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Drugs as Research Tools in Psychology: Experiments with Drugs in Personality Research

H.J. Eysenck

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Abstract. It is suggested that psychotropic drugs act to shift a person's behaviour on the three major dimensions of personality in one direction or another, in predictable ways, and that it is possible to create a taxonomy of psychotropic drugs according to these effects. The history of this concept is traced and many examples given to illustrate how drug action and personality theory interact, and how this interaction can be used to gain greater insight into both personality and drug action.

While major traits of personality are relatively persistent over time [*Conley*, in press], genetically determined in origin [*Fulker*, 1981], and cross-culturally consistent [*Eysenck and Eysenck*, 1983], they also have a firm biological underpinning [*Eysenck*, 1967, 1981]. The major dimensions of personality, emerging from large numbers of studies in many different countries, have been variably named, but might be referred to in terms of psychoticism versus impulse control (P), extraversion versus introversion (E), and neuroticism versus emotional stability (N). *Royce and Powell* [1983], in a thorough review of the literature, agree that these are the three major dimensions emerging from work in this field, and *Eysenck and Eysenck* [1984] quote the results of analyses of many different questionnaires to indicate that here too, in spite of widely different original orientations, the same factors emerge.

In view of the consistency with which these factors operate over time and situations, it is obviously of considerable interest experimentally that drugs may change behaviour, at least over short periods of time, in such a way as to appear to change a person's position in this three-dimensional framework. Thus, anxiolytic drugs may shift behaviour in the direction of greater emotional stability; alcohol may shift behaviour in the direction of greater extraversion, and LSD and other hallucinogens may shift behaviour in the direction of greater psychoticism. From the point of view of research in personality, therefore, work with drugs would seem to be of considerable interest. Conversely, the way drugs affect behaviour can be influenced by the personality of the subject of the experiment; thus, a given dose of nicotine may have the effect of increasing arousal in extraverted individuals, and of decreasing arousal in introverted individuals, using the contingent negative variation (CNV) as a measure of arousal [*Eysenck and O'Connor*, 1979]. The interaction between drugs and personality is, therefore, of interest both with respect to the way drugs can change behaviour along the axes defining personality and along the lines that personality may determine the way drugs affect behaviour.

The author has suggested [*Eysenck*, 1957, 1963] that the theory of the relationship between the major dimensions of personality and the major classification of psychotropic drugs, can be formulated by way of specific postulates; the nature of these postulates is indicated in figure 1. More specifically, it is suggested that there are groups of drugs which are relevant to each of the three personality factors (P, E, and N) in such a way that one group will push the individual, and his behaviour, in one direction, while the other group will push him in the opposite direction.

With respect to the psychoticism dimension, it is postulated that hallucinogenic drugs, such as LSD, will *increase* a person's P-related behaviour, while the major tranquillizers or antipsychotic drugs, such as the pheno-

thiazines, will have the effect of *decreasing* a person's P-related behaviour. With respect to extraversion, it is postulated that stimulant drugs will make a person's behaviour more *introverted*, while depressant drugs will make his behaviour more extraverted; amphetamines and amobarbital may be cited as examples of the two drug groups relevant to this dimension. Finally, adrenergic drugs such as adrenaline and betablockers may be cited as examples of drugs pushing the individual in the direction of higher or lower emotional activation (N).

The term 'anxiolytic' drug has been preferred to tranquillizing drugs because the latter sometimes seem to have an extraverting effect on behaviour, occasionally accompanied by a release of aggression. Perhaps the betablockers fit in best on the axis, but of course specifc drugs have specific actions, and the general labels given in the diagram simply denote the group of drugs which would be found clustered around the axis in the three-dimensional space generated by the three axes in question.

One further point remains to be discussed in this connection. The term 'anxiety' is often used in psychology to denote a rather complex personality trait which has been shown to incorporate elements of neuroticism and introversion (more of the former than the latter) and would thus form a dimension slanting down on the plane of figure 1 from top left to bottom right. Anxiety in our system is not a 'pure' factor, but combines the easy production of strong fear responses of the neurotic with the ability to condition quickly of the introvert [*Eysenck*, 1967]. Anxiety is conceived of as a conditoned fear response, and hence the hypothetical axis lies in a space defined by two more fundamental factors, N and E. There are alternative ways of looking at anxiety, and we will discuss these in connection with the work of *Gray* [1982] later on in this chapter.

Drug Dosage and Personality

There are of course many qualifications that require to be attached to these postulates. One such qualification relates to dosage; many drugs have a biphasic action, as for instance nicotine; in small doses this increases arousal, in large doses it decreases autonomic activation [*Eysenck*, 1980]. Thus, a given drug may have different, and sometimes antithetical effects, depending on dosage. Alcohol in very small doses give a different effect to alcohol in larger doses, and when taken to excess may have quite different effects again. Dose-response relations are not necessarily, or even usually, linear, and this has to be borne in mind. A second important point relates to the conditioning effect that may be observed in regular drug taking; thus, the effects of alcohol may only partly be due to the ethanol itself and partly to conditioned expectations of its effects. The same may be true of other drugs to which the individual has habituated, such as nicotine. Indeed, habituation as such may be another complicating feature, in that individuals habituating to a drug may require larger and larger doses in order to achieve the same behavioural effects. Other qualifications, such as the difficulty of assigning many drugs to one of our major six groupings, are obvious and will not be here considered. One point, however, must be mentioned, namely that it is not necessary that all drugs should fall on one of our three major dimensions; it is perfectly possible that a drug may affect two or even all three dimensions simultaneously or, in other words, be located not on the axes, but in the quadrants or octants of the resulting three-dimensional space. Similarly, of course, persons do not necessarily lie along one of the major axes, but are distributed at random in the three-dimensional space generated by these three axes.

Concept of Transmarginal Inhibition and Drug Effects

Testable predictions can be derived from these drug postulates, but it is important to remember in each case that thorough knowledge of the general psychological and parametric features relating to a given experimental model is required in order to make correct predictions. To take but one example, consider the importance of *Pavlov's* concept of *transmarginal inhibition* in relation to the extraversion-introversion dimension. Working originally with the conditioning paradigm, *Pavlov* began his work by formulating the *law of strength* which says, simply, that the intensity of the unconditioned stimulus will be related monotonically to the strength of the conditioned response. He found, however, that after reaching an optimal value, further increases in the strength of the unconditioned stimulus produced a *decline* in the strength of the conditioned response. He attributed this to some kind of protective inhibition, i.e., a biological mechanism protecting the integrity of the cells against too intense stimuli. This concept of transmarginal inhibition has been found to hold true in relation to many other psychological experiments and has been variously named the Yerkes-Dodson Law, or the law of the inverse U relationship.

