

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES

No. 381

**NEUROPHYSIOLOGICAL
AND BEHAVIOURAL RESEARCH
IN PSYCHIATRY**

Report of a WHO Scientific Group

WORLD HEALTH ORGANIZATION

GENEVA

1968

© World Health Organization 1968

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. Nevertheless governmental agencies or learned and professional societies may reproduce data or excerpts or illustrations from them without requesting an authorization from the World Health Organization.

For rights of reproduction or translation of WHO publications *in toto*, application should be made to the Division of Editorial and Reference Services, World Health Organization, Geneva, Switzerland. The World Health Organization welcomes such applications.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Director-General of the World Health Organization concerning the legal status of any country or territory or of its authorities, or concerning the delimitation of its frontiers.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature which are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

PRINTED IN FRANCE

CONTENTS

	Page
1. Introduction	5
2. Present state of knowledge and current trends of research	6
2.1 Conditioning and learning	6
2.2 Electrophysiology	8
2.3 Sleep	12
2.4 Psychopharmacology in relation to neurophysiological and behavioural research	15
2.5 Behaviour therapy	18
2.6 Etiology and the high-risk sample method	20
3. Prospects for future research	22
3.1 Critical periods of development	23
3.2 High-risk samples	23
3.3 Learning techniques and primary prevention	24
3.4 Sleep	25
3.5 Diagnosis and prognosis	26
3.6 Transcultural collaboration	27
4. Summary and recommendations	28
4.1 Facilitation of communication	28
4.2 Suggested collaborative research	28
4.3 International standardization	30
4.4 Collaboration with international organizations	31
Annex. Example of a combined research project	32

WHO SCIENTIFIC GROUP ON NEUROPHYSIOLOGICAL
AND BEHAVIOURAL RESEARCH IN PSYCHIATRY

4-9 September 1967

Members:*

- Dr C. Astrup, Senior Research Psychiatrist, Gaustad Hospital, Oslo, Norway
(*Rapporteur*)
- Dr M. Jouvét, Professeur agrégé, Laboratory of General and Experimental Pathology, Faculty of Medicine, Lyons, France
- Dr N. E. Miller, Professor, The Rockefeller University, New York City, N.Y., USA;
Chairman, IBRO Sub-Committee on Relations with International Organizations (*Chairman*)
- Dr K. K. Monakhov, Chief, Laboratory of Neurophysiology and Higher Nervous Activity, Institute of Psychiatry of the Academy of Medical Sciences of the USSR, Moscow, USSR
- Dr Teresa Pinto-Hamuy, Professor of Physiological Psychology, Institute of Physiology, University of Chile, Santiago, Chile
- Dr J. Saarma, Professor of Psychiatry, Faculty of Medicine, Tartu State University, Tartu, USSR (*Vice-Chairman*)
- Dr N. C. Surya, Director, All-India Institute of Mental Health, Bangalore, India
- Dr W. Grey Walter, Head of the Physiological Department, Burden Neurological Institute, Bristol, England (*Rapporteur*)

Representatives of other organizations:

United Nations Educational, Scientific and Cultural Organization:

- Dr A. Burgers, Programme Specialist, Department of Advancement of Science, Unesco, Paris, France

Secretariat:

- Dr A. Jus, Professor of Psychiatry, Chairman, Department of Psychiatry, Academy of Medicine, Warsaw, Poland (*Temporary Adviser*)
- Dr B. A. Lebedev, Medical Officer, Mental Health, WHO (*Secretary*)
- Dr S. A. Mednick, Professor, University of Michigan, Ann Arbor, Mich., USA and Director, Institute of Psychology, Municipal Hospital, Copenhagen, Denmark (*Temporary Adviser*)

* Invited but unable to attend: Dr D. Ploog, Professor, Director of the Clinical Institute and Head of the Department of Primate Behaviour, Max Planck Institute for Psychiatry, Munich, Federal Republic of Germany.

NEUROPHYSIOLOGICAL AND BEHAVIOURAL RESEARCH IN PSYCHIATRY

Report of a WHO Scientific Group

1. INTRODUCTION

A WHO Scientific Group on Neurophysiological Research in Psychiatry met in Geneva from 4 to 9 September 1967. The meeting was opened by Dr L. Verhoestraete, Director, Division of Health Protection and Promotion, on behalf of the Director-General. Professor N. E. Miller was elected Chairman and Professor J. Saarma Vice-Chairman; Dr W. Grey Walter and Dr C. Astrup were nominated as Rapporteurs.

During the last ten years the interaction between neurophysiology and psychiatry has been transformed by several independent but convergent developments. These are :

- (1) the extension of animal studies to the investigation of structures and activities related to human behaviour and to biochemical investigation of brain metabolism;
- (2) the application of systematic conditioning paradigms to the study of higher nervous activity and learning in normal subjects and patients;
- (3) the refinement of conventional electrophysiological procedures to obtain information on a wide variety of physiological variables by polygraphic recording;
- (4) the application of polygraphic techniques to the study of normal sleep and pathological alterations of consciousness, both in animals and man;
- (5) the introduction of a wide range of psychopharmacological agents with profound effects on mental state and behaviour;
- (6) the introduction of computer techniques in the analysis and correlation of data obtained from studies using the above-mentioned techniques and procedures;
- (7) the establishment of surgical procedures for the implantation of multiple in-dwelling electrodes in the human brain for diagnosis and therapy;

(8) the recognition of the difficulties involved in collecting appropriate control groups to compare with mentally ill patients, and the appreciation of the feasibility of examining, in early life, people with a high risk of becoming mentally ill.

Some details of these advances and their application to psychiatric problems are given below. In all of them and at all stages, the neurophysiologist is faced with a serious dilemma; the basic information from which he derives his capacity to investigate human beings is based on animal studies, but modern techniques permit experiments in which the "secondary signalling system" — that is, language and symbolic thinking — is of crucial importance. This means that differences between species can cause confusion, while experiments that might be regarded as crucial can often not be performed on human subjects even if they are normal volunteers, because of the familiar and rigorous ethical considerations that must always place constraints on the interaction between the experimenter and his human subjects. Questions of ethical justification arise particularly when the administration of new chemical compounds or surgical intervention affecting brain function is envisaged; thus the physicians and surgeons in charge of such cases carry a heavy burden of moral decision. In general, when therapeutic aims are foremost the ethical considerations are easily evaluated, but there is often a combination of diagnostic, therapeutic, and secondary experimental aims, and here the ethical issues are less clear and can only be resolved by prolonged and responsible discussion between all concerned, including the patient and his relatives.

2. PRESENT STATE OF KNOWLEDGE AND CURRENT TRENDS OF RESEARCH

2.1 Conditioning and learning

The classical conditioning procedure involved rather simple activities such as salivation and shock avoidance, but the methodology has evolved over the last fifty years to a point at which some laboratory methods are almost indistinguishable from real situations. At the other extreme, visceral and autonomic activity has been shown to be susceptible to conditioning to a remarkable degree, even to the point of breakdown of essential functions.

An enormous amount of experimental work has been done on animal and human learning; certain recent developments are of special relevance to problems of psychiatry, but some of the background must be given before they can be described.

It has long been known that when a neutral stimulus is associated with an unconditioned stimulus that elicits a particular response, the neutral stimulus acquires the ability to elicit that particular response. This type of learning is called classical conditioning, and it is generally involved in the acquisition of emotional responses such as fear, sexual arousal, and disgust. Many bodily processes can be modified by classical conditioning.

