RESPONSE TO DRUGS AND PSYCHIATRY*

By

EDWARD MARLEY, M.A., M.D.(Camb.), M.R.C.P.E., D.P.M.

Formerly Senior Registrar
The Maudsley Hospital, S.E.5

FASHION is more deep-rooted than contemporary custom will allow, and the current enthusiasm for drug treatment in psychiatry is no evanescent fad. The Greeks made good use of the pharmacopœia, prescribing borage, buglosse, marigold, polypodie and epithyme for melancholy, more specifically recommending wormwood, centaury and pennyroll for the hypochondriac malady. Burton (a) discussing black hellebor, relates that its virtues were extolled by Galen, Pliny and Coelius Aurelianus, the mentally afflicted being sent to the Anticyrae, or to Phocis in Achaia to be purged, the plant growing there in abundance. Burton (b) describes how the Melangoga, or melancholy purging medicines, were classified as simple or compound, purging upwards or downwards. Asarum, brassivola, laurel, scilla, white hellebor, and antimony purged upwards, whereas polypodie, epithyme, black hellebor, lapis lazuli and aloes purged downwards. Sceptics throve then, no doubt, as they do now. Meryon (1861) mentions Asclepiades—dismissed by Pliny as an impudent quack, who contended that drugs injured the stomach and induced complaints more dangerous than those which they were intended to cure.

The slow-moving pace of ideas may be gauged from Culpeper, who lived in the mid-seventeenth century. He recommends melancholy thistle, germander, viper's bugloss, motherwort and burnet for melancholy. Of pills of fumitory, he warns, "It purges melancholy. Be not too busy with it I beseech you." He also condemns the cephalecs or narcoticks as being inimical to both brain and senses.

Weyer was alive a hundred years earlier and is said by Zilboorg to have undermined the authority of the Malleus Maleficarum by suggesting that the behaviour of witches might be attributable to the effects of drugs (Zilboorg, 1941). Weyer studied response to drugs in the modern manner, being interested in affective and ideational changes after their administration. There remained a paucity of sophisticated literary descriptions of the psychological effects of drugs until, as Lindemann and Clarke (1952) point out, the evolution of romanticism in late eighteenth century England. Then followed Beddoes' *Consideration on the Medicinal Use of Factitious Airs* (Beddoes and Watt, 1796) Sir Humphry Davy's accounts of self-experiments with nitrous oxide (1800), Moreau de Tours' monograph "Du hachisch et de l'aliénation mentale" (1845) and Ludlow's *The Hasheesh Eater* (Ludlow, 1857). De Quincey's *Confessions of an English Opium-Eater* appeared in 1822. Later (according to Walton, 1938a) Gautier and Baudelaire belonged to a group who staged hashish debauches in the Hotel Pimodan of the Latin Quarter, Baudelaire later including his impressions in *Le Paradis Artificiel.* The systematic use of drugs for the production of "artificial psychoses" dates from the work of Kraepelin (1883). By the turn of the century, self-experiments with mescaline had been reported by Prentiss and Morgan (1896), Mitchell (1896) and Ellis (1897). William James dabbled with nitrous oxide and ether, suggesting that "they stimulate the

* Awarded the Bronze Medal by the Royal Medico-Psychological Association, 1958.

mystical consciousness" so that "depth beyond depth of truth seems revealed to the inhaler" (James, 1910).

As for the treatment of mental illness, one finds Harley in 1869 recommending hemlock for mania, although bromides—long to remain the sheet-anchor of psychiatric treatment, were then in use. Barbitone was introduced in 1903 and the death knell of the bromides sounded by Barbour *et al.* in 1936. The following year, Putnam and Merritt (1937) reported that the anti-convulsive effects of a series of compounds (hydantoins) were not paralleled by their anaesthetic effect. This was a portent, for it had been assumed that a drug devoid of anaesthetic properties in large doses would also lack sedative or hypnotic effect. Still in 1937, Bovet and Staub described the first antihistamine and it was from these that some of the tranquillizing drugs were ultimately evolved.

Until then drugs had been classified as stimulant or depressant—labels of predictive merit when restricted to the effect of such substances on isolated organs. With respect to behaviour (and mental phenomena) the specificity of drug action cannot be delineated adequately in similar terms. If one is to define this action, it is essential to recognize participating variables other than those confined to the organism and drug. Such is the complex interplay even at the phenomenological level, that it invites Strauss's description (Strauss, 1953) of psychosomatic relations. "We have mind acting on mind as the efficient cause, mind acting on body, body acting on mind, and body acting on body as causae agentes"—only somewhere in this particular context, a chemical spoke has been inserted.

Symptomatic relief is the minimal goal of drug administration, and Modell (1955a) suggests that the "qualities which determine both the therapeutic end-point and the toxic limitation of a drug are inherent in the substance itself, in the patient, and in the disease". If we are moving to a rational rather than an empirical basis for drug treatment of mental illness, then we must be cognizant of all factors determining drug response.

Individual Variability and Drug Response

Individual variation in drug response is well known, and Lewin (1931a) suggests that Galen was familiar with its existence. Ellis (1946) quotes from a footnote to the *Arabian Nights* illustrating this theme. "It is impossible to say how Indian Hemp—like opium, datura, ether and chloroform, will affect the nervous system on untried man. I have read a dozen descriptions of the results, from the highly imaginative Monte Cristo to the prose of prosaic travellers; and do not recognize that they are speaking of the same thing."

The precise formulation of this topic owes much to the ideas of Clark. As he remarks, "Variation may be regarded as one of the fundamental characteristics of living matter, and it is always found when the individuals of any population are measured in any way" (Clark, 1932a). The variation in response to drugs cannot therefore be a matter for surprise, and certain factors are recognized which are likely to determine variable response to drugs.

Clark (1932b) distinguishes between static and dynamic variants influencing drug response, an important differential criterion being that with the static variant there is a likelihood of the distribution of response approximating to the normal or bell-shaped type, whereas any form of distribution may occur with the dynamic variant. The symmetrical characteristic curves (curves relating dose of drug and incidence of some effect) occurring with mammals or other large organisms should approximate to the normal probability curve (Clark, 1932c). The normal probability curve is obtained when each measurement is

affected by a considerable number of independent factors, the curve expressing the chances of the various possible combinations of these factors. The curve does not show that all the factors have a symmetrical action, but a symmetrical curve is unlikely if a few of the factors are of greater weight than the remainder and have an asymmetrical action (Clark, 1932c). The classic study by Hanzlik (1913) demonstrated that the distribution in sensitivity to the toxic effects of salicylate was that of a normal curve. Newman (1947) showed the same thing for the distribution of failure at a co-ordination test after amylobarbitone sodium, as did Shagass and Naiman (1956) for the distribution of the sedation threshold.

Because a distribution follows some simple statistical parameter, it would be unwise to assume that response was determined in as simple a fashion. Clark showed that response to drugs at the simple isolated organ level is incapable of a single interpretation and he mentions three formulae each satisfactory for objectifying the identical set of dose (x) and response (y) data. These are (1) the hyperbola, $kx=\frac{y}{100}-y$; (2) the exponential, $k=\log(ax+1)$ and (3) the parabola, $kx=y$ (Clark, 1932d). He cautions (Clark, 1932e) "highly complex systems may provide the simplest quantitative relations between dosage and action of drugs, and the most probable reason for any such apparent simplicity is that a large number of variables are present but mutually cancel each other". This should be borne in mind when one attempts to isolate variables affecting human response to drugs.

Variables determining drug response include body weight, surface area, age, and sex. Orton, 1957, suggests that sex differences may determine response to tranquillizers, and that methylpentynol helps females but not males. Marquis *et al.*, 1957 found meprobamate more efficacious in reducing anxiety in females than males. Other variables may be haemoglobin levels, hepatic and renal function. Of more interest to the psychiatrist is the alleged relation between personality and reaction to drugs. Kennedy (1957) alluded to the lack of work in this field and it is salutary to find Jonathan Hutchinson (1884) remarking "Our forefathers, who knew far less about the details of pathology than we do, attached far more importance to such matters as temperament and diathesis. They were accustomed to prescribe for a man's temperament . . .". Modell enigmatically concurs—"There must indeed be constitutional features which enter into the response of a particular patient to a particular drug" (Modell, 1955b).

Burton (c) quotes from Dioscorides that "white hellebor should not be taken by old men, youths, such as are weaklings, nice or effeminate, or fear strangling". In 1858, Kidd wrote that hysterical or nervous young women require greater quantities of inhalants to produce anaesthesia. In more modern vogue, McDougall (1929) suggested that the marked extraverted personality was susceptible to the influence of alcohol, whereas the introvert was more resistant. Lewin (1931b) probably implies the same thing when he held that each person has his own "toxic equation". Sheldon classified body type into three components (endomorphy, mesomorphy, and ectomorphy) each correlating with a group of traits described as viscerotonia, somatonia, and cerebrotonia. He asserts (1942a) that cerebrotonics are resistant to alcohol and cerebral depressants. Viscerotonics respond well to alcohol, with no sense of dizziness, drowsiness or fatigue (Sheldon, 1942b) but somatonics are susceptible to central nervous system depressants (Sheldon, 1942c).

Vernon, Fleming, Eysenck and Cattell have advocated a dimensional approach to personality assessment, and Vernon, like Eysenck, believes that personality can be resolved into orthogonal dimensions along which individuals can be measured. Eysenck (1953) termed two of these dimensions "Neuroticism-Normality" and "Extraversion-Introversion" and tests were devised for

measuring these quantities (Eysenck, 1955, 1956, 1957a). Assuming that the tests do objectify these aspects of personality then it should be simple to ascertain whether extraverts are susceptible and introverts resistant to central nervous depressants. Eysenck (1957b) considers that "The most important variable in predicting the effects of a drug, and in prescribing the particular dosage required for a specific purpose, would be the excitation-inhibition ratio (in the Pavlovian sense) obtaining within the particular person concerned."

Work along these lines was initiated by Shagass. Shagass (1954) described 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 on a dose:weight basis of amylobarbitone sodium. Shagass concluded initially that the sedation threshold is an index both of anxiety, and what he designates impairment of ego-function. Shagass and Naiman (1956) elaborated this argument, contending that extraverted individuals (hysterics and psychopathic personalities) have a low sedation threshold, whereas introverted subjects (patients with anxiety states, obsessional or depressive illnesses) have a high sedation threshold. As the alterations in the electro-encephalogram and speech (increase in 15–30 cycles-per-second activity recorded over the frontal and central regions of the brain and the onset of dysarthria) taken as the end-points for the sedation threshold are those indicating intoxication by the particular drug, it follows that extraverted individuals would manifest susceptibility to central nervous system depressants while introverted patients would be resistant.

Justifiable criticism of Shagass's work has been forthcoming (Thorpe and Barker, 1957; Ackner, 1958; Pampiglione, 1958) the objections being to the difficulty of determining accurately the specified end-points. Pampiglione (1958) 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."

Apart from susceptibility there are other qualities of drug response. Kornetsky and Humphries (1957) found that subjects with high scores on the Depression and Psychoaesthenia scales of the Minnesota Multiphasic Personality Inventory responded with maximum subjective changes after chlorpromazine, meperidine, secobarbitone or lysergic acid diethylamide (LSD). It was surmised that there are reactors and non-reactors to drugs of whom the reactors are likely to be individuals who are depressed and/or likely to experience unreasonable fears, as well as to over-respond to environmental stimuli. Felsinger *et al.*, 1955 believed that subjects with abnormal personalities responded atypically to amphetamine and morphine. By degrees then the emphasis is changing from drug reaction and personality to psychiatric illness and drug response.