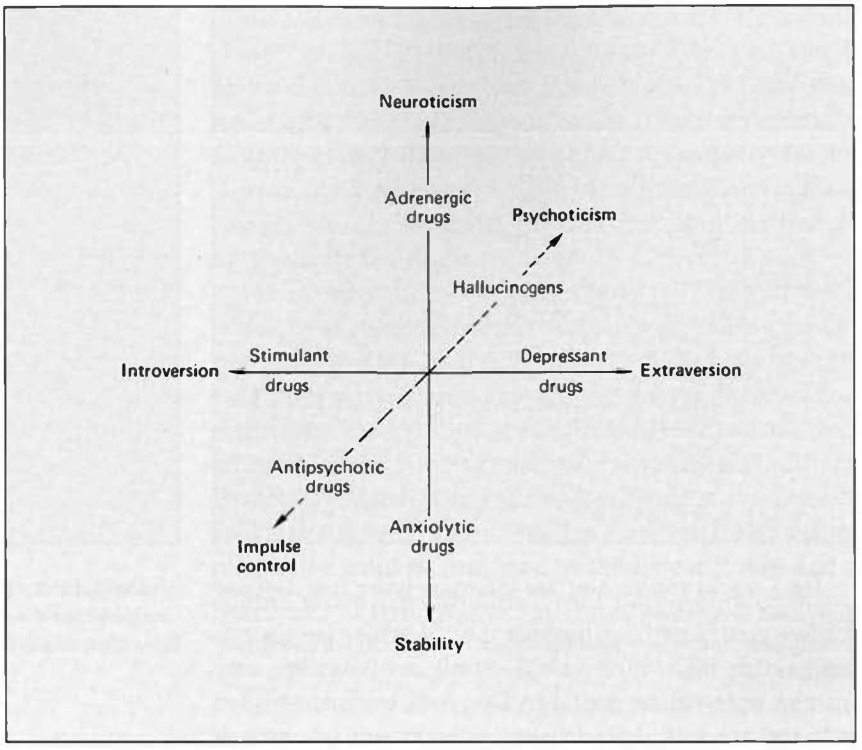

Fig. 1. Psychotropic drugs and personality. Two paradigms for studying the effects of drugs in human personality [from *Eysenck*, 1963]

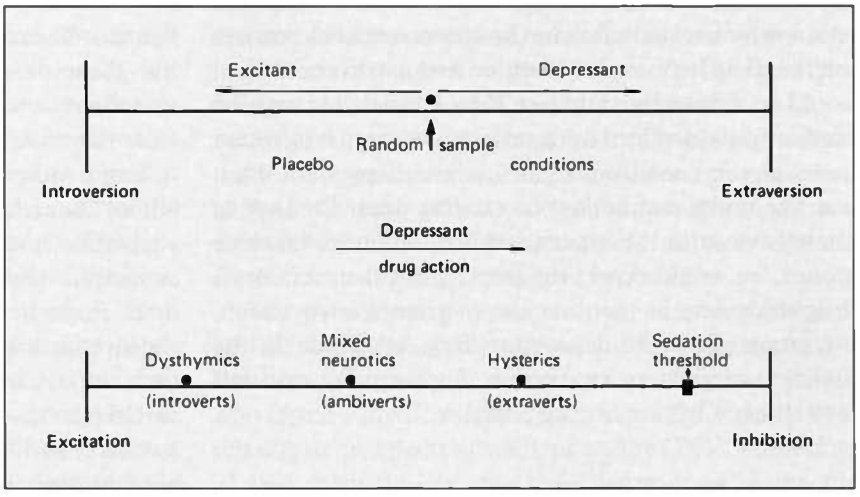

Fig. 2. The *Eysenck* drug postulate in diagrammatic form [from *Eysenck*, 1963].

This law is intimately related with personality, as can be shown for instance in relation to human conditioning. Assuming that transmarginal inhibition applies to human conditioning, and that introverts have a higher level of cortical arousal than extraverts [*Eysenck*, 1967], then it would be expected that the optimal level of UCS intensity would be lower for introverts. This would lead to the prediction that introverts would condition better than extraverts with relatively low levels of UCS intensity, but that extraverts would condition better than introverts with high levels of UCS intensity. The available evidence fully bears out this prediction [*Levey and Martin*, 1981]. The implication of this finding for work with drugs will be considered presently.

Paradigms for the Study of Drugs and Personality

Eysenck [1963] has suggested two major paradigms to be used in the study of the interaction between drugs and personality; these are diagrammed in figure 2. Let us consider paradigm A first. Using the introversion-extraver-

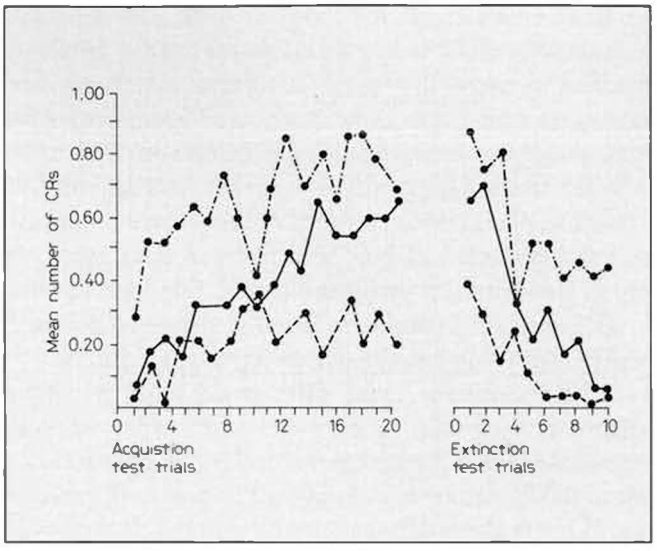

Fig. 3. Eyelid conditioning and extinction under stimulant and depressant drugs [from *Franks and Trouton*, 1958]. – · – · – = Dextroamphetamine; —— = placebo; – – – = Amytal. CR = Conditioned response.

