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**RESEARCH IN
PSYCHOPHARMACOLOGY**

Report of a WHO Scientific Group

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CONTENTS

	Page
1. Introduction	5
2. General considerations	6
3. Psychotropic drugs and their classification	7
3.1 Operational definition and classification	7
3.2 Development of new psychotropic drugs	9
4. Clinical psychopharmacology	9
4.1 Clinical effectiveness of psychotropic drugs	9
4.2 Adverse clinical effects	15
4.3 Significance of psychopharmacology for research in clinical psychiatry	19
5. Methodology of clinical drug evaluation	20
5.1 Trials in phases	20
5.2 Clinical controls	21
5.3 Problems with double-blind experiments	22
5.4 Statistical analysis of data	23
5.5 Other methodological problems	24
6. Modes of action of psychotropic drugs	24
6.1 Biochemical mechanisms	24
6.2 Neurophysiological mechanisms	29
7. Behavioural studies in animals and man	32
7.1 Types of behavioural study	32
7.2 Psychopharmacogenetic studies	34
7.3 Predictions of human responses from animal experiments . .	34
8. Recommendations	36
8.1 General principles	36
8.2 Research topics	37
8.3 Suggested collaborative research	37

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Geneva, 5-10 December 1966

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RESEARCH IN PSYCHOPHARMACOLOGY

Report of a WHO Scientific Group

A WHO Scientific Group on Research in Psychopharmacology met in Geneva from 5 to 10 December 1966. The meeting was opened by Dr J. Karefa-Smart, Assistant Director-General, on behalf of the Director-General. Professor H. E. Lehmann was elected Chairman, Professor P. Deniker Vice-Chairman, and Professor P. B. Bradley Rapporteur.

1. INTRODUCTION

Following the recommendations of the WHO Scientific Group on Mental Health Research in 1964,¹ a programme of research in biological psychiatry and neurology was drawn up, concentrating on four main topics: psychiatric genetics, psychopharmacology, neurophysiology, and biochemistry of the brain.² A considerable amount of research on these subjects has been carried out in various countries and discussed during international conferences. It was considered, however, that WHO could play an important role in helping to take stock of knowledge in these fields of biological psychiatry, elucidating the lines of research that should receive further emphasis, and recommending improved methods of research. In particular, WHO is in a position to promote research where international collaboration is likely to be most productive.

Psychopharmacology as a branch of science dates only from the early 1950's. It developed so rapidly, however, that in 1957 WHO convened a study group to review the state of knowledge at that time. Their report³ was considered by the present Scientific Group to provide a valuable exposition of the situation, much of the information being still valid. The present report outlines recent additions to knowledge, and emphasizes points that are of particular significance to research.

¹ No report of this meeting was published, but its work was reviewed in *WHO Chronicle*, 1964, **18**, 380.

² It should be noted that these four topics are closely interrelated. For this reason, the present report overlaps, to some extent, that of the WHO Scientific Group on Genetics in Psychiatry which met in 1965 (see *Wld Hlth Org. techn. Rep. Ser.*, 1966, **346**).

³ *Wld Hlth Org. techn. Rep. Ser.*, 1958, **152**.

2. GENERAL CONSIDERATIONS

Man has used various substances to alter his state of mind and behaviour since the dawn of history, and certain plants, foods, and beverages able to produce such an effect have long been used in religious ceremonies and medical practice. In this sense, psychopharmacology is as old as human culture. It did not become a scientific discipline, however, until there had been systematic study of the fact—first observed by chance—that minute amounts of lysergic acid diethylamide (LSD) produce transient but profound mental and emotional alterations, including vivid hallucinations. The discovery that chlorpromazine and the *Rauwolfia* alkaloids are effective in the treatment of a variety of psychiatric disorders furthered the development of psychopharmacology as a science.

Psychopharmacology has now become a meeting place for various disciplines and has both clinical and laboratory branches. Pharmacology, physiology, biochemistry, genetics, and other biomedical sciences have contributed to an increased understanding of the influence of drugs on interactions between an entire organism and its environment. Many new classes of drugs have been shown to have beneficial clinical effects, and psychotropic drugs are now being used in the treatment of a variety of psychiatric disorders, including schizophrenia and other psychoses, manic syndromes, depressive states, neurotic and personality disorders of children and adults, organic syndromes, and acute alcoholic episodes and other drug-related states. The rapid introduction of many new compounds into clinical use has stimulated advances in the methodology of clinical research; the conduct of drug trials has also improved, with the use of techniques such as comparison against placebos, single- and double-blind designs, statistical analyses, and rating scales. The importance of careful clinical observation and accurate attention to the details of psychopathology and neurological behaviour is recognized. Moreover, these new compounds have provided common ground for communication and collaboration between clinicians and scientists of various disciplines in different countries.

These developments have affected the organization of mental health services and the concepts and theories of brain-function, human behaviour, and mental illness. The advent of psychopharmacology coincided with wide-spread movements in social psychiatry and community mental health. In certain respects, drug treatment and community mental health practices are synergistic. In fact, the increasing effectiveness of drug treatment in aborting incipient and borderline psychoses and in preventing the need for hospital care—or, where it is necessary, in shortening its duration—results in a greater need for organized out-patient and rehabilitative facilities, and related social psychiatric programmes.

3. PSYCHOTROPIC DRUGS AND THEIR CLASSIFICATION

3.1 Operational definition and classification

In this report a psychotropic drug is defined as a drug that acts on psychic function, behaviour, or experience. Psychotropic drugs include a wide variety of pharmacological agents, including those that may produce behavioural effects by direct or indirect action on the central nervous system or by peripheral actions, but this discussion is limited to drugs of interest in psychiatric treatment and investigation.

Psychotropic drugs are not easy to classify satisfactorily, for reasons discussed in a previous report.¹ In the 1930's psychotropic drugs were divided into "stimulants" and "depressants". However, the terms "excitation", "inhibition", "stimulant", and "depressant" lack any precise meaning—or, rather, they have too many different meanings in different contexts for them to be reliable for classification. In the past decade, a number of classifications have been proposed but none has been universally accepted. The literature on this subject is already extensive, and interest and research in the area are continuing. A particular stimulus to research is the fact that many classifications attempt to relate clinical and behavioural effects of drugs to their chemical structure and the ways in which they act.

For the purpose of its deliberations, the Group adopted the classification given in Table 1. This classification is based on clinical efficacy; the drugs or classes of drugs are listed according to their principal actions and are representative only. To a large extent it represents a compromise between different schools of thought and is based on available knowledge of pharmacological action and clinical uses of drugs. Other classifications can be made on the basis of chemical structure, pharmacological properties, etc. This classification is not intended to be definitive, and it will be necessary to revise it from time to time in the light of new knowledge.

In developing this classification, the following working definitions were made.

Neuroleptics, also known as "antipsychotics" and formerly "major tranquillizers" or "ataractics": drugs with therapeutic effects on psychoses and other types of psychiatric disorders. These drugs also have certain neurological effects, such as the production of extrapyramidal symptoms.

Anxiolytic sedatives, formerly called "minor tranquillizers": substances that reduce pathological anxiety, tension, and agitation without therapeutic effects on disturbed cognitive or perceptual processes. These drugs usually

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1958, **152**, p. 20.

TABLE 1. CLASSIFICATION OF PSYCHOTROPIC DRUGS

Category	Representative members
Neuroleptics	(a) Phenothiazines (b) Butyrophenones (c) Thioxanthenes (d) Reserpine derivatives, benzoquinolizines
Anxiolytic sedatives	(a) Meprobamate and derivatives (b) Diazepoxides (c) Barbiturates
Antidepressants	(a) Monoamine oxidase (MAO) inhibitors (b) Imipramine and other tricyclic compounds
Psychostimulants	(a) Amphetamine, methylphenidate, pipradrol (b) Caffeine
Psychodysleptics (hallucinogens)	(a) Lysergic acid diethylamide (LSD) (b) Mescaline (c) Psilocybin (d) Dimethyltryptophan (DMT) (e) Cannabis (marihuana, hashish, etc.)

increase the convulsive threshold, do not produce autonomic or extrapyramidal effects, and often have potential for producing dependence.

Antidepressants : drugs effective in the treatment of pathological depressive states. Drugs in this category have sometimes been called "psychic energizers" and "thymoleptics".

Psychostimulants : drugs that increase the level of alertness and/or motivation. These effects are usually manifest in normal animals and humans.

Psychodysleptics : drugs producing abnormal mental phenomena, particularly in the cognitive and perceptual spheres. These drugs are also called hallucinogens, psychotomimetics, and in some cases psychedelics.

In addition to these established categories, a number of other psychotropic drugs are being intensively investigated. Among these are lithium, whose value in the treatment of acute manic states and as a prophylactic in manic-depressive cycles is being tested; cyclazacine and methadone, which are being studied for possible usefulness in narcotic addiction; and drugs like disulfiram that are of value in the treatment of chronic alcoholism. As the uses of these drugs become better established, new categories will have to be created to provide a comprehensive classification.