Goodman and Gilman (1955) mention that "hang-over" the day after barbiturate administration is indicative of idiosyncrasy to the drug, and that this is prone to occur from small doses of the substance in neurotic patients. Dickel and Dixon (1957) recounted their experience of tranquillizing drugs prescribed to 8,200 individuals with psychosomatic illnesses. They found that 4–5 per cent. of their population (328 cases) developed physical disturbances during treatment, while over 30 per cent. (2,527 subjects) showed behavioural changes or striking alterations in the mental state. Anxious patients became so depressed as to attempt or commit suicide; calm people became hypomanic, others seemed more anxious, and some exhibited amoral behaviour alien to their previous character. Dickel and Dixon linked the presence of anxiety with adverse response to drugs.

Dickel and Dixon's conclusions are novel in that they point to the adverse effects of drugs hitherto considered most suitable for alleviating anxiety, and although Kornetsky *et al.*, 1957 have indicated a possible dichotomy between the objective and subjective effects of a drug making it impossible to predict accurately the extent of one from the other, the fact that so many anxious individuals developed physical signs with tranquillizing drugs reflects doubt on Shagass's contention that anxiety can be equated with a high sedation threshold and that only one personality dimension (extraversion-introversion) is linked with drug susceptibility. It should be a simple matter to elucidate to what extent say the dimension of Neuroticism-Normality contributes, if at all, to subjective and/or objective response to drugs.

The type of psychiatric illness also determines the dose of drug required. Variation in reserpine requirements for neurotic and psychotic populations was noted by Kline (1956a) who suggests that this may be due to some fundamental metabolic difference. Kline (1956b) also mentions that the scatter in reserpine dosage is greater among neurotics than among psychotics. Moore and Martin (1957) who used reserpine, epitomized their conclusions thus, "Each case must be treated individually, and dosage modified according to the side-effects and the mental state." Rees and Lambert (1955) found considerable variation in the optimum dose of chlorpromazine for anxiety states, while for psychotics, Lieberman and Vaughan (1956) allude to the variability in response to the drug. Mayer-Gross *et al.*, 1953 mention that schizophrenics have greater tolerance to LSD than normals, while Lindemann (1934) found distinct differences between schizophrenic and neurotic individuals in their reaction to drugs, Sargant and Slater (1954a) point to the wide range of response to amphetamine sulphate, and it is known that some psychopathic patients may receive continued large doses of the substance without sleep disturbance (Hill, 1947) as can children with behaviour disorders associated with electroencephalographic abnormalities (Sargant and Slater, 1954b). Anomalous response to amphetamine was encountered by Cameron and Kasanin (1941) in two patients whose sleep improved after the drug.

Sargant seems always to have been interested in variability of response to drugs, noting of soldiers with acute psychiatric illness that some respond well, but others by worsening of their symptoms, to heavy sedation (Sargant and Shorvon, 1945). He comments (Sargant, 1956) that it is the hysterical subject who is likely to become ataxic after less than 1 gr. of phenobarbitone daily, whereas the strong constitutionally aggressive patient may get only a modicum of sedation from half-a-bottle of whisky. Sargant subscribes for explanation to Pavlov's work (1927) demonstrating that dogs with dissimilar constitutions require different doses of bromide to restore nervous stability. Pavlov's "strong excitatory dogs" which easily developed stable conditioned salivary responses (said to correspond with the aggressive subject) needed eight times more bromide than a dog of the same body weight but with a "weak inhibitory" constitution and which developed conditioned salivary responses with difficulty (apparently corresponding to the hysterical patient).

This is an argument capable of verification. Franks (1957) demonstrated a relation between the conditioned eyeblink response and personality dimensions. He showed that conditionability was linked with introversion-extraversion (extraverts condition badly, introverts condition well) but was unrelated to neuroticism. Franks extended his work to the clinical field, discovering that neurotics of the introverted type (anxiety and neurotic depressive reactions) condition easily, but extraverted neurotics (conversion hysteria)

condition with difficulty (Franks, 1956). Using such an approach, supplemented by personality questionnaires, one should be able to quantify personality attributes in terms of susceptibility. The difficulty about personality or questionnaire studies applied to psychiatric patients is that test-retest data rarely exist for patients who once ill have since recovered. An atypical response (susceptibility) to the drug may therefore be related primarily to the illness or to the basic personality. The other objection in this instance, is of grafting conclusions from animal work on to humans, and that the factors involved in the development of conditioned salivary responses may bear no relation to those implicated in the development of the conditioned eyeblink response.

Other factors contribute to drug response. Hill *et al.*, 1955 showed that motivation was an important variable, for the effects of morphine and pentobarbitone on reaction time could be altered by penalizing slow responses with an electric shock. They amplified this work (Hill *et al.*, 1957) this time substituting pleasant rather than unpleasant incentives for the testee. They found that morphine and phenobarbitone might retard, facilitate, or have no effect on the performance, depending on the incentive.

It has also been construed that individuals with a predisposition to mental disorder may react abnormally to medication, a special instance being the response to ACTH and cortisone (Evans and Rackemann, 1952; Cope, 1953). In a typical searching article, Lewis and Fleminger (1954) confound these strictures, concluding that predisposition to develop untoward mental symptoms with ACTH or cortisone could not be assumed in patients with unstable neurotic personality or a history of mental illness.

So far we have confined ourselves mainly to the patient himself but there are other external variables influencing his reaction to drugs. As Foulkes and Anthony (1957) remark, "Even in the most isolated and insulated conditions, in certain kinds of stupor and catatonic episodes, human beings do retain some relationship with the environment." Some intriguing facts have been thrown up by animal investigations. Chance (1946) noted that mice given amphetamine evinced little response when kept separately, but if grouped together, then aberrations of behaviour appeared. It seemed that the activity of one mouse excited another, eventually communicating itself until all the animals were hyperactive. It was found that the LD 50 of amphetamine for solitary mice was 90 mg./kg. but only 7 mg./kg/ when groups of mice were kept in a confined space. Chance (1956) also reported that the response of rats to follicle stimulating hormone was modified by the environment. Similarly, Chen (1954) noted that the effect of a hypnotic in rats and dogs varied with the degree of isolation of the animal. Woolley found, after the administration of LSD to mice to make them walk backwards, that the effect could be abolished by injecting carbamylcholine into the mouse's lateral cerebral ventricle. It was vital to keep the mice caged separately for at least a day before the experiments, otherwise the drug either failed to abolish the LSD effect or there was a greater scatter in the amount of drug required to do so (Woolley, 1955). Woolley attributed the discrepancy to the fact that "excitement engendered by suddenly creating a new social group may have influenced the production of endogenous acetylcholine".

Lindemann and Clarke (1952) say this in respect of human reaction to drugs, "Situational factors, both those in the patient's life and those in the immediate experimental situation, may significantly alter the prospect that a given response will occur." Rathod (1958) indicated that environmental factors play a large part in the apparent effectiveness of tranquillizers in the treatment of disturbed patients. Sabshin and Eisen (1957) listed a number of social factors

likely to determine response to drugs. These included (1) the attitude of the psychiatrist towards such treatment, (2) the quantity and quality of the ward personnel, (3) the physical construction of the nursing unit, the number of patients per room, the size of the unit, and the available recreational space, and (4) the type of patient being treated together with the degree of disturbance on the ward.

Lindemann and Malamud (1934) suggested that "each drug has certain specific characteristics, but these are quite closely related to the conditions present at the time when these specific effects are produced". Grace (1954) writes, "In evaluating a drug one needs to know not only the nature of the drug but also the status of the individual at the time the drug is given." An amplified statement comes from Savage (1956). He considers that among the factors determining response to LSD, the personality of the subject, his psychological defences and psychopathology are important. Individuals with good defences evince little reaction; on the other hand, pre-schizophrenics may develop a full unfolding of their latent psychosis. The mental set of the individual at the time of the experiment also contributes, as well as the reasons for taking the drug. Individuals with moderate anxiety tend to minimize or deny the onset of the LSD experience, but subjects with overwhelming anxiety undergo an intense reaction. (Denber and Merlis, 1955 suggested that anxiety seemed to be the determinant of response to mescaline, its presence being associated with a florid mescaline picture, its absence being correlated with apathy and an absence of symptoms.) Neurotic motivations for receiving the drug portend a severe response because of the guilt engendered in acquiescing to hostile or dependent wishes. A subject who takes the drug when anxiety free, and on another occasion suffering from marked anxiety, will then have a more severe reaction. The presence of another person minimizes the toxic response; loneliness exacerbates it.

Before leaving the matter of individual drug response, reference must be made to the "placebo responder", recent interest being sparked off by Wolf (1950). Apart from the fact that previously this has been an unsuspected quantity in drug response, either enhancing or subtracting from drug effects, the practical importance of the placebo responder is that a 15–58 per cent. favourable response may follow its administration (Beecher, 1955). Tibbetts and Hawkings (1956) claim that the majority of "novel physical treatments" such as carbon dioxide inhalation and intravenous acetylcholine "are likely to prove placebos".

Symptomatic Response to Drugs

The personal equation is encountered in the variability of symptomatic response to drugs. Walton (1938b) says this of response to marihuana, "Some individuals seem to be very limited in the sensations they experience, whereas others are subject to an almost infinite variety of emotional and physiologic reactions." Ayd (1957) mentions that patients who complain of depersonalization or feelings of unreality are often made temporarily worse by chlorpromazine. Moreover, obsessionals and hysterics are prone to react to the side-effects of tranquillizers which they then make the subject of their complaints. Kinross-Wright (1956) noted that neurotics became more anxious with chlorpromazine, and neurotic depressives more depressed. Salisbury and Hare (1957) remark that central nervous stimulants are not of benefit in schizophrenia. Sargant and Slater (1954c) are more dogmatic: "Benzedrine, in the schizophrenic, may precipitate an unexpected outburst of excitement, or provide the initiative to carry out a murderous attack inspired by the patient's delusions." Esoteric behavioural responses have been ascribed to the tranquillizers. A house-

breaking and motor-cycle fatality occurred after two youths had each taken between 0·75–1·0 g. of methylpentynol (*Lancet*, 1955) and Pratap (1956) refers to motor accidents and to individuals submitting to seduction by strangers after drugs. As Weatherall (1957) interpolates "Controlled studies are particularly lacking in these circumstances and it is very uncertain whether some of the events described would not have occurred without the intervention of a tranquillizer." Leiberman and Vaughan (1957) remarked on the indirect effect of chlorpromazine on the behaviour of chronic psychotics: "When the most disturbed members of the community become quiet and co-operative, other patients become more settled and socially improved."

Most drug-induced symptoms are non-specific in character, probably on account of the limited number of behavioural, affective, and ideational responses available, the brain (personality) acting, in the Sherringtonian sense, as the final common path for their determination. It may seem facetious to emphasize the non-specific symptomatic effect of drugs, but Curran after experience with bromide intoxication (Curran, 1938) believed that he could distinguish features specific to drug intoxications, asserting that paraphasia and hallucinations at a distance were the hall-marks of bromide deliria (Curran, 1944). There seem to be no logical grounds for assuming such symptomatological exclusiveness, and Mayer-Gross *et al.* (1954a) allude to paraphasia in delirium tremens. Stengel and Mayer-Gross (1945) refer to paraphasic disturbances during recovery from hypoglycaemia. They noted, in deference to Paterson's criticism of a quantitative one-dimensional idea of consciousness (Paterson, 1944) that there were at least four levels of consciousness during hypoglycaemic arousal, paraphasia being associated with least clouding of consciousness. Paraphasia has also been encountered with methylpentynol intoxications (Marley, 1955; Marley and Chambers, 1956). Weinstein and Kahn regard paraphasia as one manifestation of the language of denial. They were able to reproduce symptoms of denial (anosognosia) by barbiturate administration in patients with pre-existing brain damage. It seemed that the type of denial expressed was predominately determined by the character of the premorbid personality (Weinstein and Kahn, 1955a). Paraphasia was evident only when the patients were required to name objects associated either with their illness or some personal problem (Weinstein and Kahn, 1955b). They concluded that motivation to deny illness and incapacity exists in everyone and that the phenomena of verbal denial such as disorientation, reduplication, and paraphasia, are modes of adaptation to stress rather than individual deficits (Weinstein and Kahn, 1955c). It is intriguing then that Teitelbaum (1941) demonstrated visuo-spatial disorders and anomalies of body image induced by hypnotic suggestion, as was shown for Gerstman's syndrome by Stanton (1954).