Another type of learning has been called instrumental or trial-and-error learning, operant conditioning, or type II conditioning. It is much more flexible, in that it does not require an unconditioned stimulus that already elicits the response to be learned. Instead, a reward strengthens any immediately preceding response. Relief from strong fear or pain or from hunger or thirst constitutes a reward, as well as what may loosely be described as the achievement of a goal or the experiencing of pleasure. There is good reason to believe that what psychiatrists have described as "secondary gains" function as rewards to reinforce the learning and development of symptoms. At present many powerful human rewards have to be identified empirically by their effects on behaviour; what serves as a powerful reward for one person may in some cases have little effect on another. An independent physiological means of identifying rewards for human subjects would be extremely valuable, but it is not yet in sight.

Recent experimental work is greatly extending the domain of rewarded instrumental learning in ways especially relevant to psychiatry. The recent discovery that glandular and visceral responses can be learned in the same way as other somatic responses can by rewarded training opens up the possibility that psychosomatic symptoms may be reinforced by secondary gains. The availability of techniques for recording glandular and visceral responses opens up the theoretical possibility, which should be subjected to clinical tests, that symptoms like psychogenic high blood pressure or spastic colitis might be treated by promptly rewarding first small, and then larger, visceral changes in the therapeutically desired direction.

In recent carefully controlled experimental situations animals have been trained to exhibit different kinds of electrical activity of the brain, to resist pain and fear, to give up and fail to solve a simple avoidance problem, or to be either pugnacious or submissive. Since human beings are presumably also capable of such learning, the clinical implications of such types of learning need to be explored at the human level. Yet other experimental work emphasizes the practical importance of "shaping" behaviour by giving immediate rewards for small changes in the desired direction, then progressively increasing the size of the change demanded before giving the reward. Finally, once a habit is learned, it can be maintained without rewarding each performance. It has been found that certain schedules of reward are much more efficient in maintaining beha-

viour than others; this could be relevant to the extreme persistence and intractability of certain functional symptoms.

The results obtained from investigations of the higher nervous activity in mentally ill patients suggest that it may be possible to elaborate objective systems of diagnosis and prognosis which could be complementary to clinical methods and might help in the selection of suitable treatment. The etiology of certain disorders has also been envisaged in terms of the morbid acquisition of conditioned responses.

2.2 Electrophysiology

Techniques and methods. Changes in behaviour, whether during controlled experiments or in free life, provide an inadequate description of what happens in living animals, since they reflect only those changes in higher nervous activity that are embodied in overt action. During the last few years electrophysiological methods have been developed that permit correlation of electrical events in the brain with human behaviour and, moreover, reveal specific features of cerebral activity that may have no external counterpart or may precede decision or action. Although these methods have evolved from the familiar techniques of electroencephalography (EEG), they represent, in effect, a new departure.

The essential feature of this development is the provision of controlled stimuli and semantic signals in isolation and in conditioning paradigms. By this means the active, adaptive function of the brain can be studied, as opposed to observation of its passive activity as in the conventional EEG. Perhaps the most important aspect of such procedures is that with contemporary devices, such as closed-circuit television and videotape, normal subjects and patients can be presented with complex experiences that closely resemble real life or form a part of diagnostic or therapeutic sessions. The brain responses to certain complex experiences can be extracted by computation from background activity and related to other physiological variables, behaviour, and psychological assessments of mental state and temperament.

Unfortunately, these procedures, which are already in use in several research centres, need far more complex equipment than that adequate for a routine EEG. The brain responses to complex meaningful signals and the electrical events that precede conscious decision and action are usually smaller than the background activity or "chatter" of the brain, and the details of their topography are of great importance in comparing normal with abnormal conditions. This means that computers, as well as elaborate signal generators, are essential, and the cost of the installation, both in capital investment and running expenses, is high and tends to rise as the equipment is applied to wider ranges of use. In particular, the collection of clinically valuable data in mental hospitals, child guidance

clinics, and prisons requires high-grade data-tape systems for the storage and transfer of the physiological information; these instruments alone cost more than a conventional EEG machine.

The precise specifications of the equipment needed for this work and the details of the observations made are available elsewhere, but in considering such research it should be appreciated that, although a small special-purpose computer is adequate for preliminary trials, the enormous amount of relevant information calls for access to a general-purpose computer which can deal both with multichannel on-line data and with the numerical calculations needed to estimate the correlation and significance of the physiological and clinical parameters.

Emphasis on electrophysiological methods and phenomena does not mean that these phenomena are considered as unique or basic components of brain function. All events in the brain are *electrochemical*. A potential change indicates some sort of chemical reaction, and is often the only accessible indicator of such reactions. When it is possible to correlate certain types of electrical event with specific chemical reactions, the alliance of neurophysiology and neurochemistry will greatly extend the rational basis for psychiatric practice.

Strenuous efforts are being made at the present time to simplify the procedure and to identify the most valuable and crucial measures from the psychiatric standpoint.

Applications to diagnosis. The aspects of cerebral electrogenesis that seem most likely to be of direct value in psychiatric diagnosis are the following:

- (1) The degree of spatial synchronization or coherence between various cortical regions. This involves calculation of the correlation coefficients between two or more simultaneous electrical activities such as evoked responses or intrinsic rhythms. The interrelationship between the electrical events in different functional regions can be compared with the characteristics of conditioned reflex activity and this combined measure can be used to define the psychological significance of various states of the organism. These complex measures have already been found to vary with the mental state of normal subjects and with the nature of the mental disturbance.
- (2) The range and character of habituation to sensory stimuli.
- (3) The form and responsiveness of the slow potential changes in the frontal cortex that link conditional and unconditional stimuli (contingent negative variation [CNV] or expectancy wave). In certain types of psychopathy this last effect seems to be extremely small, even in favourable conditions, while in patients with chronic anxiety neurosis it displays a highly significant proneness to attenuation by distraction.

The maturation of these effects has been studied in groups of normal, institutionalized, and disturbed children, and the CNV wave seems to reflect very faithfully the slow development of the integrative capacity in normal children and its failure in children with mental disturbances. The relation of the variations of the CNV wave to other physiological variables — e.g., muscle tension, the heart rate, electrodermal conductance — forms a rational pattern which demonstrates the complex and sometimes paradoxical interaction of cognitive and affective processes.

These electrophysiological procedures have already emerged from the laboratory; more recently, with the introduction of radiotelemetry, studies using them have been carried out on free-ranging normal subjects and patients. The observations suggest that the variations in intrinsic rhythm, the interaction of evoked responses, and the development of slow potential changes seen in laboratory conditions also occur in normal activity and the performance of everyday tasks.

It is technically feasible to monitor quite unobtrusively the cerebral events that precede and accompany variations in attention, the formation of temporary associations, the making of decisions, and the sense of achievement. With computer assistance, these effects can be related to other physiological variables and the psychological appraisal, and the results interpreted in operational terms compatible with psychiatric requirements.

Applications to therapy. Apart from electroconvulsive therapy, electrophysiology has not generally been regarded as directly related to psychiatric treatment. However, during the last few years there have been detailed reports of trials of prolonged electropolarization of the brain with very small steady currents. In normal subjects, currents of less than one milliamperere with the forehead positive to the body produce a sense of irritation and sometimes heightened awareness, while negative polarization generally has an unpleasant effect. In depressed patients sustained positive polarization lightens the mood over a period of several hours or even days.

The reason for these electrotonic effects is obscure. In animal preparations positive polarization of the cortex is known to enhance the surface negative components of evoked responses, and this effect may be responsible for the influence on mood in human beings. There is some clinical and electrographic evidence of delayed and rather persistent cerebral disturbance following polarization for periods of several days, even with these very small currents. This suggests the possibility of a cumulative and rather widespread disturbance of chemical equilibrium as well as a short-term electrotonic action.