3.2 Development of new psychotropic drugs

There are some indications that, after the rapid development of new drugs following the introduction of the first neuroleptics and antidepressants, such activity is now slowing down. Whether or not this is a consequence of new regulations covering the introduction of new drugs is uncertain. There is little question that there is now more concern than before over toxicity and safety, and higher safety standards are now applied. This has led to an increase in laboratory experimentation and clinical study in areas where the need for fuller information is particularly pressing.

New drugs are being sought for the following purposes :

- (a) the treatment of mental retardation ;
- (b) the treatment of personality disorders, in particular by raising the tolerance levels for anxiety and frustration and combating feelings of inadequacy without the development of drug tolerance and addiction ;
- (c) research on psychoses, such as the use of chemical analogues of hallucinogenic drugs (e.g., pentamethoxyphenylethylamine) in studies of the relationships between chemical structure and action. (Information on the molecular structure of hallucinogens may throw light on their biochemical mode of action and on the configuration of the receptor site where they act, and this in turn may suggest new hypotheses of the nature of the biochemical lesion in schizophrenia.) Related to these drugs are others that are used to treat psychoses and that have been developed on the basis of a specific hypothesis of the biochemical etiology of psychoses. Examples of such drugs now being tested are *O*-methyl transference inhibitors, hydroxychloroquine, and penicillamine. Such research may lead to useful new drugs, but even if it does not, it may be expected to yield information on abnormal brain functioning in mental illnesses.

New combinations of drugs may also be developed according to a specific hypothesis ; an example is the combination of tryptophan and an MAO-inhibitor used in the treatment of depression.

4. CLINICAL PSYCHOPHARMACOLOGY

4.1 Clinical effectiveness of psychotropic drugs

Numerous reports on the clinical effectiveness of psychotropic drugs have been published. Such reports show wide agreement and only the essential trends are summarized in this section.

Ideally, each psychotropic drug would be effective in the treatment of specific mental diseases. However, in the present state of knowledge, clinical effectiveness of psychotropic drugs is best expressed in terms of modification of symptoms or syndromes, since concepts of the clinical mode of action of such drugs are possible only at the level of symptomatology.

In evaluating the clinical effectiveness of psychotropic drugs, the circumstances in which they are used should be taken into consideration. Clinical effectiveness in a patient depends upon : (a) whether he is in hospital or being treated as an out-patient ; (b) whether or not he has previously received other psychotropic drugs or physical therapy such as electroshock treatment ; and (c) whether the drug is used alone or in combination with other drugs and treatments, including psychotherapy. Tables 2 and 3 list commonly used drugs and the conditions for which they are indicated.

TABLE 2. PSYCHOTROPIC DRUGS USED TO TREAT PSYCHIATRIC DISORDERS

Disorders	Drugs
Schizophrenic disorders, including childhood schizophrenia ; other delusional states	Phenothiazines Butyrophenones Thioxanthenes Reserpine
Depressive disorders	Tricyclic compounds MAO-inhibitors Phenothiazines Barbiturates
Manic disorders	Phenothiazines Butyrophenones Lithium carbonate
Organic (brain) disorders	Phenothiazines Psychostimulants
Neurotic disorders	Meprobamate Benzodiazepines Barbiturates, alone or in combination with amphetamine
Personality disorders	Phenothiazines Meprobamate Benzodiazepines Amphetamine (in children only)

Since the causes of most psychiatric disorders are not known with certainty, treatment that is specific for a given disease can hardly be expected. Nevertheless, available clinical evidence indicates substantial symptom and syndrome specificity. Certain symptom constellations typical of some psychiatric disorders are highly responsive to drug treatment, whereas others are not. Table 3 lists the drugs that have proved most useful in the treatment of psychiatric disorders. It should be repeated that this tabula-

TABLE 3. PSYCHOTROPIC DRUGS THAT ARE MOST EFFECTIVE AGAINST MAJOR SYMPTOMATOLOGIES

Drugs	Major symptomatologies
Phenothiazines and, selectively, other neuroleptics	Acute or chronic excitement states ; confusional states, anxious-depressive agitation ; delusional and hallucinatory states ; pathological impulsivity and aggressiveness ; abulia
Butyrophenones	Manic excitement
Tricyclic compounds MAO-inhibitors	Depressive states
Meprobamate Diazepoxides	Tension and anxiety states
Amphetamine Amphetamine with barbiturates	Childhood hyperkinesia Depression with psychasthenic dysphoria and fatigue states

tion does not mean that the drugs are specific for the listed disorders, but only that they have selective therapeutic effects on certain symptom constellations typical of these disorders. Furthermore, it should be borne in mind that the clinical course of most psychiatric disorders varies ; conditions may be acute, cyclic, or phasic, and the type of drug used, the dosage, and the duration of treatment may have to be varied accordingly. Since many psychiatric disorders show changing combinations of manifestations, various drugs with different effects are listed for each of the disorders. Dosage levels are important since some drugs—e.g., imipramine—have anti-depressant effects at low to medium doses, but other effects at very high doses.

In addition to psychotropic drugs, other forms of somatic therapy continue to play an important part in psychiatric treatment, as shown in Table 4.

TABLE 4. FORMS OF SOMATIC TREATMENT OTHER THAN DRUGS

Treatment	Status
Electro-convulsive therapy (ECT)	Widely used for : (a) severe depression with acute danger of suicide, marked retardation or agitation, or intense suffering ; (b) depressions that do not respond to drug therapy ; (c) drug-resistant schizophrenia (in some countries).
Insulin coma therapy (ICT)	Use has decreased markedly (a few centres continue to use it in selected cases of schizophrenia)
Sub-coma insulin	Fairly widely used in anxiety and tension states and in certain cases of schizophrenia
Prolonged sleep therapy	Use has declined
Lobotomy	Replaced by drug therapy except for certain syndromes

4.1.1 *Variability among the neuroleptic drugs*

During the last ten years or so, many neuroleptic drugs have been made available—e.g., phenothiazines, butyrophenones, and reserpine. Even drugs with only slightly different chemical formulae have proved to be not entirely identical in their effects. Knowledge of such differences in effects makes it possible to classify drugs according to their pharmacological properties. Some authors place the neuroleptics in a series with, at one extreme, drugs with maximum sedative and anxiety-relieving action and few neurological effects (levopromazine, promazine, and the piperidine phenothiazines such as thioridazine), and, at the other extreme, drugs with weak sedative effect but maximum antipsychotic and cataleptic action (piperazine phenothiazines such as thioproperazine and trifluoperazine, and butyrophenones such as triperidol). Chlorpromazine occupies a position intermediate between these two extremes, combining qualities of both but with less intensity.

In recent controlled and statistically designed clinical studies, attempts have been made to correlate the characteristics (particularly those related to psychopathology) of patients with their responses to the various neuroleptics described above. Earlier clinical studies had demonstrated the importance of psychopathology for understanding such responses. The aim of these investigations is to find, among a number of given pre-treatment factors, those valuable for predicting responses to treatment with a particular neuroleptic. For example, in one such study of acute schizophrenics, patients with the best response to chlorpromazine were those who showed irritability, hostility, agitation, tension, and confusion, whereas those who responded better to fluphenazine were those who suffered from auditory hallucinations, ideas of grandeur, and poor sociability. None of these symptom patterns or the new classifications proposed by various investigators corresponds to the usual nosological sub-divisions. Further research in this area is under way.

4.1.2 *Selectivity and specificity of antidepressants*

Since the introduction of (1) imipramine and the related tricyclic compounds and (2) monoamine oxidase inhibitors, their specificity has been subject to discussion and investigation. Although there is wide agreement that members of these two classes of antidepressants are effective drugs, there are few universally accepted criteria for measuring specific psychopathologic effects.

Earlier clinical reports described the therapeutic efficacy of chlorpromazine in certain types of depression. Recent controlled studies have shown little difference in the over-all effectiveness of imipramine, chlorpromazine, and thioridazine. It is, however, probable that these drugs

have specific actions on symptoms such as anxiety, insomnia, and disordered thinking. Although this seems to indicate that there may be no clear-cut distinction between depression and schizophrenia, it is generally accepted that the antidepressants do not have a favourable effect on schizophrenics and may even aggravate previously latent or quiescent psychotic manifestations.

Considerable work has been devoted to attempts to discover factors that could be used to predict the response to therapy. It has included symptomatology, psychological tests, rating scales, and the premorbid personality, and has provided interesting indications of the greater effectiveness of a given drug than of others on specific aspects measured.

Research is needed on depressions that do not respond to chemotherapy. Few studies have been made of these therapeutic failures, although such studies might well provide valuable information. In cases of depression in members of the same family, differences between those who respond to treatment with MAO-inhibitors and those who respond to treatment with tricyclic derivatives coincide to a great extent, suggesting that genetic factors play an important role.

These results might seem to indicate that depressive states are a single entity in the sense that there is one primary disturbance, whether of endogenous or reactive origin, on which antidepressants (to the extent to which they are specific) could act. On the other hand, differential responses have been interpreted as indicating the pluralistic nature of depressive states. However, the disparity of these studies and of their results makes it impossible to foresee any possible new nosological grouping or to gain any confirmation of the usual classifications of depression. These studies are based upon a "Meyerian" concept, with combinations of symptoms corresponding to types of reaction more than to an etiological process, and it is unlikely that they will lead to criteria for the classification of disease.