Affective changes follow the administration of many drugs, being categorized as non-specific by Cleghorn (1952). Elevation of mood is conventionally associated with the administration of dextro-amphetamine sulphate (Peoples and Guttman, 1936; Guttman and Sargant, 1937) and more recently of "Preludin" (Randell, 1957) and "Meratran" (Begg and Reid, 1956; Fullerton, 1956). Depressive mood changes may also follow the ingestion of cerebral stimulants (Cleghorn, 1952; O'Flanagan and Taylor, 1950; Shorvon, 1945; Bethell, 1957; Connell, 1957a). Both elation and depression may complicate barbiturate therapy (Curran, 1944; Stafford-Clark, 1957). Walton (1938c) reports: "Euphoria or apprehension may follow marihuana. The extent to which these effects occur is thought by some to be due to the preliminary state of the mind." Anderson and Rawnsley (1954) noted a differential effect of

LSD on mood. They say, "On occasions the drug may seem to underscore the clinical picture, e.g. depression may become enhanced, but next day the same dose may elicit a state of euphoria in the selfsame patient". Mood changes are common with the tranquillizers, occurring with methylpentynol (Glatt, 1955; Marley and Chambers, 1956) meprobamate (Hollister *et al.*, 1957), chlorpromazine (Ayd, 1955) and reserpine (Freiss, 1954; Wilkins, 1954; Wallace, 1955; Platt and Sears, 1956). Kline (1956c) suggests that depression associated with reserpine therapy is not a specific drug effect but is due to the breakdown of the individual's ego defences. In a controlled trial with benactyzine, Hargreaves *et al.* (1957) found that five patients became more depressed. However, at the conclusion of the investigation, the mean "depression scores" for patients receiving the drug and those taking inert tablets were identical.

Wikler (1952a) points out that euphoria is a term with a variety of meanings, being conventionally defined as a sense of unusual well-being. However, what constitutes well-being for one person may differ radically from that in another, or for the same person at different times in different situations. Thus, a post-addict may vomit and appear pale after morphine, but reports of feeling unusually well. The euphoric state then seems to be related to reduction of pain, hunger and sexual urges. This type of person does not experience unusual well-being after barbiturates except in doses which produce gross intoxication, when euphoria seems to be associated with loss of self-control, "acting-out" of hostility and sexual aggressiveness, and impairment of the sensorium with anosognosia or denial of illness. Euphoria in non-addicts also describes phenomena with a wide spectrum of meaning. Wikler concludes that euphoria and dysphoria are related each to the other in that they usually crystallize out in the presence of an impaired sensorium. Many drugs may produce euphoria in post-addicts and normal individuals (Wikler, 1952b). He cites alcohol, cocaine, cannabis, antihistamines, and large quantities of coca-cola and coffee. Mood changes are predominant in association with ACTH or cortisone treatment (Pearson and Eliel, 1950; Galdston *et al.*, 1951; Kirsner and Palmer, 1954) and with isonicotinyl hydrazide (Robitzek *et al.*, 1952). It would appear then that the terms "stimulant" or "depressant" outside the isolated organ context are not specific enough to be rigidly adhered to. In the human frame of reference such drugs may produce antipodal mood effects even in the same person.

Alteration in appreciation of the self, or what Schilder (1953a) terms "ego-experience" may follow administration of drugs. It would be a mistake to dismiss these changes as merely side-effects. Alteration in subjective time may occur with cerebral stimulants or depressants. Subjective time may appear to pass faster or slower, even culminating in an apparent standstill or timelessness. The rate of passage of subjective time may then be related to mood changes, or even, due to the effect of the drug, to alteration of body temperature. Pieron, who extended to temporal phenomena the idea relating chemical velocity to temperature (Arrhenius's equation), found that subjective time passed more rapidly with a lowered temperature, whereas with an increase of temperature, subjective time appeared to decelerate. Like other aspects of drug action, alteration of subjective time must be gauged against the background of the individual. "Psychological time is only an aspect of ourselves" (Carrell, 1948) and as Chessick affirms, "Time perception may be disturbed like any other perception, the experience of time being interwoven with emotional factors and the actual biological situation of the percipient" (Chessick, 1956). Alterations of subjective time can be elicited after many drugs, the most usual being LSD

and mescaline. Hughlings Jackson (1952) suggested that this "prolongation of time was the outcome of shallow dissolution of the highest centres and could be interpreted as a more rapid succession of a Time Constant peculiar to each individual". In fact "the dissolution of the highest centres" may not be obvious by ordinary clinical tests.

Disorders of subjective time are frequently associated with depersonalization. Again to quote Schilder, "Cases of depersonalization whose total experience is splintered, all have an altered perception of time" (Schilder, 1953b). Mayer-Gross (1935) regarded symptoms of depersonalization as of non-specific origin although resulting from a "preformed functional response of the brain". That depersonalization should occur in drug intoxications is not surprising for "Anything which leads to an altered state of consciousness or interferes with the final associative integration is bound to result in some changes in the relationship of the individual to his world, his body or his own psychic functioning" (Ackner, 1954). However, depersonalization (as well as subjective time disorder) may follow the administration of placebos. (Tyler, 1947 reports even hallucinations after administration of placebos.) For this reason, one is driven to enquiring what the symptom or drug represents to the patient, the psychodynamic basis being as applicable for drugs as for placebos. This personal and overvalued attitude towards drugs may be epitomized by Fenichel's comment, "Drug prescriptions, in so far as the patient believes that 'good stuffs' may neutralize 'bad stuffs' serve as a kind of artificial paranoia" (Fenichel, 1946).

The presence of illusions and hallucinations is also regarded as evidence of abnormal drug response, being almost constantly elicited by the "hallucinogens". Again it would be unwise to underestimate the personal element, and Ardis and McKellar (1956) comment, "With both mescaline and hypnagogic images, as with dreams, personal interests together with possibly deeper psychodynamics, seem to play a part in determining content." The lay writer Ward (1957) believes that LSD and mescaline "merely reveal the content of the subject's psychological being". Noyes (1951a) remarks that not only are illusions likely to be determined by the prevailing trend of the patient's pre-occupations, but that the mental material which is externalized in the form of hallucinations, is of a most intimate, subjective, and personal nature (Noyes, 1951b). Hadfield (1954) suggests that the hallucinations of fevers relate to repressed emotional experiences with which the subject's mind was already preoccupied.

Disorientation has already been briefly referred to in terms of denial of illness. Levin (1956) distinguishes between delirious and paranoid disorientation and that with organic brain disease. He considers the disorientation of toxic delirium the easiest to understand, being in Hughlings Jackson's words a "reduction to a more automatic condition" (Levin, 1936), the tendency being for the patient to mistake "unfamiliar for familiar" (Levin, 1945). Levin (1951) also formulated the entity of "partial delirium", which depended on the fact that orientation for time, being an abstract concept, was more vulnerable and consequently more likely to be upset than either orientation for place or person. In fact, one may not even find "partial delirium" and Connell (1957b) noted absence of disorientation as a symptom of amphetamine intoxications.

The extreme response to drugs is either stupor or delirium. Hoch (1921) comments that "If a stupor be a reaction type, its laws must be psychological." Bleuler (1944) considered delirium one of the basic modes of cerebral reaction. Mayer-Gross (1951) held that "Differences in symptoms found with various drugs have been attributed to differences in the personality of the intoxicated.

This may be true for an early stage or for cases of mild intoxication. The delirious picture, on the other hand, is probably common to all intoxicants when their effect is most severe. Between the two ends of the scale is a stage in which probably each drug shows certain special features." Hoch (1906) observed that excessive amounts of sedatives produce indistinguishable deliria, while earlier still, Anstie (1864a) likened alcohol to chloroform intoxication. He also quotes a case of belladonna poisoning with features resembling delirium tremens (Anstie, 1864b). Knauer and Maloney (1913) noted similarities between mescaline poisoning and alcohol intoxication. Leake (1957) discussing the hallucinogens, states that although these are related to the indoles, the same kinds of effects may be caused by ethanol and cannabis which are unrelated to the indoles. Mayer-Gross *et al.*, 1954b suggest that the patterns of reaction to intoxicants are best understood from a study of the effect of anoxia. They consider oxygen deficiency an important chapter in pharmacological psychiatry. MacFarland (1939) evidently believed this, demonstrating that the same degree of oxygen deprivation may elicit a variety of behaviour responses in normal subjects.

An important contribution came from Wolff and Curran (1935). After analysing deliria due to 27 different agents, they concur with Bonhoeffer and Krisch that there is no single aspect of a delirious reaction attributable to one substance alone. They point out that although Lewin described a number of specific reactions to drugs, he cites no information regarding the environmental setting or the personality status of the patients involved. As for the content of the deliria, they find that the more timid, shy, or insecure the patient, the greater fear they show, whereas those with the greatest self-confidence react with least. The age, sex, and intellectual endowment of the subject are reflected in the content. Persons with marked characteristics preserve these in their deliria—the bombastic, the pathologically suspicious, and those with obsessional trends manifesting these traits but in an intense form. Jellinek (1942) is more sceptical. "Although personality characteristics break through into the picture of intoxication, it is not possible to construct a law of relation between types of alcohol reaction and personality."

Validation of the Effect of Drugs Used in Psychiatry

Lewis (1958) says this in his Bradshaw lecture: "The cause of a mental illness is affected by so many factors, within the patient and his environment, it is so subject to unforeseen turns of fortune that a change cannot safely be attributed to therapeutic intervention unless it is frequently and regularly produced or comes prompt on the heels of the treatment. This . . . can be overcome by rigorous trials using, as controls, patients closely comparable to those who are treated. But matching psychiatric groups for this purpose is a daunting business, since they should be at least alike in the distribution of sex, age, intelligence, duration of illness, form and severity of illness, and previous illness."

Finney (1955) has declared as false the notion that investigations can be conducted statistically or non-statistically at the whim of the investigator. Claude Bernard, who showed no relish for the statistical method, would probably have granted it essential for the validation of drugs used in psychiatry. As he says, "Statistics therefore apply only to cases in which the cause of the facts is still indeterminate" (Bernard, 1949). Nevertheless, reluctance to employ sound methodology persists in spite of the fact that a statistical assessment implies ultimate economy of effort. As Hume (1957) remarks, "The theory of statistics enables an experiment to be planned so that the maximum information may be obtained from a limited number of observations required for a given conclusion."

The procedure adopted in 15 drug trials with reference to psychiatry and reported in British journals will now be analysed. The list is not intended to be comprehensive although in each instance control groups were employed (see Table I).

Selection of Patients. The patients were neurotics or psychotics, the neurotics being selected on the basis of symptomatology—usually the presence of anxiety and tension (Trials 2, 6, 7, 11, 13). In the case of psychotics, either one category of diagnosis was studied, e.g. schizophrenia (Trials 3, 5, 14, 15) or groups of mixed psychotics (Trials 1, 8, 9). In trials 10 and 12, both neurotics and psychotics seem to have been included, while in Trial 4 no diagnosis is specified, patients being selected because they were "restless, agitated, and showed psychomotor excitement". It is obviously an advantage to study a group as homogeneous as possible.

Sex. No sex was specified in Trials 10, 12 and 13. One sex was studied in Trials 3, 4, 5, 9, 15 and both sexes in Trials 1, 2, 6–8, 11, 14. In view of the possible differential response to tranquillizers (Orton, 1957; Marquis *et al.*, 1957) it would seem desirable to include patients of both sexes.