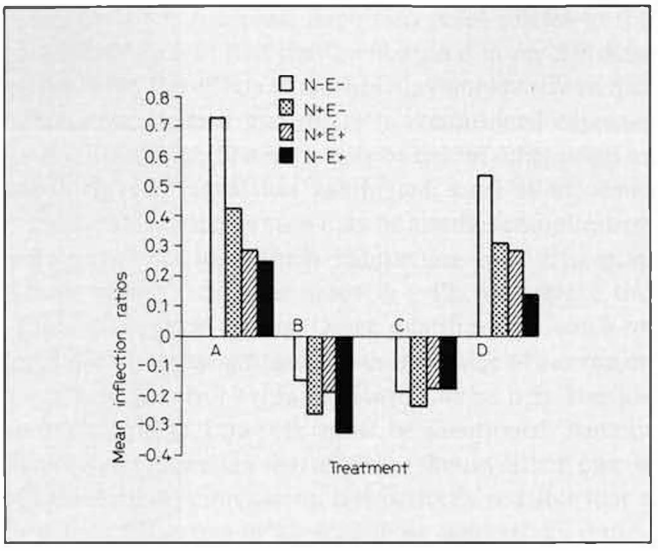

Fig. 4. Effects of stimulant and depressant drugs on verbal conditioning [from *Jawanda*, 1966]. A = Dexedrine; B = phenobarbitone; C = chlorpromazine; D = ephedrine.

sion dimension, consider a random sample of the population, which would of course on the average have scores intermediate between introversion and extraversion, i.e., would be effectively ambivert. Now let such a sample be randomly divided into three subsamples, one being tested under placebo conditions, one under a depressant drug, and one under a stimulant or exciting drug. Comparing the behaviour in the experimental situation of the three groups, we would expect the group given the excitement drug to deviate in the direction of greater introversion, the group given the depressant drug to deviate in the direction of greater extraversion. Such a prediction follows directly from our drug postulate.

Drugs and Conditioning

Consider as an example of the application of this paradigm work on eyelid conditioning carried out in our department. *Franks and Laverty* [1955] showed that intravenous Sodium Amytal® reduced the number of conditioned eyeblink responses during acquisition and also increased the rate of extinction. Placebos did not produce any effects as compared with no drug treatment. *Willett* [1960] found that Doriden® (glutethimide) depressed the rate of conditioning significantly, and *Franks and Trouton* [1958] used both a stimulant drug (dextroamphetamine sulphate; Dexedrine®) and a depressant drug (amobarbital sodium) and obtained the results shown in figure 3. The results of the Amytal group look very much like those obtained by *Franks* [1956, 1957] for extraverted subjects, while the results for the Dexedrine group look very much like his results for introverted subjects.

Some other studies might be mentioned. *Hobson* [1966] studied the effects of three ethanol doses at three adaptation levels upon the acquisition and resistance to extinction of the conditioned eyeblink response in 135 men. Regardless of dosage, the action of ethanol was shown to interfere with the learning of new response patterns. *Jawanda* [1966] looked at the effects of drugs on verbal conditioning. He used four subject groups, high or low on N and E, and five drug treatments (placebo, phenobarbitone, chlorpromazine, ephedrine, and dextroamphetamine (Dexedrine). The results are shown in figure 4. Drug effects were significant, and for all personality groups the stimulant drugs produced a greater amount of verbal conditioning, the depressant drugs a lesser amount, as compared with the placebo group.

Many phenomena other than conditioning have been studied in relation to the drug postulate, of course. An example of a perceptual phenomenon is the so-called Bidwell effect [*Eysenck and Aiba*, 1957; *Aiba*, 1963]. The Bidwell effect consists of the suppression of the primary visual stimulus and the simultanous production of the negative afterimage of the stimulus suppressed. If a brief exposure of a red stimulus is followed by a brief exposure

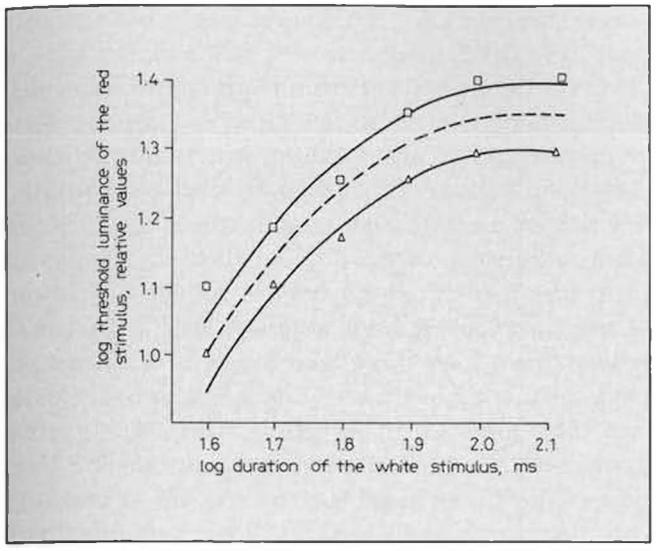

Fig. 5. Effects of stimulant and depressant drugs on visual masking (Bidwell effect) with various durations of the white stimulus [from *Aiba*, 1963]. □ = Sodium Amytal; △ = Dexedrine; – – – = no drug.

of a white stimulus, then, provided that suitable time intervals have been chosen, the subject does not see the red stimulus (suppression of the primary stimulus), but only the green afterimage. Durations of the red primary stimulus vary from 5 to 50 ms, while the white stimulus varies from 50 to 100 ms. The phenomenon is regarded as a special case of visual masking. Figure 5 shows the result of an experiment comparing log threshold luminance of the red stimulus for three groups of subjects, receiving Sodium Amytal, Dexedrine, or no drug. With the depressant drug a primary stimulus of greater luminance is masked than when a placebo is used, while with the stimulant drug the opposite effect is produced. In these experiments, therefore, stimulant drugs have an introverting, depressant drugs an extraverting one. In other experiments, *Holland* [1963], using a more usual method of backward masking, obtained similar results for Sodium Amytal and Dexedrine. Other experiments used nitrous oxide and oxagen as depressant and stimulant substances, respectively [*Eysenck*, 1963].

Drugs and Vigilance

Another experimental paradigm frequently used is that of vigilance, where the higher cortical arousal of introverts and the lower cortical arousal of extraverts have frequently been shown to produce the effect that introverts show higher scores than extraverts. *Mackworth* [1948], *Treadwell* [1960], *Bakan* [1961], *Uhr* et al. [1964], *Haward* [1965], *Payne and Hauty* [1955, 1957], *Hauty and Payne* [1955, 1958], and many others reviewed by *Eysenck* [1967] show that stimulant drugs avert the decline in performance which is so characteristic of control and placebo performance, whereas depressant drugs tend to accelerate the decline.