4.1.3 *Psychodysleptics and their relation to schizophrenia*

The relationship between "mental alienation", the disorders now referred to as schizophrenic, and those produced by toxic substances is a problem of very long standing. More than a century ago, in discussing hashish, Moreau de Tours said: "I was convinced that through it it should be possible to penetrate the mystery of alienation and make our way back to the hidden source of those numerous varied and strange disorders usually referred to collectively as madness". Despite much discussion it remains a moot point whether experimental psychoses and the psychoses observed in clinical practice are identical or even analogous, but developments in psychopharmacology make it possible to delimit the problem more successfully.

The effects of mescaline, LSD, and psilocybin, the psychodysleptics that have been the most studied, seem to differ significantly only in duration and intensity. The disorders reported in records of actual experiences are closely reminiscent of what is described in depersonalization syndromes, oneiric confusion syndromes, and thymic changes.

Schizophrenia is progressive and chronic, whereas the disturbances produced by the dysleptics are transitory and usually have no sequelae. However, if the comparison is made with acute psychoses, and if the polymorphism of the clinical picture of schizophrenia in its initial stages is remembered, there is a striking similarity in the observed symptoms, and a skilled clinician would find it difficult to make a differential diagnosis. Finally, the neuroleptic drugs that are used to treat psychoses in clinical practice also counter the action of the hallucinogens and cause the symptoms of these artificial psychoses to disappear. Nevertheless, it is generally held that, despite the similarities in symptoms, these effects do not form a schizophrenic syndrome.

4.1.4 *Role of therapeutic programmes and environment*

Psychotropic drugs in comprehensive therapy

Psychotropic drugs are seldom used alone; they are, rather, used as part of a comprehensive treatment programme that also involves psychotherapy (individual, group, or family), various forms of milieu therapy, work therapy, and rehabilitation. There is no evidence that treatment with psychotropic drugs is incompatible with these other kinds of therapy. Different combinations of drug therapy and psychotherapy are used as indicated for a particular patient.

The advent of effective neuroleptics coincided with the emergence of social psychiatric practices in hospitals and community services.¹ The effectiveness of early discharge, day hospitalization, work therapy, and other programmes has been enhanced by the use of drugs. There is now serious concern that the increased numbers of psychiatric patients in the community are not receiving adequate follow-up care. This may be a special problem for potentially suicidal or aggressive patients, whose symptoms may return readily if they discontinue effective medication abruptly. In many areas, special clinics have been established. In some quarters there is concern that the early discharge of psychiatric patients may shift the burden from the mental health service to social welfare agencies in the community and to the family. This problem is receiving careful assessment, particularly in view of the expense, both financial and professional, of maintaining patients in the community.

¹ See *Wld Hlth Org. techn. Rep. Ser.*, 1958, 152.

Environmental factors

The effect of the environment upon the effectiveness of drug treatment has been carefully reviewed in a previous report¹ and only certain salient features require discussion here. The implied dichotomy between "internal" and "external" must be avoided in attempting to understand the complicated inter-relationship between drug treatment and environmental factors. Internal and external factors are not only interdependent in determining drug effects, but to some extent they also change from time to time: external factors may become internal, and internal processes exert influences on receptors of environmental stimuli.

The reaction of organisms to drugs may be substantially influenced by the following environmental factors: (1) climate, season and weather; (2) diet and nutrition; (3) variations in sensory and social stimulation patterns in clinical settings; (4) inter-relationship of biological and social factors such as social class, ethnic composition, and nationality; and (5) cumulative effects of previous somatic treatment, and of psychotropic drugs in particular.

Moreover, it must be recognized that there are dissimilarities in the social structure of professional environments in which drug studies are carried out. Professional attitudes reflect the preponderantly psychodynamic, biological, or social orientations of different centres; consequently, there is only minimal standardization of methods of drug administration, and observational data may vary considerably from centre to centre.

Cross-cultural observations

Striking variations in dosage requirements and therapeutic responses to certain psychotropic drugs have been observed and studied in similar drug trials carried out in different countries—e.g., Germany and the USA. It is not known whether such variations are due to genetic differences, as has been assumed by some investigators, or to differences in the medical, psychiatric, and social characteristics of the patients in the two countries, as has been assumed by others.

4.2 Adverse clinical effects

The main adverse clinical effects of psychotropic drugs may be summarized as follows: sedative-hypnotic effects, psychopathological reactions, convulsive seizures, extrapyramidal dysfunctions, jaundice, blood dyscrasias, autonomic effects and potential for drug dependence.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1958, **152**.

Sedative-hypnotic effects involve drowsiness and slowed reactivity. At moderate doses, psychomotor, sensory, and cognitive performance may decline; at high enough doses, some drugs induce sleep. These effects are caused to some degree by neuroleptics and sedatives, and to a lesser extent by certain tricyclic antidepressants.

Psychopathological reactions are often variable. Pathological depressions have occurred in patients treated with reserpine derivatives and some of the butyrophenones. The MAO-inhibitors and the tricyclic antidepressants induce hypomanic states, paranoid reactions, and activation of latent psychoses, particularly in predisposed individuals. Toxic-confusional states have occasionally been observed with the phenothiazines and thioxanthenes. Chronic ingestion of psychostimulants, especially the amphetamines, may lead to paranoid states. Prolonged psychoses may be a particular danger of unsupervised use of LSD and other psychodysleptics.

Convulsive seizures may be caused by high doses of phenothiazines, imipramine, certain hydrazine MAO-inhibitors, and reserpine derivatives. Although most of these drugs lower the convulsive threshold, the occurrence of clinical seizures depends upon factors such as individual susceptibility, dose, route of administration, and rapidity of dose elevation. Convulsive seizures may also occur as part of the withdrawal syndrome.

Extrapyramidal dysfunctions include parkinsonism-like effects, excito-motor syndromes, dystonic reactions, and akathisia. They occur particularly frequently in patients treated with piperazine phenothiazines and butyrophenones and may also occur in patients treated with thioxanthenes, rauwolfia derivatives, and other phenothiazines. Tremor and related phenomena may occur in patients treated with imipramine and other tricyclic antidepressants.

Jaundice of cholestatic type may be a problem with certain phenothiazines, particularly chlorpromazine. It occurs in more benign form with the thioxanthenes and imipramine. Jaundice from hepatic cellular toxicity has occurred with a number of MAO-inhibitors, particularly iproniazid and pheniprazine.

Blood dyscrasias, such as leucopenia and agranulocytosis, are serious complications with a number of phenothiazines, especially chlorpromazine and mepazine, and with etryptamine, a MAO-inhibitor. Agranulocytosis has occurred less commonly with imipramine and thioxanthenes.

Autonomic effects are frequent with neuroleptics, antidepressants, psychostimulants, and psychodysleptics and may include cardiovascular changes, a dry mouth, blurred vision, sweating, and changes in gastrointestinal motility. These effects may cause discomfort but they are seldom serious.

Of course, not every drug in a given class produces all the adverse effects common to the class. Furthermore, the frequency and intensity of any adverse effect depend upon the dose, rate of administration, and duration

of treatment and upon the age, sex, nutritional and metabolic state, and clinical condition of the individual.

4.2.1 *Drug dependence*

It is important to recognize that three classes of psychotropic drugs are potentially dependence-producing: anxiolytic sedatives, psychodysleptics, and psychostimulants, particularly the amphetamines.¹ The type of dependence varies with the class of drug.

Anxiolytic Sedatives. It has been well-known for many years that the barbiturates and other sedative hypnotics—e.g., glutethimide and paraldehyde—produce tolerance when taken repeatedly. If tolerance develops, withdrawal of the drug may cause a syndrome characterized by EEG changes, confusion, delirium, inco-ordination, hyperpyrexia, nystagmus, convulsions, and—in rare cases—death. It is now apparent that meprobamate and diazepam derivatives may produce similar, although considerably less severe, effects. Although both types of drug—particularly the diazepam derivatives—have much less potential for producing dependence than do the barbiturates, they nevertheless pose a problem that requires attention.

Psychodysleptics (hallucinogens). Repeated use of LSD, psilocybin, mescaline, and other psychodysleptics, such as is reported to occur among college students and other groups in the USA and elsewhere, may produce personality changes with signs of emotional withdrawal, social ineffectiveness, impaired judgement, and, in certain cases, persistent psychoses.

Psychostimulants. The amphetamines and other psychostimulants are widely misused, and the fact that they produce tolerance and psychic dependence is often not appreciated. The misuse of amphetamines has often been associated with the development of chronic paranoid psychosis, resembling schizophrenia in some clinical aspects.

4.2.2 *Interactions between psychotropic and other drugs*

Although summation and potentiation effects may result from combining psychotropic drugs with other agents that affect the central nervous system, a number of interactions have particular clinical significance and warrant special attention.