Type of Trial. It is axiomatic that drug trials should allow for proper controls, or, as Gaddum (1954) indicates, errors of the first order will result. Adequate control may be obtained by allotting the patients (preferably randomly) to the placebo and drug group (Trials 3, 4, 6, 7, 10, 11, 13, 15). In three trials, patients were more exactly matched for "neuroticism" (Trial 7) age, sex and aggressive behaviour (Trial 8) and suggestibility (Trial 11). Thorpe and Baker (Trial 15) resorted to the device of matching at the end of the experiment by use of analysis of covariance. A more sensitive method was utilized by Rees and Lambert (Trial 2) the drug and placebo being alternated and the groups split up so that a cross-over design could be applied. They say, "The method of using the patient as his own control has much to recommend it, especially if such methods as the double blind and sequence control procedures are utilized enabling the effect of suggestion to be ascertained and also the control of factors unrelated to the pharmacological effects of the drug." They echo the sentiments of Reid (1954): "Since each drug is tested consecutively on the same patient, variations due to differences in responsiveness between patients is eliminated." The "self-controlled" technique was used also in Trials 1, 5, 8, 9, 12, 14.

Hill (1951) has emphasized the difficulties in interpreting the results of trials in which the precaution of randomization has not been followed. Where drugs (or placebo and drug) follow one another in randomized sequence there may be a "residual" or "carry-over" effect from one drug to the next. This can be overcome by use of a special Latin Square for randomization, as elaborated by Williams (1949). The majority of the above investigators adhered to the "Double-blind" type of trial which according to Modell (1955c) is essential for studying the effects of drugs on symptoms.

Dose. Ideally at least two dose levels of the drug should be alternated with placebo, as it increases the probability that at least one of the doses will fall in the steepest part of the dose-response curve for the group. If three dose levels are employed then a dose-response regression and relative potencies of the drugs can be obtained. If two or more dose levels are used then they should be related geometrically to each other, as geometric increments or decrements of dose are associated with arithmetic increase or decrease of drug response. Drugs were given at two dose levels in Trials 1, 3, 8 and 15.

Analysis of Results. Although all the above drug trials were controlled,

TABLE I

Trial	Author	Drug	Dose Per Day	Diagnosis	Sex	Method	Assessment	Statistics	Results
1	Elkes and Elkes, 1954	Chlorpromazine	75-300 mg.	Chronic psychotics Mixed diagnoses	12 M 15 F	Blind and self-controlled	By doctor and nurse observers	No statistics	Drug may have its place in the management of the chronically overactive psychotic.
2	Rees and Lambert, 1955	Chlorpromazine	75 mg.	Anxiety states	49 M 101 F	Double-blind self-controlled	By patients' subjective responses and by clinical assessment	Critical ratio	Chlorpromazine significantly better than placebo for relief of anxiety.
3	Mitchell, 1956	Chlorpromazine	150 and 300 mg.	Chronic schizophrenia	36 M	Double-blind control group	Effect of drug on number of defined aggressive incidents	Statistical analysis, although no statistics given	Drug had no effect on aggressive outbursts.
4	Vaughan, Lieberman and Cook, 1955	Chlorpromazine	75-450 mg.	Diagnosis not specified	48 F	Double-blind control group	By clinical assessment	χ^2	Drug highly effective in control of agitation and excitement.
5	Salisbury and Hare, 1957	Chlorpromazine and Ritalin	150 mg. 30 and 60 mg.	Chronic schizophrenia	48 M	Double-blind self-controlled	Rating by doctors and nurses	P values	Significant improvement in behaviour with chlorpromazine Ritalin no better than placebo.
6	Davies and Shepherd, 1955	Reserpine	1 mg.	Neurotics with anxiety and depression	54 M and F	Double-blind control group	By doctors and patients with questionnaire	χ^2	Reserpine treated patients significantly benefited as compared to placebo group.
7	Ferguson, 1956	Reserpine	1-3 mg.	Neurotics with anxiety and tension	16 F 24 M	Double-blind control group (matched)	By clinical evaluation and 10 objective tests for anxiety	t tests	Effect of drug disappointing.
8	Wing, 1956	Reserpine	6 and 15 mg.	Chronic psychotics Mixed diagnoses	17 M 34 F	Double-blind Self-controlled in part	Rating by doctor, nurse and sociologist	t tests, χ^2, exact binomial product method. Analysis of variance	Reserpine decreased tension and increased sociability in aggressive and overactive chronic psychotics.
9	Fullerton, 1956	"Meratran"	6 mg.	Chronic psychotics Mixed diagnoses	40 M	Double-blind Self-controlled	Doctor and nurse clinical assessment	No statistics	Drug benefited patients with depressive features without anxiety or agitation.
10	Bockner, 1957	Methylpentynol	Up to 2 g.	Neurotics and psychotics	87 SNS	Control group	Clinical assessment	No statistics	Two-thirds of patients with anxiety improved.
11	Heller *et al.*, 1957	Meprobamate	1·6 g.	Neurotics—anxiety and tension	16 M 16 F	Matched control group	Clinical rating by doctor. Also questionnaire	t tests	Tension relieved by meprobamate.
12	Folkson, 1957	Meprobamate	0·8-1·6 g.	Neurotics and psychotics	23 SNS	Double-blind self-controlled	Clinical rating	No statistics	Drug effect disappointing.
13	Hargreaves *et al*, 1957	Benactyzene	3-8 mg.	Anxiety states less than 4 years duration	32 SNS	Double-blind Control group	Clinical rating by 3 doctors	t tests	Patients receiving drug showed greater improvement than those receiving placebo.
14	Gray and Forrest, 1958	Azacyclonal	60 mg.	Chronic schizophrenia	20 M 20 F	Double-blind Self-controlled	Clinical assessment	χ^2	Apparent superiority of placebo over drug
15	Thorpe and Baker, 1956	Chlorpromazine and "Pacatal"	Both at 150 and 300 mg.	Chronic schizophrenia	48 F	Blind. Matched control group	Doctor and nurse assessment. Rating scales	Analysis of Covariance	At dose 300 mg.daily chlorpromazine superior to Pacatal in relief of "deterioration" and restlessness.

in some instances there is no mention of the statistical criteria used; in others χ^2 or the "t" test were employed. Where quantitative data are available, analysis with χ^2 means a loss of potential information, as this is a test strictly for homogeneity of the experimental population. As indicated earlier, there are a large number of factors contributing to variability of response to drugs and use of the "t" test which only distinguishes between intergroup differences, precludes any elucidation but the summed effect of these variables. With analysis of variance, "The separation of variances ascribable to one group of causes from the variance ascribable to other groups" can be achieved (Fisher, 1950). Analysis of variance may therefore "be regarded as an extension of the 't' test appropriate to cases where more than two variables are to be compared" (Fisher, 1953). Wing (1956) used analysis of variance for validating part of her results. Thorpe and Baker (1956) relied upon analysis of covariance (an extension of analysis of variance). This allows one "to adjust experimental comparisons for extraneous causes of variation" (Kogan, 1953) and as with analysis of variance, permits the significance of interaction factors to be determined.

There are drawbacks to controlled drug trials. As Hargreaves *et al.*, 1957 say, "Although blind controlled trials are essential, they are exceedingly time-consuming." This can be overcome by using small numbers of patients. A method of sequential analysis (Armitage, 1950, 1957; Bross, 1952) has been described which is compatible with small sample sizes, and a controlled clinical trial using this method is described by Snell and Armitage (1957). Where one is attempting to evaluate the effect of a drug on a number of symptoms (e.g. anxiety, tension) and physical attributes (e.g. weight, appetite) it would be possible (Armitage, 1954) "to set up a sequential scheme for each characteristic separately, and stop the trial when a conclusion could be safely reached about some defined combination of measurements". The technique allows for individual preferences of patients for drugs and might overcome the valid objection voiced by Davies and Shepherd (1955) in that "Improvement was among the drug-treated patients as a group, and no information was obtained about the response to be expected in particular patients." Rushbrooke *et al.*, 1956 describe a trial with small samples, the drugs' efficacy being ranked by the patients themselves. There are drawbacks with psychiatric patients of relying exclusively on their opinion. and Snell and Armitage found as an additional difficulty that patients were rarely able to give a clear set of preferences for a particular drug. Foltz *et al.*, 1955 describe a trial using bio-assay statistics. Drug responses were given arbitrary ratings, the drugs being prescribed at various dose levels. The percentage of total possible drug responses were plotted against the logarithm of drug doses. (Gaddum, 1933, discussed the advantages of plotting doses on a logarithmic scale.) Equivalent potencies of the drugs could then be determined.

Assessment of Drug Effect. Assessment of drug effect may be subjective (by testee and/or observer) or objective (tests performed by patient). The ideal would be to combine as many subjective and objective criteria as expedient. Foltz *et al.* (1955) prefer to rely on the testee's opinion, averring that "objective tests require either mental activity or physical participation by the testee, which may modify or interfere with the drug's hypnotic effect". Assessment by the observer alone may also be erroneous. Mitchell (1956) suggested that evaluation of improvement by individual interview lacks objectivity, while Elkes and Elkes (1954) consider that a "false picture may be conveyed if undue reliance is placed on clinical interview alone". The nurse's impression was relied on in drug trials by Lasagna (1954) and Straus *et al.*, 1955, the latter

regarding it as consistently superior to that of the patient. Quantification of drug response by arbitrary rating rather than clinical assessment may be helpful, although Lorr (1954) comments, "attempts to refine clinical judgment with rating-scales and check-lists have not yet proved the superiority of such measures".

A statistically sophisticated paper concerning a trial of five tranquillizing drugs in psychoneurosis came from Raymond *et al.*, 1957. The patient "was asked to record his judgment of the effect of each drug day by day" on a questionnaire. "No objective rating by the interviewing psychiatrist was attempted." The authors found that four of the drugs were no better than placebo, although amylobarbitone was. However, Glaser (1953) and Glaser and Whittow (1953, 1954) have shown that completing questionnaires may give apparent responses with no drug, and repeated completion of questionnaires may diminish the number of responses, giving a false impression of habituation to the drug. Moreover, Imboden and Lasagna (1956) found a tendency for psychiatric patients to underestimate drug effects as compared with assessments by nurse observers. Findings such as these may explain why two of the above authors (Raymond and Lucas, 1956) from reports of psychoneurotics at clinical interview, had previously concluded that patients with anxiety and tension respond favourably to benactyzine as compared with placebo.

It might seem that too great an emphasis has been laid upon methodology and correct appraisal of drug response. However, "the need for statistical methods in therapeutic trials arises largely from the variability in response from one individual to another" (Robson and Keele, 1951) and it may be that variability is greater in psychiatric patients than normals. Certainly the standard deviations for results from schizophrenics are greater than those from normals (Hoskins, 1946).

Pharmacological Models

Having considered the factors contributing to, and symptomatic variability of, response to drugs—together with the statistical methods for validating response, some pharmacological models having special reference to psychiatry will be discussed. The range is considerable and only salient aspects can be dealt with embracing work on both animals and humans. It is disconcerting to find Macht even in 1920 suggesting apropos animal work that "the field of what may be termed psycho-pharmacology is virgin soil, full of possibilities".

Analogies drawn from animal work, particularly in the behavioural field, are likely to be unrealistic. Miller (1957a) indicates that "behavioural studies do not yield completely pure measures" and that some of the screening tests "may be measuring only side-effects that are reasonably specific, but irrelevant to the clinically useful effects of the drug" (Miller, 1957b). Apart from variability within species, there is variability between species—witness the difference of LD 50s for LSD and ergonovine between mice, rats and rabbits (Cerletti, 1956). Similarly the LD 50 for cerebral depressants is greater in mice and rats than higher animals. This should make us chary of transferring drug data from animal to animal let alone from animal to man. Laurence and Pond (1958) ascribed the relative failure of the tranquillizers to achieve that claimed for them, to the fact that "new drugs are perforce developed in the first place by animal experiments, that . . . are at present irrelevant to the clinical use to which tranquillizers are put".

