neurotic and psychosomatic illnesses) were prescribed 0·5 g. q.d.s. of methylpentynol for 5 days, and the relation of personality (as assessed on the M.P.I.) to susceptibility to the drug ascertained (Group 2).

Results

Of the 54 subjects (Group 1) 17 developed a maximal toxic picture, 15 were minimally affected and the remainder were unaffected by the 5-day regime of methylpentynol (Fig. 1).

The possible relation of somatic and personality variables to methylpentynol susceptibility is now examined.

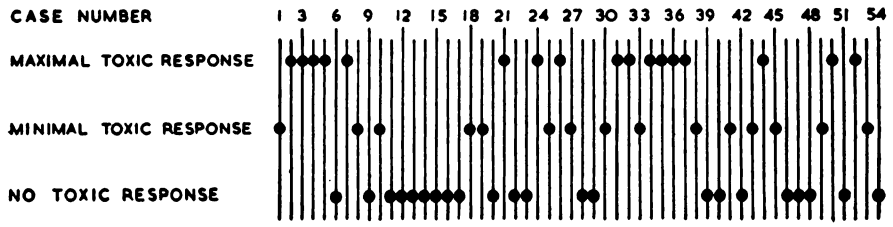

Fig. 1.—Categories of response to methylpentynol in 54 subjects.

Somatic Variables and Susceptibility to Methylpentynol

1. *Age*. The age distribution of the combined sexes and the Clinical Gradings for response to methylpentynol are presented (Table I). No statistically significant correlation was found between age and the likelihood of developing toxic phenomena with the drug ($\chi^2=3{\cdot}42$; $p>0{\cdot}05$; $df=2$).

Table I

Relation of Age for the Combined Sexes (Group I) to Response to Methylpentynol

Clinical Grading	N	Age in Years 0–25	26–35	36–60
1	22	8	6	8
2	15	3	8	4
3	17	7	5	5

2. *Body Weight*. The mean weight in pounds, range and standard deviation for the three Clinical Gradings are depicted in Table II. It was found on analysis

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TABLE II

Relation of the Mean, Range and Standard Deviation of Body Weight to Response to Methylpentynol (Group 1)

Clinical Grading	Weight in Pounds			
	N	Mean	Range	Standard Deviation
1	22	147·2	104–278	34·2
2	15	137·6	106–212	31·3
3	17	146·0	108–209	25·6

of variance that there is no statistically significant difference between mean body weight for the three groups of subjects ($F=0·44$) despite their dissimilar susceptibility to the drug, thus precluding any relation between body weight and susceptibility to methylpentynol.

Source of Variation	df	Sum of Squares	Mean Square	V.R.	p
Between samples	2	913·8	456·9	0·44	>0·05
Residual	51	51938·2	1036·3		
Total	53	52852·0			

3. *Sex*. The data in respect of the sex distribution for the Clinical Gradings of response to methylpentynol are shown in Table III. There is no significant

TABLE III

Relation of Sex Distribution to Response to Methylpentynol (Group 1)

Sex	Clinical Grading		
	1	2	3
Male	10	5	9
Female	12	10	8

correlation between sex and liability to develop toxic signs with methylpentynol ($\chi^2=1·31$; $p>0·05$).

4. *Haemoglobin*. The mean haemoglobin values (grams per cent.) with the range and standard deviation for the three Clinical Gradings are presented in Table IV. The number of subjects to which this Table refers is 33. A two-way

TABLE IV

Relation of the Mean, Range and Standard Deviation for Haemoglobin Level to Response to Methylpentynol for 33 Subjects of Group 1

Clinical Grading	Haemoglobin Values (G. per cent)			
	N	Mean	Range	Standard Deviation
1	9	13·3	10·3–15·6	1·45
2	12	12·7	10·1–15·3	1·76
3	12	13·1	9·3–15·3	1·48

analysis of variance was performed. The finding of a variance ratio of 0·31 confirms that there is no statistically significant difference between the mean haemoglobin values for the three gradings and thus no relation between susceptibility to the drug and haemoglobin level.