The neuroleptic drug reserpine poses special problems if patients under its influence receive general anaesthesia, and special precautions must be taken if surgery or electroconvulsive therapy become necessary.

¹ See also *Wld Hlth Org. techn. Rep. Ser.*, 1964, 287; 1965, 312; 1966, 343.

The anxiolytic sedatives, including meprobamate, diazepoxides, and particularly barbiturates, interact with most CNS depressants, particularly alcohol. Sudden deaths have occurred when patients taking barbiturates and other sedatives ingest large or even moderate amounts of alcohol.

The most dangerous interactions occur in patients receiving MAO-inhibitors. Severe hypertensive crises that may involve elevated blood pressure, headache, sweating, tachycardia, coma, and even death have been precipitated by pressor drugs such as ephedrine and sympathomimetic agents, and by foods such as cheese, wine, chocolate, and other substances containing tyramine. Special incompatibilities also exist between the MAO-inhibitors and imipramine and its derivatives and a number of other drugs such as pethidine.

4.2.3 *Long-term treatment with psychotropic drugs*

Long-term maintenance treatment of schizophrenic patients with neuroleptics has become well established and many psychiatric programmes provide after-care, including supervision of drug treatment. The continuation of such programmes depends upon evidence of their efficacy in alleviating symptoms, preventing relapse (and consequent necessity of further hospital care), and facilitating social adjustment and rehabilitation. Moreover, drugs used for such long-term treatment must be safe and nontoxic. On the whole, these conditions have been met. However, two types of adverse effect of long-term phenothiazine administration have recently been reported: (1) a skin-eye syndrome, in which pigmentation may occur in the skin, cornea, and lens (photosensitivity appears to be a necessary condition for the development of this effect; functional impairment of visual activity is uncommon); and (2) in older patients and those receiving prolonged courses of treatment, persistent dyskinesia involving choreiform movements of the upper limbs and peribuccal movements (to be distinguished from the transient dyskinesia that frequently occurs as one of the extrapyramidal dysfunctions produced by neuroleptic drugs).

The significance of these effects cannot be fully evaluated at present and further investigation is necessary. However, patients on long-term phenothiazine treatment should receive careful medical supervision.

4.2.4 *Monitoring adverse drug effects*

Since discovery of the adverse effects of thalidomide, increased attention has been given to the rapid and accurate international reporting of such effects. The ways in which adverse effects of psychotropic drugs are reported should be reviewed. Continuing attention should be given to possible teratogenic effects as well as to the effects of psychotropic drugs given to pregnant and nursing women upon the emotional and physical develop-

ment of their children. No serious problems in this area have been discovered and there is no cause for alarm. However, while the search for new drugs continues, procedures for monitoring adverse effects must be kept up to date.

Special interest continues in the observation of neurological dysfunctions caused by psychotropic drugs. The lowering of the convulsive threshold by neuroleptics and tricyclic antidepressants has already been mentioned. Signs of dysarthria, cerebellar inco-ordination, and intention tremor have recently been observed in patients receiving high doses of chlorimipramine. The relationship of this syndrome to the diverse extrapyramidal dysfunctions produced by neuroleptics is being investigated, particularly in France.

Special problems are caused by the long-term use of phenothiazines and other psychotropic drugs. From time to time concern has been expressed over possible harmful effects of long-term medicaments. Currently attention is being given to the "skin-eye" syndrome and to the reports of persistent neurological and cardiac dysfunction.

4.3 Significance of psychopharmacology for research in clinical psychiatry

In addition to its therapeutic value, psychopharmacology has significance for research in clinical psychiatry and for the study of theories and concepts of psychopathology. It has provided techniques and observations that are of use in the analysis of clinical syndromes, the clarification of psychopathological mechanisms, and nosological delineation. Information derived from pharmacotherapy provides as much evidence for as against the theory of the unity of psychoses. Experience to date does not invalidate the hypothesis of mental "alienation" or psychosis as a modification of the personality. Moreover, available data favour the hypothesis of psychopathological diversity, put a differential value on symptoms, and perhaps open the way to new symptomatological findings and groupings.

Up to a point, psychopharmacology has confirmed the concept of schizophrenia, although the concept is still wide in scope. It has not invalidated the concept of manic-depressive psychosis, but some investigators find in it a confirmation of particular theories, such as those that contrast bipolar disorders (manic-depressive dysthymias) with monopolar disorders (periodic depressions).

The concept of "target symptoms" has been widely used in decisions regarding drug treatment. This concept is based on evidence that most psychotropic drugs act on the manifestations or symptoms of psychiatric disorders, such as depression or hallucination. As used by Freyhan, and subsequently by others, it does not view symptoms in isolation or as being independent entities divorced from their context. From the point of view of the action of psychotropic drugs, the target symptoms are part of the

entire pattern of symptoms characteristic of a psychiatric disorder. However, pharmacotherapy modifies not only the symptoms of a disorder, but also its clinical course. In some syndromes, the course may be shortened, whereas in others it may be "covered up". Pharmacotherapy has not yet made it possible to solve the problem of the underlying periodicity of certain cyclic depressive syndromes—e.g., in manic-depressive disorders it is uncertain to what extent one phase (depression or mania) is shortened merely by increasing the probabilities of the other.

5. METHODOLOGY OF CLINICAL DRUG EVALUATION

Systematic psychopharmacology is a fairly new branch of clinical research. Many of its experimental methods have been taken from pharmacology, one of its parent disciplines in the biological sciences; however, it also shares many of the characteristics of the behavioural sciences—e.g., multifactorial rather than monofactorial causality, inconsistent cause-effect relationships, the importance of intrapersonal and interpersonal factors, the significant role of symbolic relationships, the prevalence of qualitative over quantitative factors, and the need for a holistic ("gestalt") approach to observed phenomena rather than an attempt to achieve total reductive analysis. Furthermore, conditioning processes involving generalization and discrimination and functions of the second signal system play a much more important role in psychopharmacology than in general pharmacology or neuropharmacology.

However, although the psychopharmacologist recognizes all these features, the fact that he uses potent—and potentially toxic—agents obliges him to make every effort to attain quantitative precision, consistent cause-effect relationships, and maximum reduction of intrapersonal and interpersonal factors in his clinical trials.

5.1 Trials in phases

The system of dividing trials into three phases has been widely adopted. In phase I, the effective dose range, side effects, and possible toxic properties of a new drug are determined. In phase II, the therapeutic range and effectiveness of the drug are studied. Phase III trials are designed to validate the observations made in phases I and II, using strictly controlled techniques.

Phase I experiments require no control group and are usually carried out on groups of 5-10 patients. They should be carried out only with a therapeutic goal and by investigators who have considerable experience of drug research in human beings. In such trials, good clinical observation is essential.

Phase II trials, which may or may not be controlled, are usually carried out with somewhat larger sample groups than phase I trials; the number of patients is usually 10-30. The investigator should be a perceptive observer, able to use imagination and follow clinical "hunches".

Phase III trials should always be controlled and should be carried out with a larger group (more than 20 patients) so that sensitive statistical tests can be used in evaluating the final results. Phase III trials, therefore, call for carefully conceived and executed experiments and for skilful evaluation of the results.

Clinical assessment and rating scales

In almost all clinical trials, the effects of drugs on symptoms, ward behaviour and aspects of psychopathology are assessed. Some method of evaluating and recording clinical phenomena is therefore required. Rating scales, the number of types of which has increased during the past decade, are now being used with increasing frequency.

Clinical behaviour lends itself easily to descriptive and anecdotal recording. Some psychiatrists feel that their sensitivity and perceptiveness may be impaired if they are forced to fit observations into the stereotyped framework of a standardized rating scale. However, as pointed out earlier, changes in behaviour caused by psychotropic drugs must be measured in some way if research in clinical psychopharmacology is to be safe and orderly.

In choosing a rating scale, the experimenter often has to decide whether to emphasize comprehensiveness or practicality. Comprehensive scales are more sensitive, but they often contain a large number of items. Scoring may therefore take a long time, causing fatigue and resistance in the scorer and thus seriously reducing the reliability and validity of the rating. Brief scales, containing 15-20 items, provide cruder estimates, but they induce less fatigue and resistance and thus are probably more reliable when used in different localities and under varying conditions.

Moreover, it must be remembered that behaviour-rating scales, interview schedules, and personality inventories require the most careful translation and restandardization if they are intended for use in a language and culture other than that in which they were compiled. It may often be simpler and more reliable to construct an entirely new scale than to use an inadequate translation.

5.2 Clinical controls

The scientific evaluation of any therapeutic procedure, including the use of psychotropic drugs, requires controls. Even so-called "uncontrolled trials" have implicit controls—the clinician's estimate of results, made on

the basis of either (a) the clinical changes he would expect in patients without the new treatment ("retrospective" or "historical" controls), or (b) other treatment currently being given to comparable groups of patients (particularly when the clinical outcome is quite regular and predictable or the clinical condition is considered stable or irreversible). Controlled trials are designed so as to make these controls explicit by the concurrent use of sample and control groups.