1. *Drugs and Normal Behaviour.* As early as 1898 investigators were interested in the effect of alcohol on the rat's activity (Stewart, 1898). A prodi-

gious number of stimulant and depressant substances have been subsequently tested as to their effect on activity (Shirley, 1929; Searle and Brown, 1957). Refined techniques for quantifying animal movements have been developed such as the jiggle-cage of Tainter and co-workers (Schulte *et al.*, 1941). Interest was directed to the effect of drugs on learning and memory by use of maze experiments (McDowell and Vicari, 1921; Miller and Miles, 1936; Varner, 1933) and on the formation and extinction of conditioned reflex responses (Dworkin *et al.*, 1937; Gantt and Freile, 1944; Funderburk and Case, 1947). Dicker *et al.*, 1957 investigated the effect of methylpentynol on activity of rats using both an activity cage and a cruciform-shaped runway. The effect of the drug was to augment general activity and increase exploratory behaviour of the rat in the runway—in contrast to the effect of an equi-molecular dose of ethanol which decreased exploratory behaviour. Almost analogous investigations are made in man and Hilgard (1948) comments, "The pharmacologist uses animal subjects in the try-out stages, to the extent that he finds that animals react somewhat comparable to man. He rests finally, however, only when he has established his findings on man."

Earlier reviews of the psychological effects of drugs were by Poffenberger (1914, 1916, 1917, 1919), Meyer (1922), Darrow (1929), Spragg (1941), Gray and Trowbridge (1942). This work has been criticized by Eysenck (1957c) as not forming part of a theoretical system and not leading to any rational prediction. Similar censure was passed by Trouton (1958). Eysenck postulates that depressant drugs increase central inhibition whereas stimulant drugs have the opposite effect. He gives references supporting his theory that stimulants should decrease reaction time, improve performance on psychomotor and intellectual tasks, increase tapping rate, inhibit ergographic fatigue, while depressant drugs have the opposite effect (Eysenck, 1957d). Other work from this laboratory concerns the effect of drugs on the after-effects of the Archimedes spiral and work decrement (Eysenck *et al.*, 1957a, b). The prediction (from his theory) that stimulant drugs would prolong after-effect and delay work decrement, came true.

It was shown too that the ingestion of amylobarbitone sodium is associated with an increase of extraversion as measured on the Guilford R scale (Franks and Laverty, 1955; Laverty, 1958). Franks and Laverty demonstrated that the drug depresses the formation of conditioned eyeblink responses, whereas (Franks and Trouton, 1958) amphetamine facilitates their formation. Work such as Eysenck's accepts for its credo that variable response to drugs may be in part and even a major part, determined by personality. Such a theory, to be comprehensive, must be able to explain phenomena such as drug specificity, tolerance and susceptibility. The ideas of McDougall and Sheldon regarding susceptibility have already been mentioned, including those of Shagass which were accepted by Eysenck. Shagass's work has come in for criticism and it is almost certain that susceptibility is not simply related to the extraversion-introversion continuum of personality.

If the work of psychologists would seem to lack pharmacological sophistication, they have nevertheless pointed the need for objectification of drug response. This has been sporadically applied by clinical workers. Objective criteria were used by Osmond (1956) and Abramson (1956) when investigating the effect of LSD. Abramson tackled the problem of tolerance and found he could predict acquisition and loss of tolerance to LSD from questionnaire responses. Loss of tolerance could be represented by the formula $\log \frac{A}{A-x} = k_A t$ where A is initial tolerance to LSD, x the amount of tolerance lost in time t,

and k_4 a rate constant. Idestrom (1954) demonstrated tolerance to phenobarbitone on flicker fusion. Hoffer (1957) employed objective tests in assessing response to adrenolutin. Dicker and Steinberg (1957) found 0·5 g. methylpentynol depressed autonomic reactions to a difficult motor task, and impaired the level of aspiration for performance as well as performance, results in contradiction to those of Trotter (1954) and Galley and Trotter (1958).

No unifying theme emerges from such work, apart from that inherent in the pharmacological action of the drug. Eysenck's attempts to predict effects in terms of personality must therefore warrant interest even if his conclusions be premature. It may be significant that Brengelmann (1958) found that "the results obtained with amytal and amphetamine are better understood on the basis of the implied pharmacological than from personality theory (Eysenck's) point of view".

One fruitful development in this field has been a better understanding of the placebo responder. Jellinek (1946) who investigated the comparative effectiveness of analgesics and found "an example of the rare U-shaped distribution" in his population, concluded there were individuals who tend to respond and individuals who do not tend to respond to placebos. Similar conclusions were reached by Beecher *et al.*, 1953 and Lasagna *et al.*, 1954. Trouton (1957) suggested that secondary rather than primary suggestibility was the trait related to placebo reactions, a trait not associated with any known personality dimensions.

If the field of psychopharmacology is to prosper, even in the absence of an integrating motif, sound pharmacological tenets must be adopted. The policy of determining drug effects at a single dose level should be recognized as fallible and proper dose-response curves constructed. This would lessen the possibility of recording artefacts of drug action as significant which could be shown to fall outside the dose-response range. A case in point is that of methylpentynol. A daily maximum dose level was initially recommended which was later discovered to fall in the toxic and not the therapeutic dose range (Marley and Bartholomew, 1958).

Of more potential interest to the psychiatrist is the relation of drugs to abnormal behaviour.

2. *Drugs and Abnormal Behaviour.* Pavlov (1927) described a method for producing "experimental neurosis". Considerable objections have arisen to this term, and it may be happier to substitute that suggested by Russell (1951) of "aberrant behaviour". Pavlov found that dogs developed behaviour resembling neurotic disturbance in man. Such disorganization of behaviour occurs when "incompatible response tendencies of similar strengths are simultaneously elicited under experimental conditions" (Russell, 1953a). Pavlov found that bromides ameliorated these disturbances in certain types of dogs. Not unexpectedly there is a species difference, Dworkin (quoted by Gantt, 1944) noting that hyperactive cats do not respond favourably to bromides. Developments along similar lines were made by Masserman (1943) and Maier (1949) ultimately inspiring work such as that of Jacobsen and Skaarup (1955a, b) who studied the modification of conflict behaviour in cats by anticholinergic compounds.

To obtain a definite answer in such experiments "the experimenter has invariably to restrict the animal's normal ways of behaving" (Katz, 1953). This is dwelt on by Russell (1953b). "Although such conflicts appear to be essential to the development of behaviour disorders they alone are not completely adequate. They must be accompanied by restraint of voluntary move-

ment, either physically, as in the case of the Pavlovian harness, or in terms of the subject's set, or past learning." Hebb (1947) who took for granted that the concept of neurosis is anthropomorphic as applied to animals, considered that the refusal of Masserman's cats to eat after feeding had been associated with a frightening air-blast was too specific to a particular situation to be identified with neurosis.

Brady (1957) feels that a more fruitful analysis of behaviour will stem from the operant conditioning techniques. Estes and Skinner (1941) first reported the technique of superimposing a conditioned emotional response on the lever pressing behaviour of rats. Since then the conditions for use of the free operant have been outlined by Skinner (1953) and Ferster (1953). As Brady and Hunt (1957) indicate, it is possible with this technique to study the effects of pharmacological agents "by separating the more specific emotional changes from the general behavioural and motor disturbances, debilitation, and the like that often appears as temporary and non-specific residuals of such treatments".

This may be a part answer to Chance (1957) who paraphrased the present situation thus: "The advent of the tranquillizers has found us completely unprepared. Some of the investigations throw up information of a non-specific nature. When the behaviour of the animal is used as the criterion of response, the attempt is not made to understand the behaviour but merely to define certain components which are then classified and modification by drugs noted". Chance indicates that a comprehensive notion of the normal behaviour of animals is required first as a yardstick for comparison.

Apart from modification of behavioural anomalies by drugs, aberrations of behaviour have been produced by drugs. De Jong found he could produce catatonic-like states in higher animals (1945a) with a wide range of substances (1945b). With inspired prescience (in view of the contemporary interest in indole, tryptamine and adrenaline derivatives) he examined a series of compounds related to mescaline and adrenaline for "catatonizing properties". Feldberg and Sherwood (1954, 1955) produced catatonic-like states in cats by intraventricular injections of dyflos (DFP), eserine, and bulbocapnine, as did Schwartz *et al.*, 1956 with adrenochrome and adrenolutin. The behavioural changes were related only to the motor component of catatonia, and not to catatonic schizophrenia.

What conclusions then are to be drawn from the interaction of pharmacology and animal behaviour? Can the findings be translated in a modified form to man, or considered primarily as an essay in comparative pharmacology? Perhaps the most reasonable answer is that of Blough (1957) who deemed that "the most far-reaching value of behavioural research with drugs is that it may lead to a better understanding of basic laws governing the normal behaviour of individuals of all species".

Mescaline and LSD have been used to produce "model psychoses" in man. Denber (1957) insists that it is meaningless to speak of mescaline psychosis, as the response is unpredictable, not every patient developing the so-called psychosis. Fischer (1957) gives five reasons (which taken singly or together are not crucial) for assuming that the model psychosis is not a drug intoxication but related to schizophrenia. Hoffer (1956) concurs with this. Osmond and Smythies (1952) are more discriminating, comparing mescaline intoxication not with chronic, but with acute schizophrenia. Hoch (1956) is adamant that the "psychosis-producing agents and the blocking agents are non-specific in action". Rothlin and Cerletti (1956) also regard the LSD picture as devoid of specific features.

The discovery that LSD antagonized 5-hydroxy-tryptamine (5HT), a putative central transmitter, lent wider significance to the above findings. It was suggested that artificial psychoses and even schizophrenia might be due to inhibition or accumulation or 5HT in the brain. It is important to recognize that this work bears only an indirect relation to events in the central nervous system. For instance, LSD was first found to be a 5HT antagonist on muscle receptors *in vitro*, e.g. rat uterus, guinea-pig ileum (Gaddum and Hameed, 1954; Gaddum *et al.*, 1955; Savini, 1956; Woolley and Shaw, 1953) or *in vivo* (Salmoiraghi *et al.*, 1957). Gaddum and Picarelli (1957) concluded there were two kinds of tryptamine (5HT) receptor. LSD acts at the muscle or D receptors, but not at the M or ganglion receptors. To explain the effect of LSD, one may have to postulate both D and M receptors in the brain. That there may be some connection between 5HT activity at muscle receptors and central phenomena was suggested by Vane (1958) using the rat stomach strip (Vane, 1957). The hallucinatory potency of a number of drugs (amphetamine, mescaline) paralleled their activity on tryptamine receptors in the rat stomach. Moreover, tryptamine derivatives such as N,N dimethyl and diethyl tryptamine may produce model psychoses (Szára, 1957; Böszörményi and Brunecker, 1957) and even athetoid movements. The only parallel between the effect of 5HT on muscle receptors and possible central nervous system receptors is outlined by Woolley (1957). Apparently, rat or human oligodendroglia contract in the presence of 5HT, but not after the addition of 5HT anti-metabolites. Woolley suggests this is a possible way interference with brain 5HT leads to hallucinations and convulsions.

Data have appeared which make the relation between LSD and 5HT difficult to reconcile with a simple antagonism hypothesis. Thus 2-brom-LSD (BOL) is as potent a 5HT inhibitor as LSD *in vitro* and *in vivo* (Cerletti and Rothlin, 1955) but has no effect on the mental state in man (Snow *et al.*, 1955). Ginzel and Mayer-Gross (1956) demonstrated that pre-treatment with BOL would abolish the effects of LSD, whereas BOL given intravenously at the height of LSD symptoms had no effect. Bradley (1958) found synergism rather than antagonism between the central effects of 5HT and LSD in cats. Moreover, Lessin and Parkes (1957) suggest the antagonism of LSD and reserpine for 5HT is non-specific, while Gaddum and Vogt (1956) conclude that the central antagonism between 5HT and LSD is unrelated to peripheral antagonism between the two.