The physiological technique of electrode implantation in animals has a long history and is the main source of information about brain function. In man, however, this procedure was impossible until the

introduction of biologically inert metals and insulating varnish and the development of insertion procedures acceptable to neurosurgeons. The first cases studied in this way were epileptics in whom frequent violent seizures and behaviour disorders could not be adequately explained by the scalp EEG. The intracerebral electrodes were used to locate abnormal regions beyond the range of scalp electrodes, and in many cases the exploration disclosed local lesions which could be dealt with by surgical resection or ablation, with excellent clinical results.

More recently the technique has been extended to other severely disabling conditions that have resisted all other forms of treatment. The rationale of the procedure derives from the limited success of the various leucotomy operations and the need to avoid the undesirable associated side effects that have brought such major interventions into disrepute.

The procedure as used on a number of patients treated at the Burden Neurological Institute, Bristol, England, is as follows. A large number (60-80) of electrodes in carefully measured sheaves are implanted through two burr or trephine holes in the frontal lobes so as to cover a wide plane just anterior to the anterior clinoid process. Records of brain activity are then obtained from all the electrodes in order to ascertain that they are correctly placed and connected. Next each is stimulated in turn to observe whether there is any after-effect, either as a coherent after-discharge or as a sustained slow rhythm; this is to establish which of the electrodes are in white and which in grey matter, the latter, identified by the after-effects, being excluded from the therapeutic scheme.

The next stage is to block neural transmission around the tip of each electrode with a small polarizing current during a psychiatric interview intended to elicit signs of the patient's mental disturbance. When polarization produces relief of a particular symptom such as anxiety or compulsive thinking, the electrode number is noted for possible later coagulation of the area involved. By this means regions of white matter can be identified where reversible interruption of function produces subjective relief, often with such objective signs as normalization of the heart rate, muscular relaxation, and the reappearance of normal brain responses to conditioned stimuli.

The next stage is to pass larger currents through the selected electrodes so as to produce small permanent lesions. This procedure may extend over several weeks or even months, and the patient is usually discharged for a week or two during this stage, with the electrodes still in place, in order to assess his capacity to support the full strain of normal life. The relief of symptoms is gradual and progressive and is assisted by general supportive therapy, group activities, and excursions.

When the patient reports full capacity for work and independent life with regression of symptoms and this is corroborated by staff observers and relatives, the electrodes are withdrawn.

During the whole of this period extensive and repeated observations are made of the neurophysiological features most closely related to the mental state (e.g., the CNV wave and autonomic lability), and intelligence tests are carried out.

The selection of patients for such treatment is based empirically on the success obtained with different conditions. All the patients accepted so far have had long histories of crippling neurotic disturbance unrelieved by conventional treatments (shock therapy, psychopharmacology, psychotherapy, and even leucotomy). All have benefited in some degree, and 80% of 60 patients have obtained full subjective and social relief. The two conditions that seem particularly suitable for this treatment are chronic intractable anxiety (fear) and compulsive-obsessional states (ritualized and forced thinking). In the former the target for intervention seems to be the supra-orbital white matter, while in the latter coagulations in the paracingulate region relieve the compulsive symptoms.

Correlation of these results with analysis of the electrophysiological features before, during, and after treatment has already suggested a close concordance between objective and subjective signs of cerebral competence that may provide a basis both for the development of theory and for prognosis.

2.3 Sleep

In recent years great interest has been shown in the neurophysiological problems of sleep. Since 1958, polygraph recordings in man and animals have revealed the presence of two successive states during behavioural sleep: sleep with slow cortical activity and sleep with rapid cortical activity corresponding to dreaming in man (paradoxical or rapid-eye-movement sleep). It is now thought that the old "passive" concept of sleep (according to which sleep is due to fatigue or passive deafferentation of the awakening or ascending activating reticular system) is no longer tenable. For this reason research has turned towards the delimitation of hypnic systems able to block *actively* the awakening system. This work has employed the two classic methods of neurophysiology: stimulation and lesion. The former method has not come up to expectations, since one by one almost all regions of the brain have been proved able to induce sleep on stimulation. This is why the lesion method seems at present to be one of the most useful lines of attack, although this procedure is acceptable only in subhuman species. If sleep is an active phenomenon it should theoretically be possible to bring about insomnia by lesion. The delimitation of a hypnic structure would therefore involve finding the smallest lesion able to bring about the most intense and most prolonged insomnia. Very recently there have been advances in classic neuroanatomy as a result of new techniques by the aid of which histo-

chemical systems within the brain can be delimited. Thus, using histo-fluorescence methods, the neurones containing monoamines (noradrenalin, dopamine, serotonin) can be located. It was then suspected that the systems responsible for sleep coincided with structures containing monoamines. Because of this, neuropharmacology, which offers a means of acting dynamically on the cerebral monoamines, also appeared to be the technique of choice for an understanding of sleep mechanisms.

Phenomenological aspects of sleep states. The quantity of different states of sleep can be determined by long-term recordings. It is known that behavioural sleep can be considered as a succession of :

(a) Sleep with synchronized cerebral activity and slow cerebral waves, characterized by the persistence of muscular tonus. This state is relatively monomorphous in animals, but can be broken down into four stages in man. It constitutes about 75%-80% of behavioural sleep. It is periodically interrupted by paradoxical sleep.

(b) Paradoxical sleep (rapid-eye-movement sleep), characterized by the appearance of a desynchronized rapid cortical activity similar to that of the waking state in the animal, by a very specific subcortical phasic electric activity, by complete disappearance of muscular tonus, and by rapid eye movements. This is a deep sleep state, since it is accompanied by a very marked increase in the arousal threshold. Human subjects awakened during this stage have very clear memories of dream activity: This state of sleep constitutes about 15%-20% of behavioural sleep in most mammals and in man. It has also been shown that during paradoxical sleep a very large number of changes occur at the vegetative level — including in man arterial hypotension, respiratory changes, and erection.

Structures responsible for sleep. This problem is far from being solved. Some recent attempts have been made to study the role of histo-chemically well-defined brain stem structures in relation to sleep. The structures responsible for initiating "slow sleep" (whose destruction leads to total insomnia) appear to be situated in the lower brain stem. It also seems probable that these structures coincide with the raphé system, which is composed of neurones containing serotonin. Destruction of the whole of this system leads on the one hand to almost complete disappearance of sleep and, on the other, to a selective decrease in cerebral serotonin (the noradrenalin does not change).

Paradoxical sleep seems to depend on structures distinct from those causing slow sleep, for it can be suppressed selectively in the animal by the destruction of an area in the mediodorsal pontile tegmentum, with little effect on arousal or on slow sleep. This area is particularly rich in neurones containing noradrenalin.

Mechanisms of sleep states. The discovery of the histochemical individuality of some structures, the destruction of which alters the sleep states, has naturally led to a search for monoaminergic mechanisms initiating these states.

Any reduction in cerebral serotonin (through inhibition of its synthesis by blocking tryptophane hydroxylase, for example) leads to a considerable decrease in sleep and a parallel increase in wakefulness. Conversely, any increase in cerebral serotonin brought about by injection of its precursor, 5-hydrotryptophane, which alone is able to cross the blood-brain barrier, leads to an increase in sleep.

The problem of the mechanisms of paradoxical sleep has not yet been solved; although it appears probable that noradrenergic neurones are responsible for initiating it, the evidence for the participation of noradrenergic mechanisms while it lasts is indirect only. Cholinergic mechanisms are also thought to participate in sleep mechanisms, whereas the mechanism of action of short-chain fatty acids which may induce sleep in certain conditions is still not understood.