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Source of Variation	df	Sum of Squares	Mean Square	V.R.	p
Between samples	2	1·61	0·85	0·31	>0·05
Residual	30	77·95	2·59		
Total	32	79·56			

5. *Hepatic and Renal Function.* As indicated under Methods, subjects with a history of hepatic or renal disease or damage were excluded from the group. It has already been stipulated that abnormality of hepatic function could not be attributed to the effect of the drug itself and routine tests of renal function showed no change during the drug administration.

6. *Sedated Basal Metabolic Rate.* A sedated basal metabolic rate was obtained for 8 patients prior to commencing the drug (Cases 24–27, 32, 33, 35 and 36). The results ranged between −6 and +10 per cent. and there was no relation to susceptibility to methylpentynol.

Personality Variables and Susceptibility to Methylpentynol

The distribution of extraversion (as measured on the M.P.I.) for the 54 subjects is shown in Figure 2. The mean E score from the raw data was 12·28 (S.D. 5·26) which is only slightly greater than that for the standardization series.

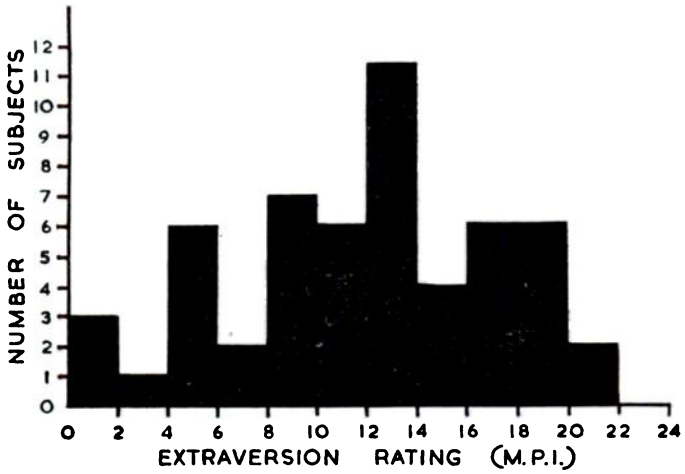

FIG. 2.—Histogram for distribution of the individual raw extraversion scores derived from the Maudsley Personality Inventory (54 subjects).

The distribution of neuroticism (as measured on the M.P.I.) for the 54 subjects is shown in Figure 3. The mean N score from the raw data was 14·85 (S.D. 5·79) as compared with a mean N score of 9·12 for the standardization series. The high mean N score obviously derived from the inclusion of patients with neurotic illnesses. (As the N distribution is skewed, the possibility that transformation of the data might assist in their interpretation was excluded by employing the recommendations of Davies (1954). This involves, for the three gradings of susceptibility to methylpentynol, plotting the standard deviations of the three N scores against their three mean N scores, their variances against

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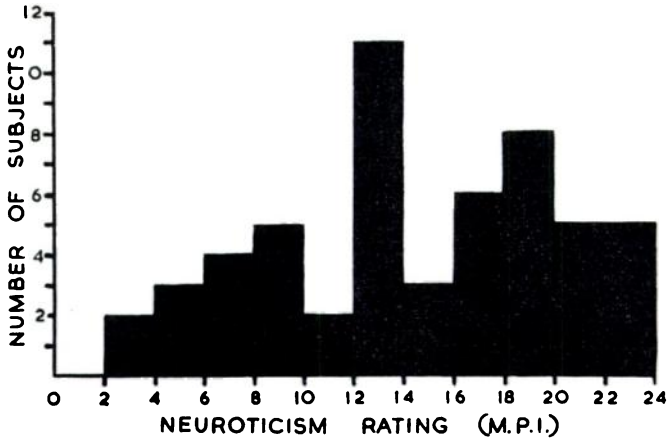

FIG. 3.—Histogram for distribution of the individual raw neuroticism scores derived from the Maudsley Personality Inventory (54 subjects).

the mean N scores, and their standard deviations against the squared mean N scores. The resultant parameters all departed slightly, but almost identically, from linearity and so no transformation was undertaken.)