A possible link of such work with mental illness is that tranquillizing drugs which are alleged to alleviate schizophrenias also antagonize (or simulate) the effect of 5HT. Costa (1956) found that LSD and mescaline increase 5HT evoked contractions of the rat uterus, but that tranquillizing drugs antagonize the effect of 5HT. Gyermeck (1955) reported that chlorpromazine antagonizes the effect of 5HT *in vitro* and *in vivo*. Marrazzi (1957) demonstrated that cerebral synaptic inhibition produced by mescaline could be prevented by the tranquillizers. One clinical application is the use of iproniazid (which inhibits amine oxidase, a 5HT catabolist) for the treatment of depression (Costa *et al.*, 1957). Complete recovery in patients who would normally have only responded to electroplexy was found by Pare and Sandler (1958).

It is difficult to accept a simple one-to-one relation between 5HT and antagonizing substances for the production of predictable mental anomalies. To begin with, the central effects of a drug may not be reflected by their peripheral activity (as noted for 5HT, reserpine and LSD already by Gaddum and Vogt, 1956). Thus Meyers and Abreu (1952) compared quantitatively some synthetic atropine-like drugs both as to their effectiveness in producing central

phenomena and as peripheral acetylcholine blocking agents, and found no correlation between the two. Even drugs antagonizing 5HT may produce their effect by acting on other possible central transmitters. For example, chlorpromazine has atropine activity (Burn, 1954) and reserpine may deplete not only 5HT but also noradrenaline (Burn and Rand, 1957, 1958). To further complicate matters Elkes (1956) suggests that "rather than thinking in terms of acetylcholine, noradrenaline, and 5HT alone as possible neurohumoral mediators, it would be wiser to think in terms of families of compounds related to but not identical with the parent molecule". Vogt (1958) concludes that the "antagonistic effects of 5HT and LSD on behaviour depend on selective sensitization or inhibition of a characteristic group of centres by each drug and not on simple interaction by competition for the same receptors within the brain".

A more general thesis is presented by McIlwain (1957) who comments, "The relationship of chemotherapy to the central nervous system is inherent in the reaction of the body to chemical substances." He then goes on to quote Barcroft's proposition that "The fixity of the internal environment is in short the condition of mental activity" (Barcroft, 1934) implying that constancy in the composition of body fluids is more important to the functioning of the brain than it is to other body activities. This would account for central changes after substances which find difficulty in crossing the blood-brain-barrier, e.g. the hexamethonium compounds which may produce delirium (Smith, 1956) but because they are quaternary salts, central effects are precluded on account of permeability considerations (Paton, 1957).

These then are a few of the ramifications between psychiatry, response to drugs, and pharmacological investigation. Recently there has been a closer integration of these than hitherto. In conclusion, therefore, although one might like to agree with Tainter (1956) when he remarks with reference to experimental psychiatry, "the signs pointing to the right experimental approaches have been perceived, so that we may look forward to a period of unprecedented progress from what has been a most disheartening morass", one should remember as did Cholden (1956) that "Today psychiatry feels itself somehow to be at the crossroads. It may be the same crossroads that investigators have been many times in the past when important information seemed forthcoming." One should then temper enthusiasm with scepticism, and recall that Bertrand Russell defined scepticism as "not merely doubt, but what may be called dogmatic doubt".

References

Abramson, H. A., *Neuropharmacology*, 1956. New York: Josiah Macy Jr. Foundation, p. 259.
Ackner, B., *J. Ment. Sci.*, 1954, **100**, 854.
Idem, *Proc. Roy. Soc. Med.*, 1958, **51**, 76.
Anderson, E. W., and Rawnsley, K., *Mschr. Psychiat. Neurol.*, 1954, **128**, 38.
Anstie, F. E., *Stimulants and Narcotics*, 1864a. London: MacMillan, p. 188.
Idem, *ibid.*, 1864b, p. 199.
Ardis, J. A., and McKellar, P., *J. Ment. Sci.*, 1956, **102**, 22.
Armitage, P., *J. Roy. Statist. Soc. B.*, 1950, **12**, 137.
Idem, *Quart. J. Med.*, 1954, **23**, 255.
Idem, *Biometrika.*, 1957, **44**, 9.
Ayd, F. J., *South. med. J.*, 1955, **48**, 177.
Idem, *Tranquilizing Drugs*, 1957. Pub. 46. Ed. H. E. Himwich. Washington: American Association for Advancement of Science. p. 176.
Barbour, R. F., Pilkington, F., and Sargant, W., *Brit. Med. J.*, 1936, *ii*, 957.
Barcroft, J., *Features in the Architecture of Physiological Function*, 1934. Cambridge: University Press.
Beddoes, T., and Watt, J., *Considerations on the Medicinal Use of Factitious Airs*, 1796. Bristol.
Beecher, H. K., *J. Amer. med. Ass.*, 1955, **159**, 1602.
Idem, Keats, A. S., Mosteller, F., and Lasagna, L., *J. Pharmacol.*, 1953, **109**, 393.

BEGG, W. G. A., and REID, A. A., *Brit. Med. J.*, 1956, *i*, 946.
BERNARD, C., *An Introduction to the Study of Experimental Medicine*, 1949. Schuman. p. 139.
BETHELL, M. F., *Brit. Med. J.*, 1957, *i*, 30.
BLEULER, M., *Schweiz. med. Wschr.*, 1944, **74,** 923.
BLOUGH, D. S., in *Psychotropic Drugs*, 1957. Amsterdam: Elsevier Publishing Company. p. 110.
BOCKNER, S., *J. Ment. Sci.*, 1957, **103,** 218.
BÖSZÖRMÉNYI, Z., and BRUNECKER, G., *Psychotropic Drugs*, 1957. Amsterdam: Elsevier Publishing Company. p. 580.
BOVET, D., and STAUB, A. M., *C.R. Soc. Biol. (Paris)*, 1937, **124,** 547
BRADLEY, P. B., *5-Hydroxytryptamine*, 1958. London: Pergamon Press. p. 214.
BRADY, J. V., *Brain Mechanisms and Drug Action*, 1957. Ed. W. S. Fields. Springfield, Illinois: Thomas. p. 111.
Idem and HUNT, H. F., *J. Psychol.*, 1955, **40,** 313.
BRENGELMANN, J. C., *J. Ment. Sci.*, 1958, **104,** 153.
BROSS, I., *Biometrics.*, 1952, **8,** 188.
BURN, J. H., *Proc. Roy. Soc. Med.*, 1954, **47,** 445.
Idem and RAND, M. J., *Lancet*, 1957, *ii*, 1097.
Iidem, *Brit. med. J.*, 1958, *i*, 903.
BURTON, R., *The Anatomy of Melancholy*, Volume 2. London: Walker *et al.* (1813 edition), p. 111.
Idem, *ibid.*, 106.
Idem, *ibid.*, 107.
CAMERON, W. M., and KASANIN, J., *New Engl. J. Med.*, 1941, **224,** 544.
CARRELL, A., *Man, The Unknown*, 1948. London: Penguin Books, p. 167.
CERLETTI, A., *Neuropharmacology*, 1956. Ed. H. A. Abramson. New York: Josiah Macy Jr. Foundation, p. 13.
Idem and ROTHLIN, E., *Nature*, 1955, **176,** 785.
CHANCE, M. R. A., *J. Pharmacol.*, 1946, **87,** 214.
Idem, *Nature*, 1956, **177,** 228.
Idem, *Lancet*, 1957, *ii*, 687.
CHEN, K. K., *Sedative and Hypnotic Drugs*, 1954. Baltimore: William and Wilkins, p. 48.
CHESSICK, R. D., *J. Nerv. Ment. Dis.*, 1956, **123,** 14.
CHOLDEN, L., *Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry*, 1956. New York: Grune and Stratton, p. ix.
CLARK, A. J., *The Mode of Action of Drugs on Cells*, 1933a. London: Arnold, p. 104.
Idem, *ibid.*, 1933b, p. 106.
Idem, *ibid.*, 1933c, p. 119.
Idem, *ibid.*, 1933d, p. 4.
Idem, *ibid.*, 1933e, p. 7.
CLEGHORN, R. A., *Amer. J. Psychiat.*, 1952, **108,** 568.
CONNELL, P. H., "Amphetamine Psychoses", 1957a. London University M.D. Thesis, p. 64.
Idem, *ibid.*, 1957b, p. 91.
COPE, C. L., *Brit. med. J.*, 1953, *ii*, 271.
COSTA, E., *Psychiat. Res. Rep.*, 1956, **4,** 11.
Idem, RINALDI, F., and HIMWICH, H. E., in *Psychotropic Drugs*, 1957. Amsterdam: Elsevier Publishing Company, p. 21.
CULPEPER, N., *The Complete Herbal*, Birmingham: Kynoch Press, 1953a. p. 502.
Idem, *ibid.*, 1953b, p. 562.
CURRAN, F. J., *J. Nerv. Ment. Dis.*, 1938, **88,** 163.
Idem, *ibid.*, 1944, **100,** 142.
DARROW, W., Psychol. Bull., 1929, **26,** 527.
DAVIES, D. L., and SHEPHERD, M., *Lancet*, 1955, *ii*, 117.
DENBER, H. C. B., in *Psychotropic Drugs*, 1957. Amsterdam: Elsevier Publishing Company, p. 26.
Idem and MERLIS, S., *Psychiat. Quart.*, 1955, **29,** 421.
DICKEL, H. A., and DIXON, H. H., *J. Amer. med. Ass.*, 1957, **163,** 422.
DICKER, S. E., and STEINBERG, H., *Brit. J. Pharmacol.*, 1957, **12,** 479.
Iidem and WATSON, R. H. J., *J. Physiol.*, 1957, **137,** 88.
DWORKIN, S., BOURNE, W., and RAGINSKY, B. B., *Canad. med. Ass. J.*, 1937, **37,** 136.
ELLIS, E. S., *Ancient Anodynes*, 1946. London: Heinemann, p. 78.
ELLIS, H., *Lancet*, 1897, *i*, 1540.
ELKES, J., *Brit. med. J.*, 1956, *i*, 512.
Idem and ELKES, C., *ibid.*, 1954, *ii*, 560.
ESTES, W. K., and SKINNER, B. F., *J. exp. Psychol.*, 1941, **29,** 390.
EVANS, R. R., and RACKEMANN, F. M., *Arch. intern. Med.*, 1952, **90,** 111.
EYSENCK, H. J., *Structure of Human Personality*, 1953. London: Methuen.
Idem, *J. Ment. Sci.*, 1955, **101,** 28.
Idem, *Eugen. Rev.*, 1956, **48,** 23.
Idem, *Rivista di Psicologica.*, 1957a, **4,** 113.
Idem, *The Dynamics of Anxiety and Hysteria*, 1957b. London: Routledge and Kegan Paul, p. 248.
Idem, *ibid.*, 1957c, p. 223.