An experiment by *Gupta and Kaur* [1978] studied the effects of dextroamphetamine sulphate on kinesthetic figural aftereffects (KFAE's). *Eysenck* [1955] had shown that extraverts would show larger KFAEs than ambiverted and introverted subjects. *Gupta and Kaur* [1978] tested their groups of subjects after preliminary investigation with the Eysenck Personality Inventory, classifying them into three groups: extraverts, ambiverts, and introverts. Dextroamphetamine sulphate was used at three dose levels, and a control group was included for the purposes of comparison, giving a three by four randomized block design which was replicated ten times. It was found that extraverted subjects showed lower KFAEs than ambiverted and introverted subjects under placebo conditions, but that under the influence of the drug the extent of KFAE was reduced in extraverted and enhanced in introverted subjects. The mean scores for the extraverts for the three drug dosages were comparable to the mean scores of ambiverted and introverted groups under the placebo condition. The opposite reaction of the introverts, as compared to the extraverts, may be due to the increase in cortical arousal beyond the optimal point predictable in terms of *Pavlov's* transmarginal inhibition hypothesis.

The possibility of demonstrating such transmarginal inhibition effects as a consequence of drug administration has been effectively demonstrated by *O'Connor* [1980] who tested a prediction by *Eysenck and O'Connor* [1979] relating to the effects of smoking on the CNV. The nature of this prediction is shown in figure 6, in which the abscissa plots arousal potential, in which according to *Eysenck* [1980] introverts are superior to extraverts, while the ordinate plots CNV amplitude. Using this CNV amplitude measure as an index of arousal, it is postulated that introverts under conditions of sham smoking have higher CNVs than extraverts under conditions of sham smoking. (Sham smoking simply means that the subject moves an unlit cigarette as if he were smoking.) Smoking a real cigarette would increase the arousal of the extraverts but decrease that of the introverts, due to the fact that they are already at the top of their arousal potential. Results reported by *O'Connor* [1980] are very much in line with prediction on all these points.

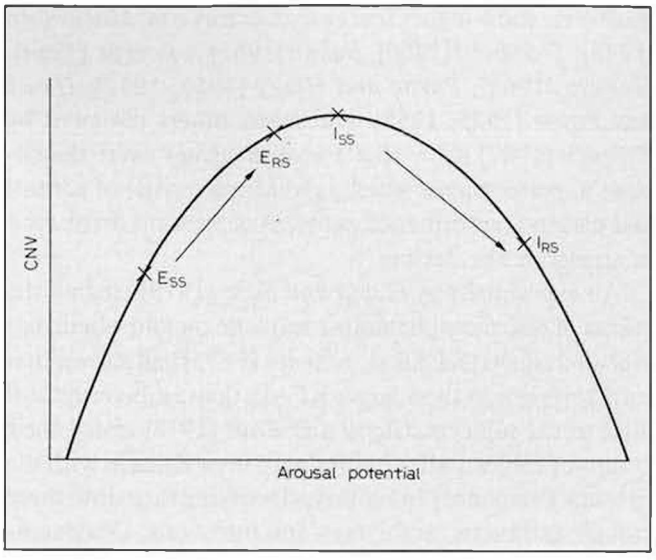

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Fig. 6 Curvilinear regression of CNV on arousal potential, showing effects of smoking 1 cigarette on extraverts and introverts [from *Eysenck*, 1980]. SS = Sham smoking; RS = real smoking.

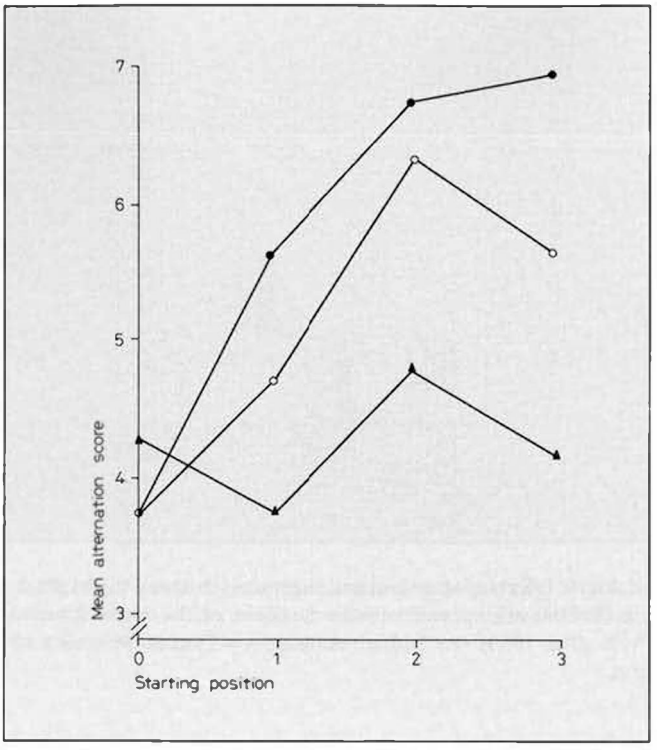

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Fig. 7. Alternation behaviour in rats as a function of stimulant and depressant drugs [from *Sinha* et al., 1958] ● = Amytal; ○ = placebo; ▲ = Meratran.

Drugs and Neuroticism

So far we have only dealt with some experiments illustrating the first paradigm of drug effects using extraversion-introversion as the dimension involved. A great deal of work has also been done with respect to the neuroticism dimension, much of it summarized in *Janke* et al. [1979]. A few typical studies will be cited and the general conclusions reached summarized.

A recent experiment by *Heinze* et al. [1983] illustrates the degree to which dosage and personality (in this case neuroticism) interact to influence behavioural performance. Using the Kieler Determinationsgerät, the authors found that low N scorers improved when tranquillizer and placebo were administered, compared with normals, whereas high N scoring subjects showed decline in performance after a dose of tranquillizer.

Older studies, reviewed by *Janke* et al. [1979], often showed a rather different result, namely an improvement in performance in high N scorers with minor tranquillizers and a worsening of performance in low N scorers. There is obviously an interaction effect between personality, drug dosage, and amount of stress imposed by the task. A detailed consideration of the evidence suggests that on the whole the data support the drug postulate, but there are also some additional findings summarized by *Janke* [1983]. As he points out, higher magnitude of drug response is usually obtained in subjects with higher neuroticism scores. As he points out, this is particularly true for the magnitude of *performance impairment* by larger doses of sedating drugs or stimulants.

What *Janke* [1983] considered 'the most impressing results of all our experiments' were that the quantity and quality of the relationship between neuroticism and drug response were not fixed (consistent). 'There was a change according to the drug type, to the dose level, to the situation in which the drug was administered and to the kind of dependent variable' [p. 50]. The reasons for some of these inconsistencies are presumably connected with the complexity of drug experiments, as will be discussed later on.