Phylogeny of sleep states. Although behavioural sleep is relatively easy to recognize in fish, there is no change in brain activity between active and resting periods. In reptiles, a slight slowing in the electrical activity of the brain appears during sleep, but there is nothing to indicate the presence of paradoxical sleep in the tortoise and alligator. This state is reported to have been detected, however, in certain lizards and chameleons. It is in birds that paradoxical sleep really begins to develop. Whereas normal sleep is easily recognizable and can be readily induced by darkness, for example in the chicken and pigeon, the periods of paradoxical sleep are still extremely brief and represent only 0.5% of total sleep. In all mammals studied so far, ranging from the opossum to man, paradoxical sleep is easily recognizable, but it is not yet possible to explain the considerable variations in its percentage between the different species.

Ontogeny of sleep states. From birth onwards, newborn (and immature) mammals such as kittens, puppies, young rabbits, and human infants show a very high percentage of paradoxical sleep, which may be as much as 90% of total sleep in the kitten and 40%-50% in the infant. The nervous mechanisms that will subsequently be associated with dream activity must therefore exist before sleep proper. In mammals born with a well developed nervous system (guinea-pig, lamb) the relative proportion of paradoxical sleep is much lower (20%-30% of total sleep), but it still remains higher than in the adult.

Sleep deprivation. It is extremely difficult to provoke insomnia by instrumental methods, for the methods employed also lead to considerable fatigue and it is difficult to know whether the disturbances observed are

due to insomnia or to tiredness. Nevertheless, paradoxical sleep can be suppressed selectively by simple methods without tiring experimental animals. Paradoxical sleep deprivation can be tolerated for a relatively long time and it has not yet been possible to find the biochemical cause of the disturbances observed after periods of paradoxical sleep deprivation extending over 15 to 20 days (hyperexcitability, exaggerated tendency to convulsions, increase in appetite, hypersexuality, and aggressiveness).

Psychopathology. A relationship between sleep disorders and mental disorders is suggested by numerous indirect data, but not proved. Insomnia is common in depressive states, but a cause-and-effect relationship cannot be deduced from this. Furthermore, there may be a considerable increase in dream activity during oneiroid syndromes or hallucinatory states in patients. Drugs that decrease dream activity (such as phenothiazine derivatives or monoamine oxidase inhibitors) may bring about a normalization of or a decrease in the rate of dream activity at the same time as clinical improvement.

Another very active trend of research is the study of the correlation between the subjective content of the dreams and their polygraphic and EEG patterns.

2.4 Psychopharmacology in relation to neurophysiological and behavioural research

Investigations of the action of psychotropic drugs on the CNS are hampered by incomplete knowledge of the function of various brain structures and of the mechanisms of action of the drugs on the function of different brain structures and on the brain as a whole. Knowledge is also incomplete of the influence of dosage, time, and mode of administration, the functional state of the CNS as a whole and the structure on which the drug is acting, the type of the CNS, the variety and species, etc.

Present state of knowledge. There are different levels of analysis of the action of psychotropic drugs: molecular, biochemical, neurophysiological, and behavioural. For the time being, even advanced research at lower levels does not make all the changes in the behaviour of the subject understandable.

Research at the molecular level, carried out on animals, concerns the action of substances on the function of cellular membranes. There is some experimental evidence that potent neuroleptics block the inflow to the cells more effectively than the outflow and diminish cellular permeability.

Research at the biochemical and neurophysiological level helps, to an important degree, to bridge the gap between clinical empirical findings and the knowledge of mechanisms of action of these drugs on the CNS.

All this research provides a tentative explanation of the mechanisms of therapeutic action of some drugs.

In animals neurophysiological studies of psychotropic drugs are based mainly on the technique of implanted electrodes. The same technique has also been used in human beings.

Biochemical and neurophysiological research in man deals with wider aspects such as the level of catecholamines, serotonin, and their metabolites during treatment by MAO inhibitors and its correlation with the clinical picture. Clinical studies also concern correlations between possible EEG changes during psychotropic drug treatment and the clinical course and outcome. This kind of research is of special interest in the study of the structure and especially of the reactivity of the EEG and of vegetative functions during conditioning.

The problem of sensory interaction with the application of the above-mentioned electrophysiological and CNV techniques seems of great interest. However, the range of normal variation should be traced with great care.

Research on the behavioural level is carried out in experiments on animal and man. Classical Pavlovian conditioning, instrumental conditioning, and the study of spontaneous behaviour are the principal methods of research in these studies.

Several main problems have to be dealt with in the analysis of the influence of psychotropic drugs on conditioned responses.

(a) The influence of the drug on the formation of a new conditioned reflex and on the learning process. Conditioning depends on factors such as the level of consciousness, motivation, the interaction of emotional factors, and the functional state of the CNS. In animals with experimental neuroses and in man with psychic disturbances, it has been shown that after the administration of certain psychotropic drugs the conditioned reflexes become weaker, but at the same time more precise. The differential diminution of conditioned reflexes after neuroleptics permits some patients to adapt more successfully to environmental stress.

(b) The influence of the drug on conditioned reflexes elaborated before its administration. Numerous studies indicate that psychotropic drugs do influence the conditioned reflexes elaborated before drug administration, even if the dosage administered has very small influence on spontaneous animal behaviour.

(c) The influence of the drug on the formation of new conditioned reflexes after its withdrawal.

Principal trends in psychopharmacology

1. The analysis of conditioned reflex activity during the medical treatment of mental disorders as an objective method to test clinical im-

provement has two difficulties which seem almost contradictory. On the one hand there is a lack of adequate conditioned reflex methods for experimental detection of some types of mental disorders; on the other, some conditioned reflex methods seem actually too sensitive — that is, the conditioned reflexes change without obvious alterations in the mental state.

2. Simultaneous application of polygraphic techniques in research on conditioned reactivity in relation to drug action permits registration of both peripheral effects and central brain responses. Longitudinal studies with polygraphic registration of the EEG and vegetative functions in selected cases of schizophrenia have yielded very promising results.

3. That the effect of a drug depends on the conditions of its administration has been reported by many authors as occurring analogously in animal and man. A different effect of drug action has been observed in animal behaviour when the drug has been administered in isolation or to a group of animals. This again can in a way be compared with the therapeutic role played by the so-called “non-specific” psychosocial factors in psychopharmacological treatment of psychiatric patients. The influence of these factors on the functional state of the CNS and on the results of psychopharmacological treatment has to be studied by applying behavioural methods of research.

4. Conditioning studies on suprathreshold and subthreshold stimuli after the administration of psychotropic drugs are of great theoretical and practical importance for psychiatry. Research on the influence of psychotropic drugs on the level of sensation and perception in man is at its very beginning. Different conditioning variants have to be analysed in order to clarify the interaction of supraliminal and subliminal stimuli in learning under the influence of psychotropic drugs and in the transformation of inborn or acquired patterns of behaviour.

5. A new trend in neurophysiological research in psychiatry is the polygraphic study of sleep and dreams during treatment with psychotropic drugs.

6. An excellent example of the possibility of “conversion” or “translation” of neurophysiological data into clinical data is the study of evoked potentials under the influence of psychotropic drugs in patients with mental disorders. This applies also to studies on CNV.

7. The influence of drugs on behaviour may also be analysed by the observation of spontaneous behaviour in different situations, for example in situations provoking anxiety, in isolation, and in sensory deprivation. This could be done in animals using the technique of implanted electrodes, chemitrodes, electrical telestimulation, radio-controlled injectors, and telemetric recording. This kind of research is very stimulating for neuro-

physiological and psychopharmacological studies in psychiatry, but needs elaborate equipment and specially trained personnel.