EYSENCK, H. J., *ibid.*, 1957d, p. 239.
Idem, CASEY, S., and TROUTON, D. S., *J. Ment. Sci.*, 1957, **103,** 645.
Idem, HOLLAND, H., and TROUTON, D. S., *ibid.*, 1957, **103,** 650.
FELDBERG, W., and SHERWOOD, S. L., *J. Physiol.*, 1954, **125,** 488.
Iidem, *Brit. J. Pharmacol.*, 1955, **10,** 371.
FELSINGER, VON J. M., LASAGNA, L., and BEECHER, H. K., *J. Amer. med. Ass.*, 1955, **157,** 1113.
FENICHEL, O., *The Psychoanalytic Theory of Neurosis*, 1946. London: Routledge and Kegan Paul, p. 558.
FERGUSON, R. S., *J. Ment. Sci.*, 1956, **102,** 30.
FERSTER, C. B., *Psychol. Bull.*, 1953, **50,** 4.
FINNEY, D. J., *Experimental Design and its Statistical Basis*, 1955. London: Cambridge University Press, p. 1.
FISCHER, R., *J. Ment. Sci.*, 1957, **103,** 392.
FISHER, R. H., *Statistical Methods for Research Workers*, 1950. 11th ed. London: Oliver and Boyd, p. 211.
Idem, *The Design of Experiments*, 1953. 6th ed. London: Oliver and Boyd, p. 55.
FOLKSON, A., *J. Ment. Sci.*, 1957, **103,** 860.
FOLZ, E. L., DRACOS, F., and GRUBER, C. M., *Amer. J. med. Sci.*, 1955, **230,** 528.
FOULKES, S. H., and ANTHONY, E. J., *Group Psychotherapy*, 1957. London: Penguin Books, p. 215.
FRANKS, C. M., *J. abnorm. soc. Psychol.*, 1956, **52,** 143.
Idem, *Brit. J. Psychol.*, 1957, **48,** 119.
Idem and LAVERTY, S. G., *J. Ment. Sci.*, 1955, **101,** 654.
Idem and TROUTON, D. S., Personal communication, 1958.
FREISS, E. D., *New Engl. J. Med.*, 1954, **251,** 1006.
FULLERTON, A. G., *J. Ment. Sci.*, 1956, **102,** 801.
FUNDERBURK, W. H., and CASE, T. J., *J. Neurophysiol.*, 1947, **10,** 179.
GADDUM, J. H., *Reports on Biological Standards. III. Methods of Biological Assay Depending on a Quantal Response*, 1933. M.R.C. Special Report Series No. 183. London: H.M.S.O., p. 7.
Idem, *Proc. Roy. Soc. Med.*, 1954, **47,** 195.
Idem and HAMEED, K. A., *Brit. J. Pharmacol.*, 1954, **9,** 240.
Idem and VOGT, M., *ibid.*, 1956, **11,** 175.
Idem and PICARELLI, Z. P., *ibid.*, 1957, **12,** 323.
Idem, HAMEED, K. A., HATHWAY, D. E., and STEPHENS, F. F., *Quart. J. exp. Physiol.*, 1955, **40,** 49.
GALDSTON, M., WEISENFELD, S., BENJAMIN, B., and ROSENBLUTH, M. B., *Amer. J. Med.*, 1951, **10,** 166.
GALLEY, A. H., and TROTTER, P. A., *Lancet*, 1958, *i*, 343.
GANTT, W. H. (quoting Dworkin), *Experimental Basis for Neurotic Behaviour*. New York: Hoeber, p. 159.
Idem and FREILE, M., *Trans. Amer. Neurol. Ass.*, 1944, **70,** 188.
GINZEL, K. H., and MAYER-GROSS, W., *Nature*, 1956, **178,** 210.
GLASER, E. M., *Brit. J. Pharmacol.*, 1953, **8,** 187.
Idem and WHITTOW, G. C., *J. Physiol.*, 1953, **122,** 43.
Iidem, *Clin. Sci.*, 1954, **13,** 199.
GLATT, M. M., *J. Nerv. Ment. Dis.*, 1955, **122,** 390.
GOODMAN, L. S., and GILMAN, A., *The Pharmacological Basis of Therapeutics*, 1955. 2nd ed. New York: MacMillan, p. 138.
GRACE, W. J., *Amer. J. Med.*, 1954, **17,** 723.
GRAY, S., and FORREST, A. D., *Brit. med. J.*, 1958, *i*, 374.
GRAY, M. G., and TROWBRIDGE, G. B., *Psychol. Rev.*, 1942, **5,** 127.
GUTTMAN, E., and SARGANT, W., *Brit. med. J.*, 1937, *i*, 1013.
GYERMECK, L., *Lancet*, 1955, *ii*, 724.
HADFIELD, J. A., *Dreams and Nightmares*, 1954. London: Penguin Books, p. 7.
HANZLIK, P. J., *J. Amer. med. Ass.*, 1913, **60,** 957.
HARGREAVES, G. R., HAMILTON, M., and ROBERTS, J. M., *Brit. med. J.*, 1957, *i*, 306.
HARLEY, J., *The Old Vegetable Neurotics*, 1869. London: MacMillan, p. 56.
HEBB, D. O., *Psychosom. Med.*, 1947, **9,** 3.
HELLER, G. C., WALTON, D., and BLACK, D. A., *J. Ment. Sci.*, 1957, **103,** 581.
HILGARD, E. R., *Theories of Learning*, 1948. New York.
HILL, A. BRADFORD, *Brit. med. Bull.*, 1951, **7,** 278.
HILL, D., *Brit. J. Addict.*, 1947, **44,** 50.
HILL, H. E., BELLEVILLE, R. E., and WIKLER, A., *Arch. Neurol. Psychiat. (Chicago)*, 1955, **73,** 602.
Iidem, *ibid.*, 1957, **77,** 28.
HOCH, A., *Rev. Neurol. Psychiat. Edinb.*, 1906, **4,** 83.
Idem, *Benign Stupors*, 1921. New York: MacMillan, p. 243.
HOCH, P. H., *Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry*, 1956. New York: Grune and Stratton, p. 72.
HOFFER, A., *ibid.*, 1956, p. 44.
Idem, *Tranquilizing Drugs*, 1957. Pub. 46. Ed. H. E. Himwich. Washington: American Association for Advancement of Science, p. 73.

HOLLISTER, L. E., ELKINS, H., HILER, E. G., and PIERRE, R. S. E., *Ann. N.Y. Acad. Sci.*, 1957, **67**, 789.
HOSKINS, R. G., *The Biology of Schizophrenia*, 1946. 1st ed. New York: Norton, p. 158.
HUME, C. N., *Lancet*, 1957, *ii*, 1049.
HUTCHINSON, J., *The Pedigree of Disease*, 1884. London.
IDESTROM, C. M., *Acta Psychiat. et Neurol. Suppl.*, 1954, **91**, 1.
IMBODEN, J., and LASAGNA, L., *Bull. Johns Hopkins Hosp.*, 1956, **99**, 9.
JACKSON, HUGHLINGS J., *Selected Writings of John Hughlings Jackson*, 1932. Vol. 2. London: Hodder and Stoughton, p. 116.
JACOBSEN, E., and SKAARUP, Y., *Acta pharmacol. et toxicol.*, 1955a, **11**, 117.
Iidem, ibid., 1955b, **11**, 125.
JAMES, W., *The Varieties of Religious Experience*, 1910. 19th impression. London: Longmans, Green, p. 387.
JELLINEK, E. M., *Alcohol Addiction and Chronic Alcoholism*, 1942. Vol. 1. New Haven: Yale University Press, p. 89.
Idem, Biometrics Bull., 1946, **2**, 87.
DE JONG, H. H., *Experimental Catatonia*, 1945a. Baltimore: William and Wilkins, p. 12.
Idem, ibid., 1945b, p. 221.
KATZ, D., *Animals and Man*, 1953. London: Penguin Books, p. 52.
KENNEDY, A., *Brit. med. J.*, 1957, *ii*, 220.
KIDD, C., *On Æther and Chloroform as Anaesthetics*, 1858. London: Renshaw, p. 22.
KINROSS-WRIGHT, V., *Psychopharmacology*, 1956. Pub. 42. Washington: American Association for Advancement of Science, p. 36.
KIRSNER, J. B., and PALMER, W. L., *Ann. intern. Med.*, 1954, **41**, 232.
KLINE, N. S., *Psychopharmacology*, 1956a. Pub. 42. Washington: American Association for Advancement of Science, p. 89.
Idem, ibid., 1956b, p. 92.
Idem, ibid., 1956c, p. 88.
KNAUER, A., and MALONEY, W. J., *J. Nerv. Ment. Dis.*, 1913, **40**, 397.
KOGAN, L. S., *Psychol. Bull.*, 1953, **50**, 1.
KORNETSKY, C., and HUMPHRIES, O., *Arch. Neurol. Psychiat. (Chicago)*, 1957, **77**, 325.
Iidem and EVARTS, E. V., *ibid.*, 1957, **77**, 318.
KRAEPELIN, E., *Philos. Studien.*, 1883, **1**, 573.
Lancet, 1955, *ii*, 146.
LASAGNA, L., *J. Pharmacol.*, 1954, **111**, 9.
Idem, MOSTELLER, F., FELSINGER, VON J. M., and BEECHER, H. K., *Amer. J. Med.*, 1954, **16**, 770.
LAURENCE, D. R., and POND, D. A., *Brit. med. J.*, 1958, *i*, 800.
LAVERTY, S. G., *J. Neurol. Neurosurg. Psychiat.*, 1958, **21**, 50.
LEAKE, C. D., *Tranquilizing Drugs*, 1957. Pub. 46. Ed. H. E. Himwich. Washington: American Association for Advancement of Science, p. 2.
LESSIN, A. W., and PARKES, M. W., *J. Pharm. Pharmacol.*, 1957, **9**, 657.
LEVIN, M., *J. Ment. Sci.*, 1936, **82**, 1.
Idem, ibid., 1945, **91**, 447.
Idem, Amer. J. Psychiat., 1951, **107**, 689.
Idem, J. Ment. Sci., 1956, **102**, 619.
LEWIN, L., *Phantastica, Narcotic and Stimulating Drugs*, 1931a. Trans. P. H. A. Wirth. London: Kegan Paul, Trench, Trubner, p. 8.
Idem, ibid., 1931b, p. 9.
LEWIS, A. J., *Lancet*, 1958, *i*, 17.
Idem and FLEMINGER, J. J., *ibid.*, 1954, *i*, 383.
LIEBERMAN, D. M., and VAUGHAN, G. F., *Practitioner*, 1956, **177**, 632.
Iidem, J. Ment. Sci., 1957, **103**, 110.
LINDEMANN, E., *Amer. J. Psychiat.*, 1934, **90**, 1007.
Idem and CLARKE, L. D., *ibid.*, 1952, **108**, 561.
Idem and MALAMUD, W., *ibid.*, 1934, **90**, 853.
LORR, M., *Psychol. Bull.*, 1954, **51**, 126.
LUDLOW, F., *The Hasheesh Eater: Being Passages from the Life of a Pythagorean*, 1857. New York: Harper and Brothers.
MACFARLAND, R. A., *Res. Pub. Ass. Res. Nerv. Ment. Dis.*, 1939, **19**, 112.
MACHT, D. I., *Bull. Johns Hopkins Hosp.*, 1920, **31**, 167.
MAIER, N. R. F., *Frustration, the Study of Behaviour with a Goal*, 1949. New York: McGraw-Hill.
MARLEY, E., *Lancet*, 1955, *ii*, 535.
Idem and CHAMBERS, J. S. W., *Brit. med. J.*, 1956, *ii*, 1467.
Idem and BARTHOLOMEW, A. A., *J. Neurol. Neurosurg. Psychiat.*, 1958, **21**, 129.
MARQUIS, D. G., KELLY, E. L., MILLER, J. G., GERARD, R. W., and RAPOPORT, A., *Ann. N.Y. Acad. Sci.*, 1957, **67**, 701.
MARRAZZI, A. S., *Brain Mechanisms and Drug Action*, 1957. Ed. W. S. Fields. Springfield, Illinois: Thomas, p. 45.
MASSERMAN, J. H., *Behaviour and Neurosis*, 1943. Chicago: University of Chicago Press.