Drugs and Alternation Behaviour

It should be noted that the drug postulates make predictions not only in the human field, but also in the animal field for instance. Thus, as *Eysenck* [1967] has pointed out, 'Alternation behaviour is frequently observed in human and animal subjects and is theoreti-

cally ascribed to cortical inhibition, which may affect motor aspects, perceptual aspects, or both. If this is so, then depressant drugs should increase alternation behaviour, while stimulant drugs should decrease it' [p. 272]. Evidence relating alternation behaviour to extraversion in humans is available [*Eysenck*, 1981; *Eysenck and Levey*, 1965]; do drug experiments with animals support the hypothesis? *Sinha* et al. [1958] carried out an experiment in which alternation was induced in rats by forcing them to make 0, 1, 2, or 3 turns in one direction before choosing whether to turn right or left to obtain a reward present in both directions. Figure 7 shows the results of administering placebo, Sodium Amytal, or Meratran to the animals. The placebo group shows the amount of alternation produced by the experimental condition; it will be seen that the animals given Amytal alternate more in all positions, while those given Meratran do not alternate at all. Thus, clearly predictions made on the basis of the drug postulate can be tested and verified in animal subjects.

Drug-Personality Interaction Using Paradigm B

We may now turn to our second paradigm. In figure 2, this is illustrated again by reference to introversion-extraversion and the cortical arousal or excitation thought to be typical of introverts and the cortical disarousal or inhibition thought to be typical of extraverts. It should be noted that, following *Jung's* hypothesis, dysthymic neurotics are considered introverts in this scheme, hysterics (and psychopaths) extraverts; evidence for *Jung's* hypothesis will be found in *Eysenck* [1947, 1957].

According to this hypothesis, hysterics and extraverts generally will be closer to the inhibition end of the continuum than dysthymics, or introverts generally, with mixed neurotics (ambiverts) shomewhere in the middle. If we now administer a depressant drug to these three groups of subjects, then hysterics should need less of the drug to reach a terminal point (here labelled 'sedation threshold') than would mixed neurotics and ambiverts or dysthymics. One could of course also imagine a reversal of this paradigm using some form of 'excitation threshold' which, upon the administration of a stimulant drug, would be reached more readily by dysthymics than by mixed neurotics, and by these than by hysterics. The so-called amphetamine psychosis might furnish such an 'excitation thereshold' which may be measurable in terms of the symptoms associated with amphetamine psychosis [*Connell*, 1958].

Sedation Threshold

Most of the empirical work published to date has actually been in relation to the sedation threshold [*Claridge*, 1983], although there is no obvious reason for disregarding the obverse relationships. *Giberti and Rossi* [1962] did in fact develop a stimulant drug equivalent, the 'stimulation threshold', using methamphetamine, but unfortunately little use has been made of this.

The quite widely used sedation threshold was originally introduced by *Shagass* [1954] in a paradigm involving determining the amount of Amylobarbitone Sodium® required to bring about a defined change in the amplitude of fast frontal EEG activity. The general strategy, as shown in figure 2 is to administer *varying* amounts of the drug to the subject and continue to do so until the subject reaches some predetermined criterion of response. Accordingly, the dose received then becomes the measure of the drug's effect and can be related across individuals to personality or other variables. In the years following the publication of the paper by *Shagass* [1954], many drugs were used, some researchers concentrating on sedative drugs, usually barbiturates, but others using EEG changes due to nitrous oxide [*Rodnight and Gooch*, 1963] and ethyl alcohol [*Kawi*, 1958]. Alternatives to EEG change have also been considered, such as lateral gaze nystagmus [*Fink*, 1958], suppression of the GSR [*Perez-Reyes* et al., 1962], and behavioural lack of response to various kinds of stimuli [*Claridge and Herrington*, 1960; *Rodnight and Gooch*, 1963; *Shagass and Kerenyi*, 1958a, b]. Actually the EEG criterion is not a very good or reliable one, and behavioural criteria are probably to be preferred, on the whole.

Experiments carried out in the early days of the sedation threshold model seem to support *Eysenck's* hypothesis that dysthymics, because of their greater introversion, should have higher sedation thresholds than hysterics [*Claridge*, 1967; *Claridge and Herrington*, 1960; *Shagass and Jones*, 1958]. It does not, of course, necessarily follow that these results could be generalized to *all* introverts and to *all* extraverts.

Dysthymics and hysterics are not only typically introverted and extraverted, respectively; both groups are also high on neuroticism, and the possibility remains that it is this interaction which produces the predicted effects.

Rodnight and Gooch [1963], following their own study of nitrous oxide tolerance in normal volunteers, noted that there was no correlation with extraversion, or with neuroticism. Neither personality trait alone seemed capa-

ble of predicting individual differences in drug response in this model. A zone analysis [*Eysenck*, 1967], however, revealed a very interesting interaction effect. In zone analysis, drug tolerance scores are looked at in individuals selected according to different combinations of extraversion and neuroticism, and by the use of this method *Rodnight and Gooch* [1962] found that there was a complex but systematic relationship between personality and the tolerance for nitrous oxide, as shown in tables I and II. Tables I and II illustrate two separate zone analyses. In the first of these (table I), subjects were divided into subjects with high and low N scores, and within each of these two subgroups sedation thresholds were correlated with E. In the second zone analysis (table II), subjects were divided according to E, and separate correlations calculated between sedation threshold and N.

Also included in the tables are two further experiments [*Claridge and Ross*, 1973; *Claridge* et al., 1981], where sedation thresholds were secured with different drugs (Amylobarbitone Sodium and Thiopentone Sodium®).

Considering first the high N versus low N analyses, it will be seen that correlations between E and sedation threshold are opposite in direction, being *negative* for high N subjects (as predicted) and *positive* for low N subjects. A similar reversal of correlation can be seen in table II, where subjects are subdivided according to their high or low E scores; N correlates negatively with sedation threshold in high E scores, and positively in low E scores.

These results support the original findings in dysthymics and hysterics; in high N scorers *Eysenck's* drug postulate is supported. However, these more recent results add the important qualification that in low N scorers the reverse is true, and the relationship between drug response and extraversion is actually opposite to prediction.