Experimental controls may involve, in order of increasing complexity of experimental design, any of the following comparisons :

- (1) comparison with no treatment
 - (a) non-blind
 - (b) single-blind
 - (c) double-blind
- (2) comparison with another drug
 - (a) non-blind
 - (b) single-blind
 - (c) double-blind
- (3) comparison with a placebo
 - (a) single-blind
 - (b) double-blind

Thus, there are at least eight different ways in which controlled clinical trials with psychotropic drugs may be carried out. If a drug treatment is compared with no treatment, the single- and double-blind conditions are incomplete, because only the nature of the drug—not the nature of the control—can be concealed from the subject and the experimenter.

5.3 Problems with double-blind experiments

It may often be very difficult or practically impossible to maintain a strict double-blind procedure in psychopharmacological experiments. Practical difficulties arise because specially trained staff and special equipment and procedures are needed for a carefully conducted double-blind experiment. Such experiments are always more expensive and take a great deal more time than single-blind or non-blind experiments. Ethical difficulties may arise because the essential point of double-blind trials is that the true nature of the therapeutic agent be concealed from the patient and the observers. Under certain circumstances this could be interpreted as deception of the patient and withholding of treatment, particularly if he is given a placebo when a therapeutically effective agent is available. These prob-

lems are lessened if, instead of a placebo, an accepted drug with known properties is used as a standard or reference treatment.

Psychological difficulties may arise when a patient is required to give written consent prior to being included in a double-blind placebo-controlled experiment and after he has been given a full explanation of the situation. Psychological difficulties are also frequently encountered in personnel who administer the drugs and observe their effect without knowing the nature of the drugs. Almost invariably there is a strong drive, among personnel, to "break the code" before the end of the experiment and discover the identity of the various agents being used. Not infrequently physicians and nurses react with suspicion and resentment to double-blind conditions, particularly if they are not used to them.

Methodological difficulties often arise from the fact that the experimental drug produces unmistakable side-effects that are difficult or impossible to disguise. If other drugs were given to counteract or prevent such side-effects, other undesirable factors might be introduced into the experiment—e.g., the second drug might have side-effects of its own or might interfere with the therapeutic effect of the first drug. Attempts have been made to use "active" placebos—i.e., inactive substances to which have been added small amounts of drugs that produce side-effects similar to those produced by the experimental drug. For example, in trials of phenothiazines, atropine has been added to the placebos given to control groups to produce a dry-mouth condition similar to that caused by the phenothiazine. However, "active" placebos have usually been unsuccessful in practice and inadmissible on methodological grounds.

5.4 Statistical analysis of data

The results of Phase II and Phase III trials should be evaluated statistically. Simple methods—e.g., chi-square or t-tests—of establishing the statistical significance of differences in the means of pre-treatment and post-treatment scores might be used, or more sensitive tests of variance and covariance might be chosen. If the problem involved determining which, of a number of factors responsible for observed reactions to a drug, carried the greatest weight, discriminant function analysis might be indicated. If the problem involved the distribution of several clusters or homogeneous subgroups, factor analysis would be useful in experiments where subjects are gradually added to a sample group over a period of time. Sequential analysis can indicate when the sample is large enough for statistical differences to reach significant values, and the experiment may then be ended.

It is often difficult to collect homogeneous sample groups of sufficient size. If a group contains less than 30 patients, the chances of finding a statistically significant difference (if a difference does, in fact, exist) are

reduced. In general, it may be stated that careful application of appropriate statistical methods is the principal safeguard against the error of declaring a difference when none actually exists. However, the chance of detecting real differences depends greatly on the size of the experimental sample.

The value of statistical techniques in clinical research is greatly enhanced when the clinical investigator and the statistician co-operate in the project and discuss its aims and problems and the data analysis. Ideally, the statistician should be involved in the earliest planning of a project.

5.5 Other methodological problems

Continuing discrepancies and contradictions in the psychopharmacological research literature indicate deficiencies in prevailing methodologies. The degree to which research designs, using controlled trials, may be based on the (erroneous) assumption that we have adequate methods for matching groups of patients should be critically re-examined. The many variables that are involved in the relationship between an organism and its environment must be recognized.

The problems of individual differences have not been sufficiently considered in clinical psychopharmacology. Specific differences are not confined to an individual, but are often shared by groups of common constitutional make-up. Population sampling of patients or controls for research purposes requires constant awareness of the danger that individual or collective differences may be hidden under such common denominators as diagnosis, age, sex, social status, and duration of illness.

6. MODES OF ACTION OF PSYCHOTROPIC DRUGS

An important task of psychopharmacology is elucidation of the processes by which a psychotropic drug alters the mental state through affecting the neurophysiological and biochemical activity of functional units of the central nervous system. Although this goal is at present quite remote, certain relationships are being found between the clinical effects of the psychotropic drugs and their pharmacological, neurophysiological, and biochemical effects. A comprehensive review of knowledge in these fields might be contemplated as a task for the future. The following sections give examples of what is known of the modes of action of selected psychotropic drugs and review current trends in basic research on these topics.

6.1 Biochemical mechanisms

Within the past fifteen years, extensive investigations of the biochemical pharmacology of psychotropic drugs have led to considerable information

on the actions of various drugs on energy metabolism, on the synthesis, storage, and degradation of biogenic amines, on transport across membranes, and on related phenomena. Concomitantly, this research has led to the development of several important concepts and is responsible for the emerging understanding that psychotropic drugs act on the adrenergic neuron and synapse.

The brain carries out specific biochemical processes. If these processes are disturbed, through either a direct biochemical influence or an indirect physiological (and probably also psychological) influence, changes may also be expected in patterns of behaviour.

Investigation of the biochemical effect of psychotropic drugs on the central nervous system is hampered by a number of factors. One is the present limited ability to define the functional biochemical units of the brain. The brain contains a mass of intercommunicating neurons; the action of drugs is not restricted to effects on single neurons, but affects even large functional units. It is, therefore, difficult to ascribe such effects, whether electrical or biochemical, to a localized site in the central nervous system. Thus a drug-induced decrease in the activity of one part of the brain can reflect either a direct effect of the drug or an indirect effect induced by a loss of the normal interactions from another part of the brain.

Another difficulty accompanying the investigation of psychotropic drugs is the fact that—in addition to acetylcholine—noradrenaline, dopamine, serotonin, GABA, and the polypeptide P are now believed to play roles in the synaptic transmission of nerve impulses. A psychotropic drug can, therefore, modify nerve-impulse transmission by acting on the neuro-hormone and/or other neuro-substances in the following ways: (*a*) by simulating their activity; (*b*) by blocking their effect; (*c*) by protecting them from enzymatic action; (*d*) by interfering with their synthesis; (*e*) by preventing their release after nervous stimuli; (*f*) by inactivating them; or (*g*) by destroying them.

Cells of the CNS are now considered to be complex and highly organized structures rather than mere containers of substrates and enzymes. There are various cell compartments in which the storage, synthesis, metabolism, and physiological release of neurochemical substances take place and where one form of energy may be transformed into another. It is in the study of these neurochemical substances that biochemistry and physiology overlap; their structure and function are one of the main problems of biochemistry.

There is evidence that psychotropic drugs act on the peripheral nervous system by modifying synaptic transmission, but the evidence of synaptic transmission in the central nervous system is still incomplete. Many investigators have studied energy metabolism, such as oxidative phosphorylation. It appears rather improbable, however, that psychotropic

drugs exert their highly specific effects on behaviour by affecting only those cellular energy processes that are found in all cells.

Another difficulty inherent in the biochemical investigation of psychotropic drugs is that of relating the physiological and biochemical processes that take place in the brain. However, biochemical processes are frequently studied in tissue homogenates—a technique that can provide only a limited picture of the physiological function of an intact structure.

6.1.1 *Current research*

Research on the biochemical aspects of psychopharmacology is being conducted in a number of major areas, including :

- (a) the organic chemical properties of psychotropic drugs ;
- (b) structural changes induced in the CNS by psychotropic drugs (being studied by electron-microscopic methods) ;
- (c) catecholamine metabolism ; and
- (d) histochemistry, especially of the catecholamines, and the mapping of the brain enzymes.

6.1.2 *Implications for biochemical bases of mental illnesses*

Attempts to discover biochemical bases for mental illnesses, particularly schizophrenia and the affective disorders, have not been as successful as efforts in the area of mental retardation. A number of imaginative hypotheses—notably those involving the indole and catechol amines—have been advanced. Many of these are based upon pharmacological studies with drugs such as the hallucinogens and with combinations of amine precursors (e.g., DOPA and 5-HTP) with psychotropic drugs. Such hypotheses are often difficult to test in human situations for various reasons, including (a) the use of widely different criteria for the diagnosis of clinical disorders, and the lack of agreement on the nature of schizophrenia and other psychoses ; (b) the unreliability of some biochemical procedures and techniques for extraction, assessment and purification ; and (c) the lack of proper clinical, dietary, and pharmacological controls.