MAYER-GROSS, W., *Brit. J. med. Psychol.*, 1935, **15,** 103.
Idem, *Brit. med. J.*, 1951, *ii*, 317.
Idem, MCADAM, W., and WALKER, J. W., *J. Ment. Sci.*, 1953, **99,** 804.
Idem, SLATER, E., and ROTH, M., *Clinical Psychiatry*, 1954a. London: Cassell and Company, p. 349.
Iidem, *ibid.*, 1954b, p. 318.
MCDOUGALL, W., *J. abnorm. soc. Psychol.*, 1929, **24,** 293.
MCDOWELL, E. C., and VICARI, E. M., *J. exp. Zool.*, 1921, **33,** 209.
MCILWAIN, H., *Chemotherapy and the Central Nervous System*, 1957. London: Churchill, p. 283.
MERYON, E., *The History of Medicine*, 1861. Vol. 1. Longman, Green, Longman and Roberts, p. 39.
MEYER, M., *Psychol. Bull.*, 1922, **19,** 173.
MEYERS, F. H., and ABREU, B. E., *J. Pharmacol.*, 1952, **104,** 387.
MILLER, N. E., in *Psychotropic Drugs*, 1957a. Amsterdam: Elsevier Publishing Company, p. 84.
Idem, *ibid.*, 1957b, p. 85.
Idem and MILES, W. R., *J. Comp. Physiol. Psychol.*, 1936, **21,** 179.
MITCHELL, P. H., *J. Ment. Sci.*, 1956, **102,** 151.
MITCHELL, S. WEIR, *Brit. med. J.*, 1896, *ii*, 1625.
MODELL, W., *The Relief of Symptoms*, 1955a, Philadelphia: Saunders, p. 80.
Idem, *ibid.*, 1955b, p. 74.
Idem, *ibid.*, 1955c, p. 88.
MOORE, J. N. P., and MARTIN, E. A., *Brit. med. J.*, 1957, *i*, 8.
MOREAU, J., *Du hachisch et de l'aliénation mentale—études psychologiques*, 1845. Paris: Masson.
NEWMAN, H. D., *Stanf. med. Bull.*, 1947, **5,** 12.
NOYES, A. P., *Modern Clinical Psychiatry*, 1951a. Philadelphia: Saunders, p. 63.
Idem, *ibid.*, 1951b, p. 65.
O'FLANAGAN, P. M., and TAYLOR, R. B., *J. Ment. Sci.*, 1950, **96,** 1033.
ORTON, R., *Brit. med. J.*, 1957, *ii*, 220.
OSMOND, H., *Neuropharmacology*, 1956. Ed. H. A. Abramson. New York: Josiah Macy Jr. Foundation, p. 183.
Idem and SMYTHIES, J., *J. Ment. Sci.*, 1952, **98,** 309.
PAMPIGLIONE, G., *Proc. Roy. Soc. Med.*, 1958, **51,** 79.
PARE, C. M. B., and SANDLER, M., Personal communication, 1958.
PATERSON, A., *Proc. Roy. Soc. Med.*, 1944, **37,** 556.
PATON, W. D. M., *Ulster med. J.*, 1957, **26,** 17.
PAVLOV, I. P., *Conditioned Reflexes*, 1927. Trans. G. V. Anrep. London: Oxford University Press.
PEARSON, O. H., and ELIEL, L. P., *J. Amer. med. Ass.*, 1950, **144,** 1349.
PEOPLES, S. A., and GUTTMAN, E., *Lancet*, 1936, *i*, 1107.
PLATT, R., and SEARS, H. T. N., *ibid.*, 1956, *i*, 401.
POFFENBERGER, G. T., *Psychol. Bull.*, 1914, **11,** 408.
Idem, *ibid.*, 1916, **13,** 434.
Idem, *ibid.*, 1917, **14,** 408.
Idem, *ibid.*, 1919, **16,** 291.
PRATAP, H. J., *Brit. med. J.*, 1956, *i*, 1116.
PRENTISS, D. W., and MORGAN, F. P., *Therap. Gaz.*, 1896, **12,** 577. 3rd Series.
PUTNAM, T. J., and MERRITT, H. H., *Science*, 1937, **85,** 625.
RANDELL, J. B., *Brit. med. J.*, 1957, *ii*, 508.
RATHOD, N. H., *Lancet*, 1958, *i*, 611.
RAYMOND, M. J., and LUCAS, C. J., *Brit. med. J.*, 1956, *i*, 952.
Iidem, BEESLEY, M. L., O'CONNELL, B. A., and ROBERTS, J. A. F., *ibid.*, 1957, *ii*, 63.
REES, W. L., and LAMBERT, C., *J. Ment. Sci.*, 1955, **101,** 834.
REID, D. D., *Lancet*, 1954, *ii*, 1293.
ROBITZEK, E. H., SELIKOFF, I. J., and ORNSTEIN, G. G., *Quart. Bull. Sea View Hosp.*, 1952, **8,** 27.
ROBSON, J. M., and KEELE, C. A., *Recent Advances in Pharmacology*, 1951. London: Churchill, p. 376.
ROTHLIN, E., and CERLETTI, A., *Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry*, 1956. Grune and Stratton, p. 3.
RUSSELL, B., *History of Western Philosophy*, 1946. 1st ed. London: Allen and Unwin, p. 257.
RUSSELL, R. W., *Comparative Study of Behaviour*, 1951. London: H. K. Lewis.
Idem, in *Prospects in Psychiatric Research*, 1953a. Ed. J. M. Tanner. Oxford: Blackwell, p. 88.
Idem, *ibid.*, 1953b, p. 89.
RUSHBROOKE, M., WILSON, E. S. B., ACLAND, J. D., and WISLON, G. M., *Brit. med. J.*, 1956, *i*, 139.
SABSHIN, M., and EISEN, S. B., *Ann. N.Y. Acad. Sci.*, 1957, **67,** 746.
SALISBURY, B. J., and HARE, E. H., *J. Ment. Sci.*, 1957, **103,** 830.
SALMOIRAGHI, G. C., MCCUBBIN, J. W., and PAHE, I. H., *J. Pharmacol.*, 1957, **119,** 240.
SARGANT, W., *Brit. med. J.*, 1956, *i*, 939.
Idem and SHORVON, H. J., *Arch. Neurol. Psychiat.*, 1945, **54,** 231.

SARGANT, W. and SLATER, E., *An Introduction to Physical Methods of Treatment in Psychiatry*. 1954a. 3rd ed. London: Livingstone, p. 168.
Idem, ibid., 1954b, p. 143.
Idem, ibid., 1954c, p. 169.
SAVAGE, C., *Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry*, 1956. Ed. L. Cholden. New York: Grune and Stratton, p. 41.
SAVINI, E. C., *Brit. J. Pharmacol.*, 1956, **11**, 313.
SCHILDER, P., *Medical Psychology*, 1953a. Trans. and ed. D. Rapaport. International Universities Press, p. 298.
Idem, ibid., 1953b, p. 310.
SCHULTE, J. N., REIF, E. C., BACHER, J. A., LAWRENCE, W. S., and TAINTER, M. L., *J. Pharmacol.*, 1941, **71**, 62.
SCHWARZ, B. E., NAKIM, K. G., BICKFORD, R. G., and LICHTENHELD, F. R., *Arch. Neurol. Psychiat.*, 1956, **75**, 83.
SEARLE, L. V., and BROWN, C. N., *Psychol. Bull.*, 1937, **34**, 558.
SHAGASS, C., *EEG Clin. Neurophysiol.*, 1954, **6**, 221.
Idem and NAIMAN, J., *J. Psychosom. Res.*, 1956, **1**, 49.
SHELDON, W. H., *The Varieties of Temperament*, 1942a. New York: Harper, p. 272.
Idem, ibid., 1942b, p. 45.
Idem, ibid., 1942c, p. 66.
SHIRLEY, M., *Psychol. Bull.*, 1929, **26**, 341.
SHORVON, H. J., *Brit. med. J.*, 1945, *ii*, 285.
SKINNER, B. F., *Amer. J. Psychol.*, 1953, **8**, 69.
SMITH, T. P., *Brit. med. J.*, 1956, *i*, 1088.
SNELL, E. S., and ARMITAGE, P., *Lancet*, 1957, *i*, 860.
SNOW, P. J. D., LENNARD-JONES, J. E., CURZON, G., and STACEY, R. S., *ibid.*, 1955, *ii*, 1004.
SPRAGG, S. D. S., *Psychol. Bull.*, 1941, **38**, 354.
STAFFORD-CLARK, D., *Proc. Roy. Soc. Med.*, 1957, **50**, 615.
STANTON, J. B., *J. Ment. Sci.*, 1954, **100**, 961.
STENGEL, E., and MAYER-GROSS, W., *ibid.*, 1945, **91**, 311.
STEWART, C. C., *Amer. J. Physiol.*, 1898, **1**, 40.
STRAUS, B., EISENBERG, J., and GENNIS, J., *Ann. intern. Med.*, 1955, **42**, 574.
STRAUSS, E. B., *Reason and Unreason in Psychological Medicine*, 1953. London: H. K. Lewis, p. 31.
SZÁRA, S., in *Psychotropic Drugs*, 1957. Amsterdam: Elsevier Publishing Company. p. 460.
TAINTER, M. L., *Trans. N.Y. Acad. Sci.*, 1956, **18**, 206.
TEITELBAUM, H. A., *J. Nerv. Ment. Dis.*, 1941, **93**, 581.
THORPE, J. G., and BAKER, A. A., *J. Ment. Sci.*, 1956, **102**, 790.
Idem and BARKER, J. C., *Arch. Neurol. Psychiat.* (*Chicago*), 1957, **78**, 194.
TIBBETS, R. W., and HAWKINGS, J. R., *J. Ment. Sci.*, 1956, **102**, 60.
TROTTER, P. A., *Lancet*, 1954, *ii*, 1302.
TROUTON, D. S., *J. Ment. Sci.*, 1957, **103**, 344.
Idem, *Science News.*, 1958, **47**, 31.
TYLER, D. B., *Amer. J. Physiol.*, 1947, **150**, 253.
VANE, J. R., *Brit. J. Pharmacol.*, 1957, **12**, 344.
Idem, Personal communication, 1958.
VARNER, W. B., *Psychol. Bull.*, 1933, **30**, 616.
VAUGHAN, G. F., LEIBERMAN, D. M., and COOK, L. C., *Lancet*, 1955, *i*, 1083.
VOGT, M., *5-Hydroxytryptamine*, 1958. London: Pergamon Press, p. 209.
WALLACE, D. C., *Lancet*, 1955, *ii*, 116.
WALTON, R. P., *Marihuana*, 1938a. New York: Lipincott, p. 58.
Idem, ibid., 1936b, p. 115.
Idem, ibid., 1956c, p. 117.
WARD, R. H., *A Drug Taker's Notes*, 1957. London: Gollancz, p. 36.
WEATHERALL, M., *Proc. Roy. Soc. Med.*, 1957, **50**, 617.
WEINSTEIN, E. A., and KAHN, R. L., *Denial of Illness*, 1955a. Springfield, Illinois, p. 120.
Idem, ibid., 1955b, p. 124.
Idem, ibid., 1955c, p. 123.
WIKLER, A., *Fed. Proc.*, 1952a, **11**, 647.
Idem, *Amer. J. Psychiat.*, 1952b, **108**, 593.
WILKINS, R. W., *Ann. N.Y. Acad. Sci.*, 1954, **59**, 36.
WILLIAMS, E. J., *Aust. J. sci. Res. Series A.*, 1949, **2**, 149.
WING, L., *J. Ment. Sci.*, 1956, **102**, 530.
WOLF, S., *J. clin. Invest.*, 1950, **29**, 100.
WOLFF, H. G., and CURRAN, D., *Arch. Neurol. Psychiat.* (*Chicago*), 1935, **33**, 1175.
WOOLLEY, D. W., *Proc. Nat. Acad. Sci.*, 1955, **41**, 338.
Idem, *Hormones, Brain Function, and Behaviour*, 1957. Ed. H. Hoagland. New York: Academic Press, p. 137.
Idem and SHAW, E., *J. biol. Chem.*, 1953, **203**, 69.
ZILBOORG, G., *A History of Medical Psychology*, 1941. New York: Norton, p. 217.