Claridge [1983] has attempted an explanation of the results in terms of a rather complex amplification of the original *Eysenck* theory; it is not the purpose of this chapter to go into details concerning the theory, or to discuss the degree to which it accounts for the data and predicts other data. The point of quoting this example of a prediction only partially borne out by the data is to make a very important point in evaluating both the theory and the empirical results obtained. Theories in science begin by making very simplistic and usually oversimplified statements which later on have to be modified in the light of empirical results. Thus, one task of what *Kuhn* [1962] has labeled the puzzle-solving activity in normal science is to further explore the implications of theories, revise them to bring them more in line with empirical data, and generally attempt to effect greater agreement between theory and fact [*Eysenck*, in press]. In many cases the alleged anomalies turn out to be no such thing, but to have originated through the action of confounding factors which were left uncontrolled. *Newton's* theory of gravitation was beset with anomalies from the beginning, but for hundreds of years these anomalies, on critical analysis, were actually found not to be anomalies at all, but could be explained in terms of the theory itself. Thus anomalous motions of certain planets could be explained by postulating the disturbing influence of other, not yet discovered planets, and indeed Neptune was discovered because of the analysis by *Adams* and *LeVerrier* of the perturbing influence it exerted on Uranus and other planets.

Table I. Interaction between personality types and drug tolerance [from *Claridge*, 1983] – E and drug tolerance in high and low N scorers

	High N		Low N	
	r	p	r	p
Nitrous oxide	−0.40	NS	+0.72	0.05
Amylobarbitone Sodium®	−0.45	NS	+0.65	0.05
Thiopentone Sodium®	−0.71	0.01	+0.38	NS

The Significance of Exception to Rules for Theory Formation

Apparent anomalies can occur (and frequently have occurred) even in the hard sciences, where complete control over all relevant variables is possible, or at least a condition that can be approached fairly closely. In psychology, and in particular at the interface between pharmacology and psychology, such control is out of the question. *Trouton and Eysenck* [1961] have tried to list some of the main variables which can influence drug effects and which in theory ought to be controlled to provide a proper test of the drug postulates; it will be obvious that no such control is in fact feasible (see table III). This should be kept in mind in judging the outcome of experiments apparently unfavourable to the theory. It is often clear from the experimental conditions that other features

Table II. Interaction between personality types and drug tolerance [from *Claridge*, 1983] – N and drug tolerance in high and low E scores

	High E		Low E	
	r	p	r	p
Nitrus oxide	− 0.80	0.01	+ 0.04	NS
Amylobarbitone Sodium®	− 0.65	0.02	+ 0.34	NS
Thiopentone Sodium®	− 0.64	0.01	+ 0.07	NS

Table III. Some variables influencing drug effects [from *Trouton and Eysenck*, 1961]

(1) Nature of the Drug
- Preparation (including concentration, vehicle of administration, and whether disguised)
- Mode (oral, intravenous injection, etc.) and rate of administration, absorption, and excretion
- Dosage (according to body weight or the same for all)
- Interval before testing

(2) Subject
- Personality (including intelligence, extraversion-introversion, neuroticism, suggestibility, etc)
- Familiarity with the situation and the amount of stress occasioned by it
- Practice, fatigue, motivation
- Tendency to react to *placebos*
- Psychiatric state and its duration
- Age, sex, physics, height, and weight
- Present state
  - General state of health, nutritional status, sleep
  - Conditions of work, e.g., temperature, humidity, oxygen lack
  - Diseases, disabilities (e.g., fever, thyrotoxicosis, liver or kidney damage), or effects of operations, etc. (e.g., leucotomy, concussion)
  - Time of day
  - Interval since last meal (if drug given orally)
  - Recent medication with other drugs (e.g., sedation) or ingestion of drinks containing stimulants or depressants
- Previous experience of drugs
  - Cumulative effect of some drugs (e.g., bromides)
  - Habituation, tolerance (including cross-tolerance)
  - Addiction
  - Idiosyncrasy of hypersensitivity

(3) Social Environment
- Interaction with other subjects
- Activities required or permitted after administration of the drug
- Suggestion
- Reinforcement of responses by the experimenter

listed in table III may have played an important part and that hence their influence may have obscured the predicted effects, or even reversed them. In psychology, theories are often rejected on the basis of contradictory evidence which is in fact quite insufficient to prove the failure of the theory; in science generally (particularly the hard sciences) theories are more frequently given a breathing space in order to demonstrate their potential. If this is true of 'strong' theory, how much truer must it be of 'weak' theories [*Eysenck*, 1960].

Drug Tolerance

One obvious experimental difficulty which arises, and which has to be taken into account in judging the effects of different drugs, is drug tolerance, as already mentioned. Tolerance usually shows itself in the need to increase the dose of the drug to obtain the effects that were previously obtained with the lower dose [*Gossop*, 1982]. For the first time user, an effective dose of heroin would for instance be in the region of 5–10 mg, and for the non-tolerant user a dose of 200 mg would probably be fatal, though non-addicts have survived overdoses in excess of 350 mg. As a regular user increases his tolerance, he takes ever-increasing doses of the drug; *Gossop* [1982] cites a case of 1 heroin user who every day consumed 900 mg, having reduced his intake of drugs to this level from more than 1,600 mg!

Barbiturates and sleeping tablets generally usually work well on first taking, but with continued use, the drug seems to lose its effectiveness, and ever-increasing doses are normally used. An increased physiological tolerance has also been observed in the case of alcohol; the user requires larger and larger doses in order to reach an appropriate stage of inebriation. Nicotine, caffeine, and other very widely used drugs probably also show tolerance effects, and these would certainly have to be taken into account in comparing the results of these and related drugs in people differing widely in their habitual consumption of these drugs.

To make things more difficult, many studies have shown that the reverse of tolerance effects can also be demonstrated and is usually known by the name of 'kindling' [*Post and Kopanda*, 1976]. In the use of cocaine and related stimulants in man, for instance, increased duration of administration without increase in dosage

may progress from the predominantly affective, euphoric effects to the schizophrenic form and psychotogenic phases. Much of this work has been done in animals [e.g., *Downs and Eddy*, 1932a, b; *Gutierrez-Noriega*, 1950; *Gutierrez-Noriega and Zapata-Ortiz*, 1944; *Stripling and Ellinwood*, 1977; *Ho*, 1977; *Post and Kopanda*, 1975; *Mago*, 1969; *Segal and Mandell*, 1974; *Klawans and Margolin*, 1975; *Ellinwood and Kilbey*, 1975; *Ranje and Ungerstedt*, 1974]; *Kramer* [1972] provides similar evidence for man. The term 'kindling' is derived from a phenomenon in which repetitive subthreshold stimulation of the limbic system is eventually associated with major motor seizures, and *Post and Kopanda* [1976] relate the 'kindling' model not only to pharmacological and behavioural phenomena, but also as an explanation for the progressive development of some psychopathological behaviour in man. Be that as it may, the possibility that some such progressive effects of certain drugs may be apparent in some if not all users would certainly create difficulties in studying the relationship of the effects of these drugs and personality in man. Tolerance and 'kindling' effects are quoted mainly to illustrate the widespread nature of the effects listed in table III.