It was also essential that the dimensions of E-I and N-N, which are theoretically orthogonal one to the other, were in fact so. As the coefficient of correlation between E and N was found to be $-0{\cdot}432$, to make the two dimensions independent of one another, two correction factors were applied to the raw data. That for the corrected E scores (Ec) was $Ec = Eo\text{-}b(No\text{-}\bar{N})$ and that for the corrected N scores (Nc) being $Nc = No\text{-}b(Eo\text{-}\bar{E})$. The corrected E mean score was now found to be 12·29 (S.D. 4·41) and the corrected mean N score 14·86 (S.D. 5·25). Thus while the mean scores for both raw and corrected data remain virtually identical, the scatter of the distribution is reduced following correction. By making certain that E and N parameters were independent, the apparent separate contribution of each of these to methylpentynol susceptibility could be ascertained. The response to the drug in terms of both the corrected and uncorrected E and N scores is now considered.

Extraversion and Neuroticism. The liability to develop toxic phenomena with methylpentynol in relation to the two personality dimensions E-I and N-N is depicted in Figure 4, for which neither E nor N scores have been corrected. The incidence of maximal toxic gradings is commonest for those individuals with high N scores and low E scores. These findings were substantiated by further analysis of the raw data. An evaluation of the association between susceptibility to the drug and each of the two personality dimensions will now be considered.

Extraversion. The distribution of the three Clinical Gradings for response to methylpentynol, the corrected E score being categorized into upper (12·5–24·0) and lower (0·0–12·49) levels, is set out in Table V. Chi-squared was found to be 7·59 which is significant at the 5 per cent. level (d.f. = 2).

TABLE V

Relation of the Individual Response to Methylpentynol to an Extraversion Rating in the Upper or Lower Halves of that Continuum (Group I)

Extraversion Rating	Clinical Grading 1	2	3
0·0–12·49	9	5	13
12·5–24·0	13	10	4

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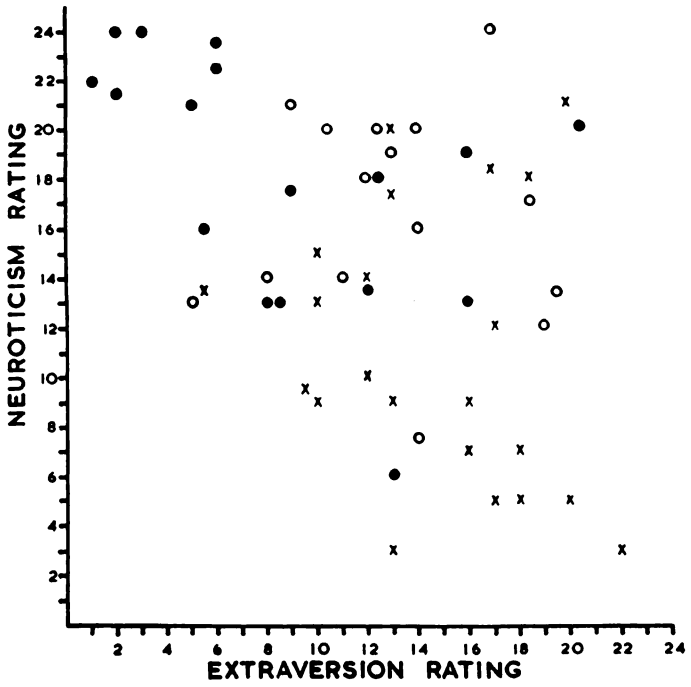

FIG. 4.—Scatter diagram of individual raw scores for extraversion and neuroticism in relation to response to methylpentynol of 54 subjects.

● ≡ Clinical Grading 3 or maximal toxicity.
O ≡ Clinical Grading 2 or minimal toxicity.
X ≡ Clinical Grading 1 or normal response.

(χ^2 for the uncorrected data was 6·12; $p > 0·05$.) Both figures suggest an association between susceptibility to methylpentynol and E-I as measured on the M.P.I. However, as the value for chi-squared is just statistically significant, the data were rearranged into a 2×2 contingency table and assessed using an arc sine transformation (Table VI). There was no significant difference between the proportion of individuals (18 out of 32 and 9 out of 22) falling into the lower half of the E-I dimension (Critical Ratio = 0·78; $p > 0·04$). This combined with the fact that equal numbers of individuals in the upper E range fell into the susceptible and non-susceptible groups, suggests that any relation between the E-I continuum and susceptibility to methylpentynol is of equivocal importance.