In spite of these difficulties promising work is proceeding. For example, the effects of drugs on transmethylolation are of interest not only from a purely pharmacological point of view, but also for testing the hypothesis of disordered transmethylolation in schizophrenia. Some evidence supporting this hypothesis, obtained from structure-activity studies of psychodysleptics (hallucinogens), indicated that most are *N*-methyl or *O*-methyl derivatives of dopamine or serotonin. Another line of evidence was obtained from studies of the use of methionine and MAO-inhibitors in schizophrenia, where high doses of methionine were found to aggravate psychotic symptoms.

6.1.3 *Metabolism of neuroleptics and dopamine*

The grouping of certain classes of drugs as "neuroleptics" is based not only on their similar clinical action in schizophrenia and other psychoses, but also on their action on extrapyramidal and autonomic functions and their ability to lower the convulsive threshold. The clinical observation that phenothiazines, rauwolfia derivatives, and other neuroleptic drugs induce extrapyramidal system (EPS) dysfunctions has stimulated attempts to discover the mechanism of this effect. In the past five years, evidence has accumulated that dopamine participates in neuropharmacological transmission in the EPS and that certain psychotropic drugs, especially the neuroleptics, influence the neuropharmacological activity of dopamine. Dopamine, a naturally occurring catecholamine, has long been known to be an intermediate in the formation of norepinephrine. Not until 1957, however, was the view propounded that dopamine might also have some physiological activity of its own. This hypothesis has been supported by neurochemical and neuropathological studies of brains of patients dying from postencephalitic parkinsonism and idiopathic Parkinson's disease.

Recently, experimental data have shown that the neuroleptic drugs, particularly the phenothiazines and the butyrophenones, influence dopamine metabolism in the brain. Reserpine had previously been shown to deplete CNS amines, including dopamine. The phenothiazine derivatives do not change the concentration of dopamine, but brain levels of homovanillic acid, the principal dopamine metabolite, are markedly decreased by various phenothiazines and butyrophenones. One possible interpretation of these findings is that the phenothiazines act by blocking receptors sites in dopaminergic centres. This "dopamine blocking" hypothesis is attractive, particularly in view of the evidence that the phenothiazines and imipramine-like substances block membrane uptake of catecholamines and other substances.

It has frequently been noted that the various classes of drugs that modify psychoses—reserpine derivatives, phenothiazines, butyrophenones, tetra-*benazine*, and thioxanthenes—also produce EPS dysfunctions. On the basis of this clinical observation a number of scientists have speculated on the role of subcortical and extrapyramidal systems in the pathophysiology of psychosis. The methoxylated dopamine derivatives are important in this research (mescaline, it should be noted, is a trimethoxylated derivative of dopamine). Moreover, the compounds isolated by Friedhoff from urine of patients with schizophrenia are claimed to be dihydroxydopamine derivatives. Research on dopamine would seem to provide a bridge between the action of neuroleptic drugs in producing EPS symptoms and the possible role of biogenic amines and subcortical systems in producing psychotic and schizophrenic symptomatology.

6.1.4 *Antidepressants and amine metabolism in depression*

In the past decade, research has shown that the effective antidepressant drugs reverse the effect of reserpine in animals and perhaps also in man. An injection of reserpine in an animal or human previously given an antidepressant does not produce the characteristic reserpine sedative effect and may even cause a paradoxical state of excitation. This blocking or reversal of the sedative effect of reserpine is now used as a pharmacological test for predicting the possible antidepressant effect of a new drug.

The sedative action of reserpine is probably linked with its capacity to mobilize the brain monoamines (serotonin, dopamine, adrenaline, and noradrenaline). Of all the derivatives of *Rauwolfia serpentina*, only those that reduce the level of the brain amines are sedative. Drugs that have a different chemical composition, such as benzoquinolizine, but that also mobilize the brain monoamines, have pharmacological and therapeutic effects that are qualitatively similar to the effect of reserpine. These amine mobilizers block the system for storing monoamines without reducing the rate at which they are synthesized.

In contrast to reserpine, the MAO-inhibitors, which inhibit monoamine mobilization by blocking one pathway of monoamine degradation, cause an increase in the level of brain monoamines. In animals the characteristic excitomotor syndrome caused by MAO-inhibitors occurs only when the brain catecholamines have reached a certain level, hence the general assumption that the action of MAO-inhibitors is linked with this action on catecholamines. In a subject given large doses of MAO-inhibitors, reserpine further mobilizes amines from the storage reservoirs. Since they cannot undergo degradation in the ordinary way, they remain active at the receptors. It is not understood why the catecholaminergic action is predominant. There are two possible hypotheses. Serotonin, when present in a very large quantity, may have its effect reversed by blockage of its receptors; blockage of the normal metabolic pathway of serotonin would involve a diversion of tryptophan metabolism towards tryptamine, a monoamine which, at least in large doses, seems to exert excitomotor effects.

Recently, the actions of the antidepressant tricyclic derivatives (derivatives of imipramine) have also been correlated with this hypothesis. Since they do not inhibit monoamine oxidase or affect the level of brain monoamines, it was difficult to understand their antidepressant effect and their effect against reserpine. However, it had been shown previously that in small doses, the tricyclic antidepressants are capable of potentiating the pressor effects of noradrenaline on blood pressure and other peripheral automatic activities. It was tempting, therefore, to postulate that they have the same capacity for catecholamine potentiation in the central nervous system, but the means by which this could be achieved were not understood. From recent experiments it now seems highly probable that

the tricyclic derivatives inhibit re-absorption of the catecholamines at central adrenergic nerve endings as they do in the peripheral sympathetic system. Moreover, depressed patients treated with imipramine and with MAO-inhibitors have reduced 24-hour urinary excretion of 3-methoxy-4-hydroxymandelic acid (VMA), the principal metabolite of norepinephrine.

These findings suggest common actions of effective antidepressants upon catecholamine metabolism in depressed patients. Studies undertaken to confirm or invalidate this hypothesis have so far had conflicting results. Significant differences have been reported in the urinary excretion of catecholamines by patients showing depressive and manic syndromes. Significant differences in the urinary excretion of 5-hydroxyindole acetic acid, a metabolite of serotonin, have been observed in different clinical forms of depression. Studies of the balance between catecholamine and serotonin metabolism are extremely promising.

In short, although all the contradictions have not yet been resolved, it now seems probable that monoamine metabolism is a mode of action common to reserpine and the antidepressants. It is therefore legitimate to wonder if a disturbance of the metabolism of these biogenic amines is an important link in the pathophysiology of depressive and manic syndromes.

6.2 Neurophysiological mechanisms

Neurophysiological techniques have been extensively used for investigating the action of drugs upon the nervous system and there is a considerable volume of literature on this subject. Such studies may also contribute to the development of new drugs and provide more information on the physiology of the central nervous system.

Research relating drug action to the interaction between an organism and its environment is greatly assisted if the neurophysiological effects can be correlated with behavioural changes. Thus, the use of chronic experiments in animals carrying implanted electrodes has enabled changes in electrophysiological potentials to be correlated with changes in behaviour when drugs are given. Experiments with such animals have shown that the pattern of electrical activity of the cortex is dissociated from behaviour patterns when certain drugs are administered, while other drugs that modify behaviour by action on the central nervous system induce appropriate changes in the EEG. Such studies, together with the results of acute experiments on unanaesthetized preparations such as the *encéphale isolé* and the *cerveau isolé*, suggest that the site of action of certain drugs, particularly those affecting levels of wakefulness, is closely related to the brain stem reticular formation. Studies of the effect of these drugs on arousal thresholds (using arousal produced by electrical stimulation of the brain stem reticular formation and also sensory-induced arousal) have confirmed the earlier hypothesis and have permitted quantification of the effects of drugs on

the central nervous system. However, whereas drugs that modify levels of wakefulness and consciousness—e.g., barbiturates and amphetamine—appear to do so by direct depressant or excitant actions on the system that activates the brain stem reticular formation, other drugs that are more potent in modifying responses to environmental stimuli—e.g., chlorpromazine and LSD—appear to have little direct action on the arousal mechanisms in the brain stem, but produce their effects by influencing the sensory inputs to the reticular system.

Extension of these investigations using conditioned and non-conditioned arousal responses has served to confirm these findings. Studies of sensory generalization and habituation of sensory stimuli have shown that chlorpromazine simulates the habituation process, rapidly reducing the significance level of all sensory stimuli to a level at which no responses occur. The action of LSD, on the other hand, appears to simulate the process of conditioning and increases the significance level of stimuli to which animals were previously unresponsive. It thus appears that the actions of these two drugs are very closely linked with the processes of filtering and integration of sensory information in the nervous system. By analysing the way in which these changes are brought about at different levels in the sensory pathway, using implanted electrodes, it should be possible to determine the level at which the changes in significance occur and the neurophysiological mechanisms that are involved in the processes of integration and filtering of sensory information.

Parallel studies in man using scalp electrodes to record evoked cortical responses should help to bridge the gap between the actions of psychotropic drugs in animals and man.