Time of Day Effect

Another complicating factor, quite different in nature, is the so-called time of day effect. A factor that may crucially affect predictions of relationships between drug effects and extraversion-introversion is the finding by *Blake* [1967, 1971] that with respect to body temperature introverts were phase advanced with respect to the circadian rhythm of arousal, being more aroused in the morning, with extraverts being more aroused in the afternoon.

Revelle at al. [1980], in a number of experiments using caffeine as the stimulant drug, found that this drug had its greatest beneficial effects on extraverts tested in the morning, suggesting that extraverts are suboptimally aroused at that time of day. In contrast, the modest effect of caffeine on introverts tested in the morning suggested that they were close to the optimal arousal level at that time.

The opposite pattern of results was obtained in the evening testing session, suggesting that extraverts are overaroused in the evening, whereas introverts are underaroused. *Revelle* et al. [1980] found other rather complex results in their work, including a reversal of the first day effect on subsequent days testing.

While there does seem to be a time of day effect of the kind suggested by *Blake* [*M.W. Eysenck*, 1982], the particular hypotheses of *Revelle* et al. [1980] have been criticized by *Eysenck and Folkard* [1980]. They pointed out that there was no evidence in the literature to support the notion of such a large phase difference in the circadian rhythm of arousal as postulated by *Revelle* et al. [1980]. Other criticisms by *Eysenck and Folkard* [1980] are contained in their paper, and *Humphreys* et al. [1980] have proposed a rather more complex model, incorporating two different activation states together with two information-processing constructs. It would take us too far here to enter into a discussion of this model or to summarize the rich literature on biological rhythms and human performance [*Colquhoun*, 1971]. Let us merely note that the time of day has not usually been taken into account by research workers in this field and that failure to do so may lead to results apparently contradicting prediction when in actual fact they support the drug postulate. Specific experiments designed to investigate the precise way in which circadian rhythms of this kind interrelate with drug effects and personality are urgently needed in order to put this particular factor on a more secure footing in predicting and interpreting experimental results.

The Question of Dimensionality of Drug Effects

The major contribution of the drug postulates is the suggestion that we would think of drug effects in dimensional terms. Experiments suggested by such an approach need not follow either of the two methods outlined in figure 2; it is possible to conduct experiments directly related to the dimensionality of a problem. *Eysenck and Eysenck* [1960] have contributed an example of precisely how this could be done.

Three groups of subjects were created, one to be tested under glutethimide, one to be tested under meprobamate, and one to be tested under placebo conditions. The three groups were made up of the same people tested under all three conditions in question. Five tests in all were used for the analysis, each of which had been employed in experiments involving these three conditions – nonsense syllable learning, reaction times, level of skin resistance, flicker-fusion, and perimeter threshold differences.

The hypothesis was that the two drugs had effects qualitatively identical and only quantitatively differentiated, i. e., it was hypothesized that the effects lie along one single dimension (that of neuroticism). A canonical

variate analysis of the test scores gave results which are shown in table IV. It will be seen that the first of the latent roots is significant at the 0.001 level, whereas the second latent root fails to be significant, even at the 5% level. The results, therefore, bear out the hypothesis and show that both meprobamate and glutethimide lie on a continuum with respect to their psychological effects and do not differ from each other in mode of action. (The term 'mode of action' does not of course refer to the biochemical and physiological mode of action, but merely to the behavioural effects of these drugs.) It is clearly possible that had other tests been used, results might have been different, but the experiment will suffice to illustrate the method.

It is curious and rather sad that this approach has not at all been used on a larger scale, using drugs involving different dimensions. This approach would seem to possess particular possibilities of falsifying the hypothesis and would hence, according to the *Popperian* criterion, be the most appropriate one for testing that hypothesis. Obviously, the choice of drugs, tests, and doses would present considerable difficulties, but it would seem that the outcome of such experiments would be methodologically of much greater interest than the usual type of psychopharmacological experiment.

Table IV. Canonical variate analysis of five tests, showing effects of two drugs [from *Eysenck and Eysenck*, 1960]

Latent vectors	χ_1	χ_2
(1) Nonsense syllable learning	−0.040971	−0.014399
(2) Reaction time	−0.013625	−0.161517
(3) Level of skin resistance	−0.080835	−0.013827
(4) Flicker fusion	1.000000	1.000000
(5) Perimeter threshold difference	−0.475330	0.147773

Latent roots: $\lambda_1 = 0.453220 = 90.03\%$; $\lambda_2 = 0.050205 = 9.97\%$; diagonal entries of matrix $G^{-1} B = 0.503425$.

Significance of roots: $R_1^2 = \lambda_1 : \chi^2 = 40.446$ ($p < 0.001$); $R_2^2 = \lambda_2 : \chi_2 = 3.450$ (n.s.).

Biphasic Drug Effects

The need to take personality into account in all drug experiments, and the usefulness of the drug postulate in explaining complex results, is illustrated very well in a recent experiment reported by *Ashton* et al. [1981]. These authors were concerned with the effects of smoking cannabis on cortical evoked responses and on performance; they used Δ^9-tetrahydrocannabinol, one of the main active principles of cannabis as the drug to be administered. We will in the description of this experiment simply refer to 'cannabis', but it is this particular drug that should be understood to be involved. As with nicotine, biphasic effects of the drug are expected, and so are differential effects on introverts and extraverts. Some of the main results may be mentioned to illustrate the complex interaction effects. The CNV magnitude was increased after 2.5 mg cannabis in introverted subjects and in those with high N scores and after 10 mg in extraverted subjects and in those with low N scores. As *Ashton* et al. [1974, 1980] and other authors [*Kopell* et al., 1974; *Walter*, 1964] point out, similar increases in CNV magnitude have been shown to occur after central stimulant drugs such as caffeine, methamphetamine, pemoline, low doses of nicotine, etc. Conversely, the CNV magnitude was decreased after 2.5 mg cannabis in extraverted subjects and in those with low N scores and after 10 mg in introverted subjects and in those with high N scores. Such decreases in CNV magnitude occur after central depressant drugs, such as ephenol, benzodiazepines, barbiturates, chlorpromazine, and high doses of nicotine [*Ashton* et al., 1974, 1980; *Kopell* et al., 1972, 1974; *Hablitz and Borda*, 1973; *Tecce* et al., 1975]. As *Ashton* et al. [1981, p. 717] point out: 'The stimulant effects of Δ^9-THC on CNV magnitude may possibly reflect an increase in sensory traffic into the reticular activating system, which is known to be involved in the genesis of the CNV [*Rebert*, 1972].' On the other hand [p. 718]: 'The depressant effects of Δ^9-THC on CNV magnitude could be due to dose- and personality-related actions in the opposite direction on the same brain system, or to separate depressant effects on different systems. Biphasic dose-related effects of marihuana on CNV magnitude have been reported previously by *Braden* et al. [1974], and the direction of CNV response to nicotine is influenced by both dose and personality [*Ashton* et al., 1974, 1980; *Eysenck and O'Connor*, 1979].