TABLE VI

Relation of a Twofold Grouping of the Individual Responses to Methylpentynol to an Extraversion Rating in the Upper or Lower Halves of that Continuum (Group I)

Extraversion Rating	Clinical Grading 1	Clinical Grading 2 and 3
0·0–12·49	9	18
12·5–24·0	13	14

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Neuroticism. The distribution of the three Clinical Gradings for response to the drug in terms of the corrected N score, categorized into upper (12·50–26·24) and lower (0·0–12·49) levels, is set out in Table VII. The results

TABLE VII

Relation of the Individual Responses to Methylpentynol to a Neuroticism Rating in the Upper or Lower Portions of that Continuum (Group 1)

Neuroticism Rating	Clinical Grading 1	2	3
0·0–12·49	14	3	3
12·5–26·24	8	12	14

were assessed by determining χ^2, a highly significant value of 11·47 being obtained; p 0·01, d.f.=2. (The value of χ^2 for the raw N scores was 15·66; p>0·001.) Both results suggest a very definite relation between high N scores and a liability to develop toxic features with methylpentynol. Again to exclude possibility of bias, the information was evaluated using an arc sine transformation; the data is set out in Table VIII. A highly significant difference was

TABLE VIII

Relation of a Twofold Grouping of the Individual Responses to Methylpentynol to a Neuroticism Rating in the Upper or Lower Portions of that Continuum (Group 1)

Neuroticism Rating	Clinical Grading 1	2 and 3
0·0–12·49	14	6
12·5–26·24	8	26

noted between the proportion of individuals falling into the susceptible and non-susceptible groups in terms of corrected N scores (Critical Ratio=3·44; p>0·01). These findings confirm the association between high N scores and susceptibility to methylpentynol.

Kinaesthetic After-Effect

Only KAE(2) correlated significantly with E as measured on the M.P.I. (r=+0·368; p>0·05). The data relating to KAE(2) and the gradings of susceptibility to methylpentynol are presented in Table IX. No association

TABLE IX

Relation of a Twofold Grouping of the Individual Responses to Methylpentynol to Scores of Kinaesthetic After Effect (2) (Group 1)

Kinaesthetic After Effect (2) Rating	Clinical Grading 1	2 and 3
+98– +3	9	14
+2–−92	8	13

between them was found (χ^2=0·003, Yates correction being applied). Contingency tables of KAE(1) and (3) are not included, as there was no association between them and susceptibility to methylpentynol.

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Pursuit Rotor. No significant correlation between pursuit rotor scores and uncorrected E values was found ($r = +0 \cdot 141$; $p > 0 \cdot 05$) nor was there a significant relation between these and susceptibility to methylpentynol.

Personality and Specific Symptomatology. Hitherto, the relation of the drug response and personality has been confined to relating the three Clinical Gradings to results of personality tests. The possibility of an association between personality (measured on the M.P.I.) and specific symptomatology is now contemplated.

TABLE X

Specific Symptomatology and Mean Personality Ratings for E and N (all Scores are Uncorrected) for Group 1

	n	Mean E Score	Range	Mean N Score	Range
Total group	54	12·28		14·85	
Behaviour:					
Overactivity	5	11·4	8·5–17·0	15·6	9·0–21·0
Aggressive	6	15·3	8·0–20·5	16·8	12·0–24·0
Mood:					
Elation and euphoria	14	14·1	8·5–22·0	14·0	3·0–21·0
Depression and irritability	23	11·6	2·0–20·5	16·8	6·0–24·0
Illusions and hallucinations	4	10·2	3·0–17·0	22·5	18·0–21·0
Disorders body image and allied states	10	8·9	2·0–19·0	16·6	6·0–24·0
Disordered subjective time experience	20	11·4	2·0–19·5	17·1	3·0–24·0

The material in Table X is comprised of uncorrected E and N scores, these differing little from the corrected E and N values. Little emerges, presumably because of the few individuals involved. The mean E and N uncorrected scores for subjects with affective changes deviates little from that of the group as a whole, patients with disorders of body image or allied phenomena tended toward introversion, whereas individuals displaying aggression while receiving the drug proved to have a mean uncorrected E score above that of the group.