2.5 Behaviour therapy

The most obvious psychiatric development in which neurophysiological procedures are implicit is the so-called behaviour therapy, which incorporates many of the traditional features of Pavlovian conditioning with adaptations to the specific difficulties of human interaction.

Although it is sometimes supposed that the basic concepts underlying these procedures are incompatible with those widely accepted in some psychiatric practice, it seems likely that all — while employing different methods for approaching the faults and anomalies underlying the development of pathological mental states — are based on the same fundamental assumption that the human brain is the organ of adaptation and learning.

Methodology. The techniques of operant conditioning have shown a very close relationship between the results of laboratory experiments in man and animals and the modification of deviant behaviour. The results achieved in autistic children, the mentally retarded, and chronic schizophrenic patients clearly demonstrate the value of these techniques. Thus, symptoms like hoarding, violence, refusal to eat, or psychotic verbalizations have been substantially modified or eliminated in schizophrenics. Great ingenuity has been developed in the use of reinforcers, which range from goods and money to attention, approval, and complex social rewards. Here the laboratory has provided more precise instruments for achieving educational and habit-training goals.

Strengthening or shaping constructive, socially adaptive responses is also possible with operant techniques. Such techniques have been tried out on psychopaths and criminals, but they have not yet been generally used in the treatment of neuroses. From a clinical point of view the operant techniques aim more at changing items of behaviour than at obtaining complete cures. This limited therapeutic goal may at the present time be realistic in chronic mental disorders and in personality deviations.

Clinical indications. Electrical and chemical aversive conditioning has found its main applications in the treatment of alcoholism and sexual aberrations. Where the patients have been followed up, the incidence of relapses has been found to be appreciable. Conditioning in enuretics has yielded good immediate results, but here too follow-up studies have shown a high incidence of relapses. The techniques of aversive and positive conditioning have the advantage of being simple to carry out. An important question is whether improvement of the techniques and follow-up conditioning sessions could stabilize the results. Electrical aversive therapy

is preferable to chemical, as being easier to administer precisely and less distressing to the patient. Anticipatory avoidance learning has been recommended as a treatment of choice, because it produces reasonably good acquisition and very high resistance to extinction. Another problem is that aversive treatment may bring about aggressiveness and hostility on the part of the patient. Good relations between patient and therapist as well as arousal of motivation for treatment are crucial factors.

A series of procedures is built upon the principle of negative practice. It has turned out that in practising previously learned "wrong" responses the "wrong" responses, instead of recurring, drop out. Negative practice has been reported as especially effective for stuttering and tics. The logotherapeutic technique of paradoxical intention is analogous to negative practice, and has been found effective in phobic and obsessive-compulsive patients. There is as yet no agreement as to which laboratory experiments can explain the mechanisms of negative practice. One factor might be overstimulation, leading to protective inhibition. But there may also be psychological factors, such as relief of tension when the patient is encouraged to do what he usually tries to stop without success.

A leading hypothesis is that anxiety plays a fundamental role in the neuroses. If a response antagonistic to anxiety can be made to occur in the presence of anxiety-evoking stimuli, so that it is accompanied by a complete or partial suppression of the anxiety responses, then the bond between those stimuli and the anxiety responses will be weakened. The coherent theoretical framework and detailed description of reciprocal inhibition methods have led to a wide use of, in particular, desensitization procedures. There are, however, many alternative ways of explaining the therapeutic mechanisms. From a Pavlovian point of view the effect can be interpreted as due to the suppression of pathological dominants or morbid foci through therapeutically induced dominants. The effect may also, to a great extent, represent extinction of maladaptive conditional reflexes.

Principal trends of research. Close correlation of research in the laboratory and clinical observations is likely to yield improved methods over the coming years. The most important trend of research is still the development of new procedures and the better understanding of neurophysiological therapeutic mechanisms. Integration of the approaches of experimenters and clinicians is also required. Experimentally trained therapists tend to be concerned with refinements of technique, but may not sufficiently appreciate the social and interpersonal skills needed in clinical work. On the other hand, clinicians need more knowledge of the behavioural, theoretical, and technological issues involved.

According to psychoanalytic theory, symptoms result from conflicts between impulses and the controlling defensive forces. Treating the

symptoms and leaving the unconscious conflicts unresolved may therefore result in symptom substitution. Behaviour therapists maintain that the risk of symptom substitution is small, although cases with the emergence of new symptoms have been described. Here it should be kept in mind that the occurrence of new symptoms may also be due to underlying neurophysiological mechanisms and are found even in animal neuroses, apparently developing spontaneously. On the other hand, behaviour therapists have noted that the removal of one symptom tends also to facilitate the removal of others and to improve feelings of well-being and interpersonal adjustment. It seems justified to conclude that the beneficial effects of symptom removal predominate, while complications are rare and not proven to result from treatment.

The evaluation of results in the treatment of neuroses poses great problems. Knowledge about the natural course of illness in neuroses is limited, and it is even questioned whether any psychotherapy adds much to the spontaneous tendencies to improvement over a prolonged time. Investigations which have included rigorous control groups have in general been confined to the treatment of specific symptoms such as isolated phobias in otherwise normal people. On the other hand, most studies of true neurotic conditions have failed to include adequate control groups and it is therefore difficult to ascertain whether behaviour therapy is more effective than other forms of treatment.

2.6 Etiology and the high-risk sample method

Problems in research on etiology. The goal of much basic research in the area of mental health is to produce information concerning the etiology of mental disease. Much of this research is on individuals who have already lived through the process of becoming and being mentally ill. It is difficult to isolate etiological factors from the results of such studies. The behaviour, biochemistry, and physiology of mentally ill individuals may be markedly altered in response to the *consequences* of the mental illness, such as educational, economic, and social failure, drug regimens, long-term institutionalization, chronic illness, and sheer misery. These factors have been shown to affect results in studies of normal subjects. If researchers used control groups equated with their mentally ill groups for *all* of these correlates, any observed differences could be ascribed to the mental illness rather than to one or more of the consequences. But such control groups are apparently not readily available. In comparisons of normal and mentally ill individuals it is often difficult to judge what portion of the reported differences is due solely to mental illness. For example, a comparison of non-psychiatric prisoners with normal individuals has produced results almost identical with a compa-

ri-son of mentally ill with normal individuals, probably because of the effects of institutionalization.

A suggested solution. A solution to this dilemma is suggested by a recent methodological innovation, the high-risk sample method. This method examines the mentally ill in their premorbid state. Young high-risk populations are studied, such as children with schizophrenic mothers (mothers since the paternity is not always indisputable). In an investigation of the relatives of over 1 000 schizophrenic patients, 16.4% of their children were found to be schizophrenic. A careful follow-up of 47 children with schizophrenic mothers showed that 55% suffered from serious psychiatric illness.

There are certain advantages in examining these high-risk individuals in early childhood.

(a) They have not yet experienced many vicissitudes of the life of the mentally ill, such as hospitalization and drugs.

(b) The researchers, relatives, teachers, and the subjects themselves do not know that they will become mentally ill. This to a certain extent obviates bias.

(c) Information on the familial, social, and developmental experiences of the subject need not be retrospective, but can be based on actual observation.

(d) Data can be uniformly and systematically obtained.

(e) One advantage of the high-risk method that may not be immediately apparent is the fact that the ideal controls for the high-risk subjects who become mentally ill are the high-risk subjects who do not. The ideal controls for the high-risk subjects who become schizophrenic are the high-risk subjects who develop other mental illnesses.