By means of the methods described above, some of the areas where drugs act in the nervous system have been located, although not very precisely. This lack of precision is particularly true of the location in the neuronal mechanisms themselves. However, a recently developed technique of micro-iontophoresis permits the application of drugs, by means of multi-barrelled microelectrodes, to the surface of a single neurone while the electrical activity of the neurone is recorded. The pharmacological responses of neurones in the brain stem have been studied with this technique, and it has been found that neurones respond to acetylcholine, 5-hydroxytryptamine, and noradrenaline, all of which may play a role in synaptic transmission in the nervous system. Each of these substances can have either an excitatory or an inhibitory effect, and with acetylcholine these two effects are related to different pharmacological characteristics of the neurones. In addition, many neurones respond to more than one of these substances and mixed effects can be observed. Thus, the neurones in this part of the brain show a wide variety of responses. This suggests that there is considerable diversity in the pharmacological characteristics of the neurones, which may be related to the diversity of functions they

subserve. The relationship between drug effects and function is not precisely known, but there is some indication that the neurones in one particular nucleus studied—the paramedian reticular nucleus—are not as diverse in their pharmacological characteristics as those in other parts of the brain stem. It is interesting to note that two drugs whose actions on sensory functions have been studied extensively, LSD and chlorpromazine, both cause depression of neuronal activity when applied iontophoretically. However, such studies are still in their infancy and much remains to be done.

Recent studies have shown that when chlorpromazine is applied to brain-stem neurones it inhibits their activity, and that it acts selectively on those neurones that respond to noradrenaline. Furthermore, chlorpromazine blocks the excitatory actions of noradrenaline but does not modify its inhibitory effects, and it alters neither the excitatory nor inhibitory effects of acetylcholine, 5-hydroxytryptamine, and histamine. Chlorpromazine, therefore, seems to have a central and specific anti-adrenaline action. If noradrenaline proves to be a synaptic transmitter, then some if not all of the central effects of chlorpromazine could be due to a blocking of synaptic transmission at those sites where noradrenaline is an excitatory neurotransmitter.

These findings, if confirmed, would be the first evidence of a psychotropic drug acting on the brain by interfering with synaptic transmission. Such studies are being extended to other drugs in the hope of understanding their precise mode of action.

The results of neurophysiological studies of the action of drugs in animals cannot be applied to man without some degree of caution, for the following reasons.

(a) More is known of peripheral pharmacological action (e.g., effects on autonomic nervous system functions) than central action. Moreover, it is often difficult to distinguish between the two. Thus, many observed effects of drugs may be due to their action on peripheral receptors which then influence the central nervous system.

(b) The clinical effects of drugs on patients may be different from those observed in experimental animals, which usually have a normally functioning central nervous system.

(c) It is difficult to translate effects of drugs in animals to man, not only qualitatively but quantitatively: it is here that behavioural studies and studies in normal human subjects can be of great help.

(d) Basic studies of drug action may lag behind clinical knowledge: the clinical use of most drugs is based on empirical grounds and not on knowledge of their mechanism of action.

7. BEHAVIOURAL STUDIES IN ANIMALS AND MAN

Experimental studies of the effects of psychotropic drugs on behaviour have several areas of application :

- (1) Better understanding of the processes of memory and learning.
- (2) Imaginative development of new therapeutic drugs—e.g., better understanding of the traumatic, endocrine, and metabolic origins of mental retardation may lead to the development of drugs for the treatment of this condition.
- (3) Elucidation of the action of drugs in facilitating or inhibiting reinforcement behaviour. This may be relevant to studies of delinquency, addiction, and personality disorders.
- (4) Development of techniques for producing animal behaviour that is specifically related to psychiatric disease in man—e.g., the techniques that permit the study of the properties of drugs that may be related to their hallucinogenic (psychodysleptic) effect in man. Such techniques may also be useful for study of the biochemical mechanisms of procedures known to exacerbate human psychosis (such as the administration of methionine with a monoamine oxidase inhibitor). They may also enable the reported “toxic” effect of the body fluids of patients with schizophrenia to be tested.

7.1 Types of behavioural study

The laboratory methods and devices first used for experimental research on psychotropic drugs were derived from those developed at the end of the last century by the founders of animal psychology. Such devices included the cage in the form of a wheel used for measuring the spontaneous motor activity of the rat, the maze, and the “problem-cage” from which the animal could escape only by digging into the sand floor on which it was placed.

Current studies are designed to investigate (a) innate (sometimes called spontaneous or instinctive) behaviour ; (b) acquired behaviour, resulting from previous conditioning or learning ; and (c) emotive or anxiety reactions. These three areas are of interest to both the pharmacologist and the psychiatrist.

Innate behaviour. Many different types of innate behaviour have been studied. It has been maintained that data on “spontaneous motor activity” can be as revealing as information obtained from more complex tests. Very few data exist for comparing the performances of the same animals under different research conditions, but enough is known to state that the measurement of spontaneous activity is not as simple as it appears and that the values recorded are subject to wide variations, depending upon the

techniques employed. Ethological techniques that have recently been developed for use in drug studies appear to be of promise.

Conditioning and learning. Conditioning and learning tests have been widely used in psychopharmacology. Two types of elementary acquired behaviour are generally distinguished: Pavlovian conditioning involving reflex behaviour or a conditioned reflex; and Skinnerian conditioning involving operant behaviour, sometimes designated by the term "voluntary" behaviour. Two main orientations of behaviour are also recognized, motivated respectively by reward or punishment; in the terms of experimental psychology these correspond to a positive or negative "reinforcement". Recently, more complex schedules of operant behaviour have been employed, such as Sidman avoidance and complex timing and discrimination schedules. Steady-state methodology offers a sensitive means of analysing fine details of drug action.

Psychopharmacological agents may have very different effects on behaviour, depending on the methods that are used to evaluate behaviour. When using different behavioural techniques, it is important to compare data obtained under the same conditions in the same species.

Psychopharmacological research on conditioning in human subjects is now being carried on in several laboratories. Various features of the conditioning response are studied in parallel with similar experiments performed on animals. The orienting reflex and its weakening or disappearance in human subjects under the influence of psychodysleptics and neuroleptics have been found to exhibit characteristic changes similar to those observed in animals under analogous conditions. Pavlovian conditioning responses in psychotic patients are being studied as possible predictors of individual therapeutic responses to treatment with psychotropic drugs. Furthermore, some investigators are attempting to correlate (a) the conditioned responses of psychiatric patients with the performance of the patients on a battery of perceptual, psychomotor, and cognitive tests, and (b) the conditioned responses, autonomic reactions, biochemical findings and scores obtained from behaviour rating scales. There is, therefore, a definite trend to introduce measures of performance into the study of human responses to drugs. Such measures are more objective than behaviour rating scales and have proved to be of heuristic value in psychopharmacological experiments on animals.

Emotive and anxiety reactions. A wide range of "abnormal" behaviour, extending from the elementary inhibition reaction of the mouse placed in an "open-field" to the refusal of rats to feed under certain circumstances, has been described from observations on laboratory animals.

We owe to Pavlov the term "experimental neurosis" and the first descriptions of techniques that produce such neuroses. During the first half of the century Pavlov's work was extended in many countries. The

concept of "experimental neurosis" and the parallels that can be drawn between the clinical and laboratory observations have been interpreted in divergent ways. The concepts proposed recognize the emotional, undesirable (or non-adaptive), and generalized nature of the reaction. Some investigators have stressed the connexions between the genesis of the neurosis and the existence of learned behaviour or behaviour in the process of acquisition, emphasizing the important role of conflict situations and frustration reactions. Others have emphasized the exceptional nature of neurosis. The conditioned emotive reaction in which a disagreeable stimulus is superimposed on a reward has provided another useful technique for the study of various types of psychotropic drug.

Combined studies. Behavioural studies have also been combined with neurophysiological methods, such as those using the EEG and evoked potential, and intracerebral stimulation and self-stimulation by means of electrical and chemical stimuli.

7.2 Psychopharmacogenetic studies

The broad field of pharmacogenetics has produced interesting observations on the susceptibility of different animal strains to psychotropic drugs.

Substantial differences have been reported in the toxic and pharmacological effects of amphetamine, barbituric acid, chlorpromazine, nicotine, and scopolamine on different strains of mice and rats.

Examples of the varying influence of social environment on the effects of psychotropic drugs in different species of animal and in different genetic lines of the same species are well known. One example is "group" amphetamine toxicity in mice and the absence of this phenomenon in groups of rats. The grouping together of mice of the BALB line ("emotional", with a high content of serotonin and noradrenaline in the brain stem) leads to aggressive behaviour if a small dose of amphetamine is administered to the animals. In mice of the C₅₇BL line ("non-emotional", with a low level of both monoamines) this phenomenon does not occur. However, in isolated mice of both lines changes in behaviour under the influence of amphetamine are identical.

It has been recently established that abnormalities in the metabolism of antidepressants may be common to close relatives, both in sickness and in health. Such abnormalities are due to genetically determined differences in the functioning of the liver enzymes that metabolize the drugs.