Personality and Prediction of Susceptibility. An anterospective prediction regarding whether the subject would prove susceptible to methylpentynol was made for 29 patients from a knowledge of their raw N scores on the M.P.I. The prediction proved correct in 24 instances. Inevitably, a number of these predictions had to be made for individuals with uncorrected N scores of 13 and 14 which is approximately that of the mean raw N score for the group. In these subjects, factors such as clinical impression and diagnosis might have biased the predictions. Therefore a retrospective prediction was made that subjects with a raw N score greater than 15 would have manifested susceptibility to the drug. Of the 27 individuals so rated, the prediction proved correct for 21.

Susceptibility to Methylpentynol and Clinical Diagnosis. The distribution of the clinical ratings for response to methylpentynol and diagnosis are depicted in Table XI. It can be seen that the bulk of individuals considered normal

TABLE XI

Relation of Response to Methylpentynol and Diagnosis in Group 1

Diagnosis	N	Clinical Grading 1	2	3
Anxiety state	6	1	2	3
Obsessional state	1	0	0	1
Mixed neurotic reaction	22	3	10	9
Conversion hysteria	1	0	0	1
Psychopathic personality	6	3	1	2
Normal	18	15	2	1

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showed no adverse effect, while the majority of subjects with mixed neurotic illnesses developed toxic manifestations.

Retest of Response to Methylpentynol in 15 Subjects After a Lapse of 1 Year. The drug in a dose of 0·5 g. q.d.s. for 5 days was given to subjects 5, 6, 11, 12, 15, 16, 24–26, 28, 30, 31, 33, 36 and 52 one year after the completion of the original investigation. An identical response was found in all but subject 12 (Clinical Grading 2 instead of 1) and subject 30 (Clinical Grading 3 instead of 2).

The Relation of Personality to Susceptibility to Methylpentynol in a Further 40 Subjects

These 40 individuals (Group 2) were administered 0·5 g. q.d.s. of methylpentynol for 5 days. To ensure that the investigation was quite blind, the M.P.I. was given and scored by a third person, the results being available to the authors only after a final grading of the patient's drug response. The mean E score for this group was 12·47 and the mean N score 14·11. The mean E and N scores for subjects in the three categories of response to methylpentynol are shown in Table XII. It can be seen that increasing severity of toxic response to the drug was paralleled by an increasing N score.

TABLE XII

Relation of Mean E and N Scores to Response to Methylpentynol in Group 2

Clinical Grading	Mean E Score	Mean N Score
1	14·09	11·41
2	11·55	14·55
3	11·29	16·89

The distribution of the susceptible and non-susceptible groups in terms of N scores categorized into upper (13–24) and lower (0–12) levels is set out in Table XIII. The value for χ^2 was 6·257 (d.f.=1) which is significant; $p<0·02$.

TABLE XIII

Relation of a Twofold Grouping of the Individual Response to Methylpentynol to a Neuroticism Rating in the Upper or Lower Halves of that Continuum (Group 2)

Neuroticism Rating	Clinical Grading 1	Clinical Grading 2 and 3
0·0–12·0	9	5
13·0–24·0	7	19

Inspection shows this to be due to the larger number of subjects in the upper N range becoming toxic, while the greater proportion of subjects in the lower N range responded normally to methylpentynol.

There was no relation between E scores and susceptibility to the drug (Table XIV) χ^2 being 1·21 which is not significant.

TABLE XIV

Relation of a Twofold Grouping of the Individual Response to Methylpentynol to an Extraversion Rating in the Upper or Lower Halves of that Continuum (Group 2)

Extraversion Rating	Clinical Grading 1	Clinical Grading 2 and 3
0·0–12·0	5	13
13·0–24·0	11	11

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Discussion

Although Mellanby (1919) in his classic work on the absorption and disappearance of alcohol from the blood gave the substance to dogs by gavage, the ideal way of studying the tolerance to methylpentynol would have been by administering the substance intravenously on a dose-weight, or a dose-surface area basis as did Newman (1935) with ethanol. However, methylpentynol in large doses given intravenously is a respiratory depressant (Marley, 1959) and in view of this potential hazard the oral route was preferred.