The choice of children with schizophrenic mothers as high-risk subjects may suggest an underlying genetic assumption. This is not the case; the choice is made on the basis of the consistent results of empirical research. (Recent research has, in fact, indicated that genetics does play a role in the etiology of schizophrenia. The biological relatives of adopted children who became schizophrenic showed considerably more psychiatric abnormality than did relatives by adoption.)

A high-risk sample has been studied at the Psychological Institute in Copenhagen. Special Danish facilities such as a national population register and the national register of psychiatric hospitalizations were of great assistance in this work, which has gone on for five years, during which some members of the high-risk group have suffered a psychotic breakdown. The subjects who succumbed to mental illness are chiefly distinguished from other high-risk subjects by the fact that they were

early separated from their mothers and by a specific pattern of autonomic and conditioning abnormality. The autonomic abnormality as measured by the galvanic skin response (GSR) consisted of relatively rapid attainment and excessive stimulus generalization of the conditioned GSR, extremely rapid and brisk autonomic response to mild stress, poor autonomic habituation to mild stress, and extremely rapid recovery from autonomic responses to stress.

The next wave of 20 mental breakdowns will serve as a cross-validation of these early findings.

3. PROSPECTS FOR FUTURE RESEARCH

The value to clinical psychiatry of the recent developments outlined above has been limited by the following factors.

(1) The experimental techniques are complex and expensive, particularly when a laboratory set-up must be converted into a trustworthy clinical test. Few centres where the resources are available have access to suitable clinical material and normal subjects; conversely, hospitals and clinics with rich sources of human material usually lack technical equipment and personnel.

(2) The rapid evolution of neurophysiological methods as applied to human problems has outstripped the capacity of the scientists to establish agreed standards of procedure and criteria of interpretation. The situation is comparable with that of the conventional EEG in 1946, when the few practitioners first met to discuss criteria of abnormality in relation to organic brain disease.

(3) Research and clinical application have proceeded in laboratories and clinics with little or no intercommunication. Occasional visits, crowded congresses, and private correspondence are inadequate for the combined operations on a wide front that are essential.

The most useful advances could be made by bringing together the techniques and the human material either directly or by the devices now available for data exchange and transmission, and by providing full opportunities for active workers to meet and exchange views.

Research on animals has made a major contribution to modern knowledge and techniques in neurophysiology and may be expected to continue to make basic contributions to mental health. In most cases, however, such research can be carried out in the laboratories of individual countries, and does not need special attention as urgently as research directly concerned with human mental illness. Furthermore, the scope of such research is too broad to be dealt with adequately in this report.

3.1 Critical periods of development

Following the original discoveries of Freud, clinical studies of persons with neurotic and other mental disturbances have indicated that there are critical periods in infancy during which certain experiences may have an especially profound effect on later development. These observations, which suffered from the various weaknesses of retrospective reconstruction, have since been confirmed by data from experiments summarized in previous WHO reports¹ as well as by carefully controlled experiments on animals. The experimental work has also demonstrated critical periods during which stress is particularly likely to produce significant and persistent physiological effects, for example on the pituitary-adrenal axis and on growth. It is highly desirable to identify and analyse these critical periods and to relate them to physiological stages of development. This analysis should be both in terms of the types of learning occurring during the action of the environmental event during the critical period and in terms of its physiological and biochemical consequences. The possibility that the present studies supported by WHO and new ones being planned can be made to yield data on critical periods should be considered. Studies in point are those on malnutrition and on the effects of twins reared in different environments. Other research aimed specifically at the problem should be encouraged, as studies on the effect of hospitalization for severe burns on children of different ages. The research programme on high-risk children contained in the annex is an example of how an investigation of critical periods can profitably be incorporated into a study with another primary aim.

3.2 High-risk samples

Longitudinal studies of high-risk samples are in their infancy. Nevertheless, early results have found psychiatric breakdowns to be correlated with disturbed early experience and specific deviations of autonomic nervous system function. The findings on early experience may be related to the extensive research showing the relative frequency of maternal and paternal loss in the early life of the mentally ill, particularly schizophrenics. The findings on autonomic nervous system deviation are corroborated by psychophysiological research on the acutely and chronically mentally ill. If these results were to be applied to the problem of mental illness, they would be best utilized for primary prevention. Three-year-old high-risk subjects and controls could be brought together in nursery schools, drugs could be used to bring their autonomic functions within the normal range and learning techniques to help them in their social

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1958, 152; 1967, 371.

interactions. The efficacy of these measures could be evaluated in the nursery schools and by future performance at school. While these prophylactic measures were being applied and evaluated, further research could be conducted on the predisposing characteristics of the high-risk group. The results of this work might direct attention to other prophylactic measures.

The annex contains an example of a research project using the high-risk sample method.

3.3 Learning techniques and primary prevention

The solution of problems in the physical environment has been enormously facilitated by the formulation of general principles, such as those of mathematics and physical science; the average pupil in a good school can learn to solve problems of the physical environment that baffled the most brilliant minds of ancient times. But we have lagged far behind in the discovery of comparable principles for the solution of social and emotional problems, including the new ones produced by rapid technological and social changes. One of the tasks of preventive medicine in the field of mental health is to discover and impart better ways of learning to solve social and emotional problems.

Recent research on animals has shown that certain types of learning situations produce excessive emotional stress, even leading to physiological symptoms such as loss of weight, the secretion of excess acid in the stomach, or the production of gastric lesions; other types of learning situations are much less stressful. Experiments on teaching animals to persist in the face of difficulties or to give up and be apathetic have already been mentioned (page 7).

Teaching beginning with an easy discrimination and then gradually working up to a more difficult one has been demonstrated to produce fewer symptoms of frustration than that beginning with a difficult discrimination in which many errors are made. Too difficult a discrimination can produce an experimental neurosis. Such experiments indicate that variables relevant to emotional adjustment can be investigated by rigorous experimental techniques. Work of this kind, however, is in its infancy with respect to its applicability to human predicaments.

One of the ways of testing means of teaching emotional adjustment at the human level might be to use a sample of high-risk individuals, such as children of schizophrenic mothers. Half of the children in such a sample could be subjected to a variety of intensive types of training believed likely to benefit their emotional adjustment. If an appreciable gain was achieved in a pilot study of this kind, the efficiency of a variety of types of training might be evaluated in a larger study with a factorial design. Even a slight reduction in the percentage of serious breakdowns would, over

the lifetimes of the individuals concerned, repay the cost of an intensive programme.

As a step towards discovering principles for teaching better social and emotional adjustment, continued research is needed on the basic principles of learning and problem solving, especially in relation to social and emotional problems. Clinical research is also needed on the application to the solution of social and emotional problems of what has already been learnt in the laboratory.

3.4 Sleep

Specific sleep disturbances that coincide with the onset of some psychosis or neurosis are often also observed in the course of the diseases; there are perhaps some mechanisms in common. These observations have opened up a new and promising field of neurophysiological investigation which may have diagnostic and prognostic value. Sleep studies may also be of value in, for instance, the understanding of the mechanism and in the control of the effect of drugs used in the treatment of psychotic disorders.

It would be of considerable value if multiple polygraphic sleep recordings could be undertaken on a well-selected group of individuals — high-risk as opposed to low-risk patients, for example, or subjects who have escaped medication and in whom a psychosis is beginning, with a weekly follow-up while they are under treatment. Information of the greatest neurophysiological value may also be obtained by recordings from subjects with implanted electrodes.