It is not necessary to comment on the skin conductance, the visual and auditory evoked response scores, or the other results reported by *Ashton* et al. [1981] in this paper to illustrate the vital need of introducing personality into the experimental paradigm, as exactly contradictory responses are mediated by given doses of the drug in extraverted and introverted or high and low N subjects.

The traffic of explanatory hypotheses is not unidimensional, going from personality to drug groups, as might appear from what has been said so far. If there is a relationship, as postulated, between personality and drug effects, then clearly the experimental use of drugs can also be of help in explicating the system of personality description, supporting or refuting theories concerning its neurological, physiological, or biochemical basis, and aid in formulating a more generalized system of describing the biological bases of personality.

Drugs and Choice between Different Descriptive Systems of Personality

An example of how research on drug effects can aid in a choice between different descriptive systems or personality models can be seen in the work of *Gray* [1981]. We have already mentioned the fact that 'anxiety', in the *Eysenck* system, is a compound personality factor combining neuroticism and introversion. *Gray* has suggested that instead anxiety and impulsivity constitute the two major axes of the E-N system and that extraversion and neuroticism are complex dimensions made up of combinations of anxiety and impulsiveness. What *Gray* [1981] has done is to rotate *Eysenck's* dimensions by 45 degrees, as shown in figure 8. In this system the stable introvert would be low on impulsivity, but average on anxiety; the stable extravert would be low on anxiety, but average on impulsivity; the neurotic introvert would be high on anxiety, but average on impulsivity, whereas the neurotic introvert would be high on impulsivity, but average on anxiety.

In this system, increasing levels of anxiety reflect increasing levels of sensitivity to signals of punishment, signals of non-reward and novelty. There is an underlying physiological system (the 'behavioural inhibition system') [*Gray*, 1977], activity which controls the level of anxiety and which consists of an interacting set of structures comprising the septo-hippocampal system, its monoaminergic afferents from the brain stem, and its neocortical projection in the frontal lobe [*Gray*, 1977, 1982].

Increasing levels of impulsivity reflect increasing levels of sensitivity to signals of reward and signals of non-punishment. There is an underlying physiological system, independent of that which underlies anxiety, activity which controls the level of impulsivity, but little progress has been made in describing the structures that go to make up with system [*Gray*, 1981].

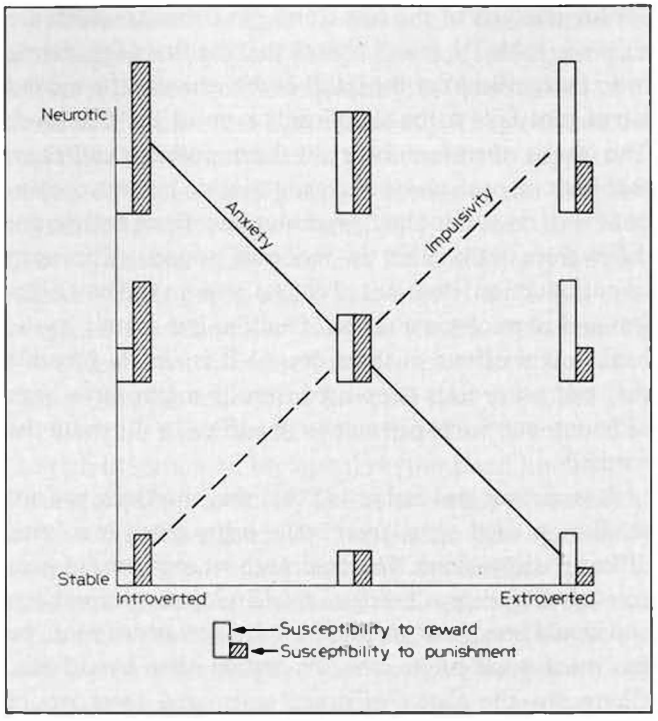

Fig. 8. Gray's model of personality [from *Gray*, 1981].

Much of the argument of *Gray* [1977] is concerned with drug effects on fear and frustration and the possible limbic sites of action of minor tranquillizers. This is not the place to discuss *Gray's* alternative theory or suggest the ways in which it would implicate changes in the drug postulates shown in figure 1. There are many arguments which speak against *Gray's* theory, and in favour of the original *Eysenck* theory, but it would take us too far afield to go into all the complexities of these theories. Let us merely note that one crucial area in which the theories and their differences can be tested is that of drug action, and hence research in this field is of importance not only for psychopharmacology, but also for psychology as a scientific study of behaviour.

Conclusions

It is not suggested that the drug postulates are *sufficient* to mediate a complete explanation of the results discussed in this chapter, but they point in the direction in which such explanations may be sought. At this stage of development of psychopharmacology, it would be unreasonable to expect much more of any hypothesis linking

personality with drug effects. The postulates merely mark a beginning for research, pointing in the direction in which fruitful research may be carried out. It is not suggested that the drug postulates are the end product of research in this direction; previous to their postulation most research was entirely ad hoc and lacking in theoretical sophistication. It is our hope that by setting down these postulates in testable form, and demonstrating that in many situations they do give positive results in the predicted direction, interest of psychopharmacologists may be aroused in adopting a more theory-oriented rather than a purely pragmatic point of view and to try to help in building up a generalized science of psychopharmacology which would inevitably soon discard these very simplistic and elementary principles. As *Popper* has always pointed out, theories in science are never 'true'; they may, however, be useful in guiding and directing research, and it is in this sense that these postulates have been set down.

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Prof. H.J. Eysenck,
Institute of Psychiatry,
De Crespigny Park, Denmark Hill,
London, SE5 8AF (England)