Eggleton (1941) found an association between central nervous system disturbance and blood alcohol concentration. It may then be argued that patients susceptible to methylpentynol were those with the highest blood methylpentynol concentration, that is, those absorbing the greatest quantities of the drug from the gastro-intestinal tract. There are two reasons why this is unlikely. The first is that methylpentynol rapidly crosses the stomach wall (Marley and Vane, 1958) and the second, that Bartholomew, Bourne and Marley (1958) found that the mean blood methylpentynol concentration over a 5-day period was identical in patients manifesting toxic signs and in those who did not.

Another objection to the validity of our conclusions could be that the Maudsley Personality Inventory has no significant test-retest reliability, but this was shown not to be so (Bartholomew and Marley, 1959). Nevertheless, the subject's response to the drug might have been fortuitous for Tucci *et al.* (1949) have stated that the effect of another central depressant (barbiturate) varies in the same individual on successive days. This factor was also demonstrated not to be important as 13 out of 15 patients responded identically to the drug on two similar 5-day regimes with a lapse between of one year.

Another objection could be that the mean neuroticism score for the first population was one standard deviation above that for the standardization series. As two-thirds (32 individuals) of this group manifested susceptibility to methylpentynol, it is to be anticipated that liability to intoxication would show some correlation with high neuroticism scores. This, however, would not explain why only 3 subjects of the 13 with a corrected neuroticism score below 10 (the neuroticism mean for a normally distributed population) displayed susceptibility, whereas 29 of the 41 individuals with a corrected neuroticism score over 10 developed toxic symptoms. The same criticism cannot be levelled at the relation between susceptibility to methylpentynol and extraversion, as the mean value and scatter for this variable deviated little from the standardization series.

To clarify further our findings, the response of another group of subjects to methylpentynol was studied. Again there was a clear correlation between high neuroticism scores and susceptibility to the substance. It is imperative to stipulate that the apparent relation between susceptibility to methylpentynol and neuroticism is no more than an observed association, and that no causality is being advocated. The results were only deemed valid in the first study after somatic variables known to affect response to drugs had been excluded.

Having acknowledged these possible demerits, then our results contradict McDougall's assertion (McDougall, 1929) that it is the extraverted personality who is susceptible, and the introverted subject who is resistant to alcohol. Methylpentynol is a branched 6-carbon alcohol (molecular weight 98; molecular weight of ethanol 46) and as the activity of an alcohol increases with the size of its molecule (Gaddum, 1956) one would have supposed that the results from

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administering the drug would emphasize rather than refute McDougall's findings.

Eysenck (1957c) considered the most important variable in predicting the effect of a drug to be the excitation-inhibition ratio (in the Pavlovian sense) for the person concerned. Pavlov (1927) had found that dogs with dissimilar constitutions are differently susceptible to bromide. Pavlov's "strong excitatory" dogs, which easily developed stable conditioned salivary responses, needed eight times the dose of bromide than a dog of the same body weight but with a "weak inhibitory" constitution, and which developed conditioned salivary responses with difficulty. Franks (1957) showed that conditionability in the human was linked with extraversion-introversion (extraverts condition badly, introverts condition well) but was unrelated to neuroticism. However, no correlation was found in human subjects relating susceptibility and conditionability (Bartholomew, Franks and Marley, 1958).

Shagass (1954) describes a technique for estimating the sedation threshold. This purports to be an objective pharmacological measurement deriving from electro-encephalographic and speech changes concurrent with the intravenous injection of amylobarbitone sodium. Shagass concluded that the sedation threshold is an index of anxiety. Shagass and Naiman (1956) elaborated this argument, contending that extraverted individuals (hysterics and psychopathic personalities) have a low sedation threshold, whereas introverted subjects (dysthymics) have a high threshold. As the alterations in the electro-encephalogram and speech taken as the end points for the sedation threshold are those indicating intoxication by the drug, it follows that extraverted individuals should manifest susceptibility to central depressants while introverted patients would be resistant.