Because of methodological difficulties, and since the classification of sleep states is still in its primary stage, international collaboration is needed for the following purposes :

(a) To develop polygraphic classifications of sleep states in normal human beings (vegetative evoked responses, scalp EEG, electromyography, subcortical recordings, etc.). This could be achieved by small seminars, the use of computers, and a manual on EEG recordings and sleep. Such classifications would serve as a basis for an objective description of specific sleep disturbances occurring spontaneously in psychiatric patients or induced by drugs;

(b) To compare the neurophysiological, neuropharmacological, biochemical, histochemical, and neurochemical data obtained in studying the mechanism of sleep in animals with specific sleep disturbances observed in psychiatric patients specially studied with regard to biochemical and neuropharmacological aspects. This may shed some light upon the specific biochemical mechanisms underlying their disorders. It could

be achieved by the development of a standardized method of telemetric recording. The use of computers in psychiatric hospitals that are also well equipped for biochemical studies and the sponsoring of meetings relating to animal and human studies might also help.

3.5 Diagnosis and prognosis

Because of uncertainty about the etiology of mental disorders, psychiatric diagnoses are mainly descriptive and empirical. Research projects should attempt to contribute to the definition of problems of classification by studying the neurophysiological basis of the various types of mental disorders. In particular, the pathophysiology of schizophrenia is of central importance. Centres engaged in the study of schizophrenia should include neurophysiological measures in their surveys as far as their resources permit.

Psychiatric diagnoses contain elements of prediction of the long-term course of illness. Clinical follow-up is, therefore, essential for the evaluation of diagnoses.

In a few centres, clinical follow-up has been combined with the recording of psychophysiological measures. It has been shown that some of these measures correlate with the prognosis; with the use of computers, prognostic formulae based on constellations of psychophysiological measures have been constructed. The tentative findings suggest that such formulae can indicate the risk of chronic schizophrenia developing in the long run as reliably as those derived from combinations of clinical symptoms. There is also evidence that measurements of brain responses in conditioning can provide an indication of liability to neurotic breakdown and recovery, both spontaneous and during treatment. The combination of clinical and experimental data may thus improve upon present-day prognostic criteria and is worthy of recommendation.

Neuropsychophysiological studies intended to help in diagnosis and prognosis are highly complex and rather variable in their results. Centres already engaged in such work should, as a first step, co-ordinate their efforts. The system now being used in the WHO International Pilot Study of Schizophrenia, using symptom evaluation, is recommended as a basis for combined research. It is also important to select appropriate experimental methods. Centres engaged in neuropsychophysiological research on psychiatric patients need assistance from a central clearing house for information on neurophysiological research related to psychiatry.

The following recommendations on further research are made:

- (1) Co-ordinated studies should be carried out in different countries on higher nervous activity in schizophrenia, various depressive states,

and other functional psychoses, from as early a stage of the disease as possible and throughout its whole course.

(2) In such studies methods should be employed to ascertain the correlation between central nervous activity and the results of a wide range of stimuli, including verbal and physiological stimuli and motor and autonomic responses.

(3) Recently developed methods for investigating special features of brain activity should be included, e.g., spatial synchronization, evoked potentials, slow potential changes, and sleep.

(4) Systematic studies should be carried out on different mental disorders by means of the above-mentioned methods in connexion with various contemporary forms of treatment.

All these neurophysiological investigations must be closely correlated with adequate clinical characterization of the patients.

Since the predictive value of a measure varies with the case to which it is applied, each study should include some standard prognostic item with which the effectiveness of the physiological method may be compared.

Data collected by different investigators and on various mental disorders must then undergo a unified complex statistical processing to explore the most valuable neurophysiological and clinical parameters and their mutual correlations, from the prognostic point of view as well as to establish specific indications for various methods of therapy.

Reliable prognostic criteria and objective differentiated indicators for treatment are to be regarded as most valuable tools for the improvement of the efficacy of treatment. It is therefore highly desirable to stimulate international studies such as those outlined.

3.6 Transcultural collaboration

Schizophrenia is a condition that seems to appear in all cultures. The assessment of the relative importance in it of biological and cultural factors requires continued effort in many centres. Its early detection and the taking of steps for its prevention are as important in developing countries as in those with highly organized social systems.

The standardization of techniques and of the interpretation of data in psychophysiological procedures in a transcultural setting is a necessary first step to the application of such procedures. The scope of such work should be extended from the clinic to the high-risk groups referred to on page 21.

The study of critical periods of development has been emphasized above (page 23). Such a study would benefit particularly from close transcultural collaboration. Patterns of social and visceral learning

developed in the early phases of life have great significance in the maturation of personality and the etiology of mental illness. They vary widely in different cultures and should be studied in the developing countries in order to establish norms and deviations in relation to social factors. The stresses imposed on the organism at these critical periods, for example by rapid socio-economic changes as well as by poverty and malnutrition, can be studied best in the developing countries.

The phenomena of sleep, altered states of consciousness, and dreaming are of great interest, from both the psychobiological and the psychopathological aspect. For an understanding of them physiologically as well as phenomenologically in conditions resembling schizophrenia, trance states, and normality, attempts should be made to study them in some of the developing countries, such as India, where alterations of consciousness are deliberately cultivated.

4. SUMMARY AND RECOMMENDATIONS

4.1 Facilitation of communication

There is a serious failure of communication between individual workers and research centres engaged in neurophysiological research related to problems of mental health. Publication delays are so long that valuable information often arrives too late to help those starting research or evaluating their results. Furthermore, in what is essentially a multidisciplinary activity, data collected in one field may be almost inaccessible to workers in another because of the extreme and increasing specialization of journals.

There is therefore an urgent need for a central agency to provide a variety of communication facilities. These should include: the distribution of a half-yearly news-sheet or bulletin containing summaries of current neurophysiological research directly related to psychiatry (both in progress and "in press"); correspondence on early results, rare cases, and special problems; new methods (e.g., computer programmes); speculation; up-to-date recommendations; select bibliographies and glossaries; and a cumulative gazetteer of centres engaged in neurophysiological research in mental health (model: IBRO Bulletin), cross-indexed for workers, topics, and places.

4.2 Suggested collaborative research

4.2.1 *Diagnosis and prognosis*

The value of neurophysiological research in psychiatry at the present time is mainly in the provision of objective measures related to diagnosis,

often in a statistical rather than in an individual context. Current developments suggest the prospect of using neurophysiological methods in the prognosis of mental disorder, for planning specific treatment, and even for instituting prophylactic measures.

This, however, will depend on the extent to which research workers can collaborate on an international basis in order to validate their methods, compare their predictive power with conventional procedures, and estimate the value of combining their methods with conventional methods.

The diversity of techniques and differences in terminology have made direct collaboration very difficult. Rapid advances in knowledge and practice would result from collaborative group studies and interchange of personnel between centres in all countries.

4.2.2 *Etiology and high-risk samples*

The psychiatric patient is markedly affected by many consequences of his illness such as a sense of failure, the drug regimens he must undergo, institutionalization, and the misery he feels, which all significantly influence his response to experimental tasks. Groups to serve as controls for all of these variables are not readily available. For this reason caution is imperative in interpreting the results of research on such patients in terms of etiology. Inferences about the etiology would be on firmer ground if objective, non-retrospective studies were conducted well before the onset of illness.

Such research is made feasible by the existence of high-risk groups as, for example, children of schizophrenic mothers. Careful early examination of such children using selected neurophysiological and behavioural research techniques may disclose the personal characteristics that predispose individuals to mental illness, and a close follow-up may disclose the background and the precipitating environmental conditions that, in interaction with predisposition, produce mental illness.

A collaborative, longitudinal interdisciplinary research programme should be initiated in several contrasting cultural settings. It should examine in each setting and follow up comparable high-risk and control samples.