7.3 Prediction of human responses from animal experiments

Animal experiments in psychopharmacology offer advantages that make them an indispensable preliminary and complement to clinical trials. These

advantages include : the abundance and ready availability of experimental animals ; the possibility of combining behaviour research with parallel neurophysiological and biochemical studies, often difficult to carry out in man ; the possibility of working on genetically homogeneous subjects ; and the fact that animal experiments are not subject to the same ethical restrictions as experimentation on man.

However, the limited nature of findings from studies of psychotropic drugs in animals is only too obvious. The level of integration of animal behaviour is relatively low, rendering comparison with man difficult. It is virtually impossible to reproduce in animals morbid conditions fully comparable with those dealt with in psychiatry by means of the analysis of symbols.

One of the major techniques for relating animal to human responses is that derived from animal conditioning (see section 7.1). However, it is important to note that almost all data on behaviour, including the effects of psychotropic drugs, have been established in individual animals—i.e., animals carrying out a particular form of behaviour in isolation, in a cage or maze, or on a stand. This applies also to experiments with self-stimulation, the excitation of individual cerebral structures, EEG observations, etc.

Knowledge of conditioned reflexes (vegetative and motor) to subliminal stimuli, particularly in man, may be extremely important for understanding of results of drug therapy of mental disorders. The effects of drugs on such reflexes have not, so far as is known, been investigated.

Since most human behaviour occurs in social situations, generalization from studies of isolated animals is questionable. There are not yet adequate grounds for extrapolating data on group psychopharmacology from animals to man. Peoples of different countries have different social, religious, and cultural traditions and the " social factors " must be relevant to the effects of psychotropic substances on behaviour.

It is well-known that one of the most frequent findings in psychiatric practice is that of individual differences in the behaviour of human beings and in the susceptibility of their psychic functions to psychopharmacological agents. In many cases, individual differences in susceptibility to psychotropic drugs may be caused by differences in metabolism of the drugs. However, few investigations have been devoted to the ways in which metabolism of psychotropic drugs determines individual differences in the pharmacological regulation of human and animal behaviour.

One of the practical tasks of preclinical psychopharmacology that is already fairly well advanced is the establishment of new tests for predicting therapeutic action and for selecting new compounds for clinical use.

Some studies have attempted to correlate the effects of neuroleptics in animals with those in man. In particular, correspondence between human neurological syndromes and certain animal behaviour patterns—e.g., catalepsy—has made prediction of new neuroleptics possible. Batteries of

tests that differentiate neuroleptics from sedatives and hypnotics have contributed to the pharmacological separation of these categories of drugs.

Batteries of tests (particularly reserpine animal tests) are also available for use with psychostimulants and antidepressants, but it is often difficult to predict antidepressive properties experimentally.

Prediction of hallucinogenic effects still remains very difficult and the available tests are not very specific.

8. RECOMMENDATIONS

8.1 General principles

(1) Many investigations in psychopharmacology require interdisciplinary collaboration. Only a few centres are conducting interdisciplinary research in clinical and experimental psychopharmacology, and more are required.

(2) Applied research in psychopharmacology should be expanded, and the establishment of research groups or special units for this purpose within hospitals or other clinical centres is desirable.

(3) The clinical psychiatrist plays an essential role in multidisciplinary psychopharmacological research. It is generally agreed that the unsatisfactory nature of much research on the biological basis of mental disorders has been due partly to inadequacy or lack of clinical controls. In clinical psychopharmacology, it is essential that close control be maintained over the precise type and clinical condition of the patients and over their diet, ingestion of drugs, and level of activity.

(4) In planning research in clinical psychopharmacology, at least as much care should be given to securing competent clinicians as to the experimental design, evaluative procedures, and statistical analysis. If clinical observations are inadequate, the best controlled designs and advanced statistical analyses are useless.

(5) New hypotheses and new therapies are developed through the spontaneous efforts of clinicians working alone, with each other, or with specialists in laboratory techniques. Flexibility and creativity are essential attributes in research workers. Stereotyped and unnecessarily rigid procedures, and unduly "structured" experimental designs and statistical techniques, may impede research.

(6) To facilitate progress in psychopharmacology, the investigator should be free of excessive constraint from legislative bodies or administrative and granting agencies. As in any field of clinical research, however,

the investigator is of course bound by the ethical codes and standards of medicine.

(7) Present training in psychopharmacology is inadequate, and greater attention should be given to this topic in the training of psychiatrists.

(8) Since psychopharmacology is developing into a speciality, training should include courses in general research methods and in statistics as well as in pharmacology, psychiatry, and psychology.

8.2 Research topics

(1) Research on the actions of psychotropic drugs using models of various human behaviour disturbances in laboratory animals should be expanded, as should research on normal animals. The effects of drugs in animals should also be studied under conditions that approximate more closely to the clinical situation—e.g., studies of long-term (rather than short-term) administration of drugs and studies of the effects of drugs on group behaviour.

(2) Research is required on the symptomatic changes caused by drugs in the manifestations of psychiatric disorders, and on possible changes in the course of a disease caused by drug therapy.

(3) Comparative studies should be made of changes brought about by psychiatric drug therapy in (a) ambulatory patients receiving treatment in out-patient and after-care clinics and (b) those receiving treatment in psychiatric hospitals.

(4) Research is required on the impact of modern therapy with psychotropic drugs on the epidemiology of various psychiatric disorders under different ethnic, cultural, and social conditions.

8.3 Suggested collaborative research

The Scientific Group made the following proposals for activities in connexion with research on psychopharmacology.

8.3.1 *Monitoring current research*

Methods could be established for continuing study of (a) the general policy or philosophy of research in psychopharmacology, and (b) the research undertaken by various centres in different areas of investigation.

8.3.2 *Collaborative studies*

(a) Collaborative studies in physically and culturally contrasting environments could be established. A major contribution could be made to the

advancement of psychopharmacological science by establishing widely accepted methodologies. Continuous screening of relevant research literature in order to identify areas of unexplained discrepancies is essential. Based on these findings, collaborative pilot studies could be developed to test hypotheses of the nature and relevance of environmental differences.

Initially, such pilot studies might be concentrated in only a few countries in order to develop familiarity with the regional characteristics. Consideration should be given to the exchange of professional staff who would participate in the investigation on unfamiliar territory. In view of the existing confusion and disagreement over diagnosis, natural history of illness, and criteria for and methods of drug treatment, the exposure of scientists to different clinical traditions and social and cultural surroundings would in itself be a major contribution to international understanding of mental health problems.

(b) In developing collaborative studies, representatives of various groups known to be engaged in such studies could be brought together to review knowledge of psychopharmacology, to discuss the methodology and logistics of collaborative studies, and to explore further the opportunities for such studies.

8.3.3 *Reference centres*

A useful service could be provided by international psychopharmacological reference centres, which could fulfil the following functions.

(a) Preparation of a list of psychotropic drugs, including their chemical formulae, generic names, names in different countries, and selected scientific references. Such a list should be revised periodically as new drugs are developed. Various classifications should be reviewed with the aim of arriving at a simple and widely accepted system. A guide to psychotropic drugs, with notes on their efficacy and validation by proper clinical trials, should also be prepared. Such a guide would improve the exchange of information and be of use in the mental health programmes of developing countries, which could use it in deciding what drugs to include in their national formularies.

(b) Periodic review of the various psychopharmacological abstracting services. Particular attention should be given to the adequacy of such services, the accuracy of translation, possible unnecessary duplication, the extent of distribution of abstracts, and the ease with which they can be consulted by scientific workers throughout the world.

(c) Development of criteria for clinical evaluation of adverse effects (e.g., ophthalmoscopic standards and films or videotape recordings of abnormal neurological movements and signs). Case registries of selected syndromes might be useful, particularly if genetic factors become involved.

(d) Promotion of research on the influence of genetic factors on psychopharmacology.¹ Such research should include family studies of patients in whom drugs (e.g., amphetamines, iproniazid, reserpine, and LSD) have induced abnormal mental reactions. Research in the pharmacogenetics of responses to psychotropic drugs such as antidepressants should be increased.

8.3.4 *Training, conferences, and seminars*

In addition to the promotion of training by means of fellowships and the exchange of research workers, it is desirable to arrange special meetings such as :

(a) international workshops on techniques and methods for studying distribution and metabolism of psychotropic drugs ;

(b) small interdisciplinary conferences on problems involved in the development of new psychotropic drugs, in which representatives of academic, clinical, and manufacturing organizations could participate ;

(c) a conference to review after-care and follow-up programmes, with particular attention to the necessity of adequate medical, psychiatric, and social services for psychiatric patients on drug therapy.

8.3.5 *Promotion of psychopharmacological treatment and research in developing countries*

From the clinical point of view, psychopharmacology provides a feasible and effective form of therapy that is adaptable to a public health approach. The use of psychopharmacological therapy in developing countries could be facilitated by means of fellowships and teaching seminars.

Developing countries may be able to make important contributions to research in psychopharmacology—for example, it may prove more feasible to evaluate the efficacy of psychotropic drugs in countries where their use is not already widespread.

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¹ See also *Wld Hlth Org. techn. Rep. Ser.*, 1966, 346.

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