Shagass's work has incurred justifiable criticism (Thorpe and Barker, 1957; Pampiglione, 1958). Pampiglione could demonstrate a definite sedation threshold in only one-third of 58 patients. He concluded, "The epiphenomenon of anxiety does not bear recognizable relationship to the patient's resistance to a sedative of the kind employed". Dickel and Dixon (1957) found that of 8,200 individuals given tranquillizing drugs 4–5 per cent. developed physical disturbances during treatment, while over 30 per cent. showed behavioural changes or striking alteration of their mental state. They linked the presence of anxiety with an adverse response to drugs. These findings are not only in sympathy with our own, but cast doubt on Shagass's contention that anxiety can be equated with a high sedation threshold and that only one personality dimension (E-I) is linked with drug susceptibility.

Similar side-effects to those noted in our subjects have been seen after placebos, Beecher (1955) recording 35 such "toxic" effects. While it is easy to comprehend signs such as ataxia appearing after administration of inert substances, it is more difficult to explain findings like nystagmus. Nevertheless, if the bulk of side-effects seen with placebos correspond with those encountered after the administration of methylpentynol and occur exclusively in subjects with high neuroticism scores, then it would be difficult to substantiate our thesis. However, none of the physical signs encountered with methylpentynol were seen when the subjects were receiving inert capsules, and Trouton (1957) suggested that the trait related to placebo response is not linked with primary suggestibility, and therefore neuroticism, but to secondary suggestibility—a factor not associated with any personality dimension so far described.

What conclusions are to be drawn? The distribution of both neuroticism and susceptibility to drugs for the general population are known to approximate

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to that of a natural curve; yet it would seem a convenient coincidence that they should be contiguous or overlap. (A similar reservation being applicable for the distribution of extraversion and susceptibility.) It could be, of course, that our two groups totalling 94 subjects are unique in that high scores for neuroticism correlate with susceptibility to methylpentynol, but this is unlikely.

Clark (1933b) refers to static and dynamic variants determining response to drugs. By static variant he implied one with a constant deviation from the mean of the particular population, there being a likelihood that the distribution of this variable would approximate to the normal or bell-shaped variety, whereas the dynamic variant alternated from one side of the mean to the other and consequently could be exemplified by many forms of distribution. It might be that neuroticism is one such static variant.

To go further and indicate any specific relation between susceptibility to the drug and central activity would be presumptuous. Certainly measures derived from other techniques purporting to quantify personality, and used by us—such as the Kinaesthetic After Effect and Pursuit Rotor—bore no relation to susceptibility to methylpentynol; indeed, none of these correlated with the N-N continuum, and only the Kinaesthetic After Effect (2) correlated with the E-I continuum.

Summary

Two investigations, with one year interval between, were performed on 94 individuals. The first group (54 subjects) received 0·5 g. q.d.s. of methylpentynol orally for 5 days preceded by a similar period on inert capsules. The second group (40 subjects) received only the 5-day regime of 0·5 g. q.d.s. of the active drug.

Toxic effects appearing between the third and fifth day of the drug regime occurred in 32 subjects of the first group and in 24 of the second.

Thirteen of the 15 subjects from the first group responded identically when given 0·5 g. q.d.s. of methylpentynol for 5 days after a lapse of one year since the original investigation.

Variables such as age, body weight, sex, haemoglobin levels, basal metabolic rate, renal and hepatic function were found not to have contributed significantly to drug susceptibility in the first group.

Personality variables as determined from the Maudsley Personality Inventory did seem to be significantly associated with susceptibility to methylpentynol. Thus a toxic response to the drug was correlated with high neuroticism scores in both groups. There was a just significant but debatable association of drug susceptibility with extraversion scores noted only in the first group. Methylpentynol susceptibility was not linked with a specific diagnosis, but normal individuals tended to respond normally to the drug.

Measures obtained with other techniques purporting to quantify personality, such as the pursuit rotor and the kinaesthetic after-effect, bore no relation to the drug phenomena.

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