4.2.3 *Critical periods in development*

Evidence from the clinic, from studies of children removed from their mothers, from cross-cultural and sociological investigations, and from animal experiments indicates that there are certain critical periods of life during which environmental factors may have a particularly great and long-lasting effect on emotion, personality, and intellect. Much more information is needed about the learning process, neurophysiology, and biochemistry involved in these critical periods. Special atten-

tion should be directed to the possibility of obtaining information on critical periods of development from studies designed for other purposes, for example of malnutrition, of twins or other genetically homogeneous groups subjected to different experiences, and of groups with a high risk of developing mental disturbances.

4.2.4 *Transcultural studies*

In some developing countries neurophysiological research is already in progress; this provides a unique opportunity for transcultural studies. Comparison of the neurophysiological features of schizophrenia, the learning process at critical periods, the physiology of sleep, and alterations in consciousness may provide transcultural information of crucial value.

The inclusion of suitable centres in the developing countries in collaborative research programmes would provide an important contribution to general knowledge as well as to local facilities.

4.3 **International standardization**

4.3.1 *Neurophysiological research techniques*

There are many discrepancies in the results reported from studies on neurophysiological problems in mental health. Some are due to variations or inadequacies in technique, some to differences in nomenclature, some perhaps to misunderstanding or ignorance of basic problems. Many could be removed by the pooling of methods and ventilation of problems and ideas in frequent meetings of investigators. The outcome of their discussions could be embodied in manuals or newsletters containing descriptions of techniques of special value in neurophysiological research on mental illness, for example experimental design, recording equipment, statistical methods, and computer applications.

4.3.2 *Sleep*

Basic research on sleep mechanisms and sleep studies in psychiatric patients should be encouraged by the development of an international classification of EEG and polygraphic patterns during sleep, and by the organization of joint meetings of neurophysiologists and psychiatrists.

4.3.3 *Therapy with implanted electrodes*

The development of techniques for using minute electrodes implanted for long periods in the brains of unanaesthetized animals is producing a rapid increase in our knowledge of brain function. In selected human patients completely incapacitated by chronic disorders resistant to all

other means of treatment, physicians are making successful use of such electrodes in diagnosis and treatment. The therapeutic use of such electrodes is yielding as a by-product highly significant information about the human brain that could be secured in no other way. Here, as in other areas of medicine, it is essential to maintain the highest ethical standards to ensure that the well-being of the patient is in no way jeopardized. As knowledge in this new field advances and electrodes can be implanted more precisely for a given purpose, the therapeutic need for initial exploration and so the legitimate opportunities for gaining new knowledge will be reduced.

Because of the unique features involved in the therapeutic use of implanted electrodes and other related techniques, the most efficient ethical use of such methods should be the goal pursued. One way of achieving it might be to assemble a small group that would include leading investigators in this field, clinicians with a critical outlook, and research experts on brain function and behaviour. Such a group could meet once or more to consider the problems of maintaining the highest ethical standards and the most urgent research problems to be investigated and the most effective ways of investigating them, and to exchange information (especially in those rare cases where a definitive histological localization has been obtained).

4.4 Collaboration with international organizations

The inclusion of neurophysiological studies in mental health projects sponsored by international organizations would add considerably to their scientific interest and practical value. In this connexion, schizophrenia, twin studies, and studies of genetically isolated or recently mixed populations deserve particular attention.

The elaborate equipment and special training needed would involve considerable expansion of the theoretical interests and of the technical resources of the centres engaged in the projects, which would therefore need special administrative and financial assistance.

In all such studies collaboration with the International Brain Research Organization, the World Psychiatric Association, the World Federation for Mental Health, The World Federation of Neurology, and the International Federation of Societies for Electroencephalography and Clinical Neurophysiology should be sought in the planning and execution of projects.

Annex

EXAMPLE OF A COMBINED RESEARCH PROJECT

The Group assigned very high priority to the encouragement or initiation of two international collaborative research projects :

- (a) the study of critical periods of development, to examine the effects of environmental factors on subsequent mental health; and
- (b) longitudinal neurophysiological studies of high-risk subjects.

The significance of both these topics is discussed on pages 21 and 23.

The numbers and variables given in the example are for illustrative purposes only.

The basic method of the proposed project involves the intensive examination and follow-up of a group of "normally functioning" children with schizophrenic mothers and a matched control group. The samples should be of children who have spent some portion of their early life in institutions. The study should observe the effects and interaction of neurophysiological characteristics, of the deprivation of "mothering" during critical childhood periods, and of environmental factors involved in the development of mental illness.

An example of a research design combining these two studies is described below.

Selection of sample

In each cultural setting 200 (high-risk) children with schizophrenic mothers and 200 (low-risk) children with "normal" parents and grandparents are examined and followed up. The two groups are matched for age, sex, rural/urban home, social class, years of education, and institutional or family rearing. The children are drawn from two age levels, early childhood and pre-adolescence. Equal proportions are chosen of high-risk and low-risk children who have been separated from their parents during selected critical periods of development (e.g., the first, second, or third year of life). Either intra-nationally or cross-nationally (or both), the quality of institutional placement is controlled so that both "good" and "bad" placements are proportionately represented in all the sub-groups.

Measures

A broad range of measures is utilized, chosen from among those that research has shown to record sensitively the effects of mental illness. As

full an account as possible of the birth and early health record of the sample is obtained. Observations should include reports from teachers, interviewing psychiatrists, and individuals responsible for the children.

The children are examined for generalization of perceptual and psychophysiological responses to conditioning and a cognitive, intellectual, and personality assessment is carried out. The psychiatric interview developed in the WHO schizophrenia project is useful in assessing the status of the schizophrenic mothers, as well as (after modification) of the high-risk and low-risk children. Some of the measures used should be selected with special reference to their culture-free or culture-bound characteristics.

It seems clear that measures thoroughly assessing autonomic function both at rest and in mild stress states are important. Autonomic characteristics such as latency, habituation, and recovery from imbalance, as well as conditioning and generalization (with a noxious unconditioned stimulus), should be carefully assessed, using as wide a range as possible of psychophysiological measures, including galvanic skin responses, electromyography, electroencephalography, and other neurophysiological measures investigators have shown to be of value. It may be of interest to record sleep patterns in some subgroups of the subjects.

Possible locations for investigations

Other than a psychiatric research centre with specialists from a variety of subdisciplines, the project does not have many essential requirements. Among the developed nations, those with national records of psychiatric hospitalizations and facilities for tracing citizens (such as Denmark) are suitable. Developing nations with psychiatric research and teaching facilities, research staff, some physiological recording apparatus, and populations of mentally ill may be considered as locations. A good example of such a facility is the All-India Institute of Mental Health, Bangalore, India.

**WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES**

<i>Recent reports:</i>		Price		
No.		s.d.	\$	Sw. fr.
341	(1966) Principles for Pre-Clinical Testing of Drug Safety Report of a WHO Scientific Group (22 pages)	3/6	0.60	2.—
342	(1966) Prevention of Rheumatic Fever Report of a WHO Expert Committee (27 pages)	3/6	0.60	2.—
343	(1966) WHO Expert Committee on Dependence-Producing Drugs Fifteenth report (18 pages)	3/6	0.60	2.—
344	(1966) Immunotherapy of Cancer Report of a WHO Scientific Group (38 pages)	5/-	1.00	3.—
345	(1966) The Training of Health Laboratory Personnel (Technical Staff) Fourth report of the WHO Expert Committee on Health Laboratory Services (31 pages)	3/6	0.60	2.—
346	(1966) Research on Genetics in Psychiatry Report of a WHO Scientific Group (20 pages)	3/6	0.60	2.—
347	(1966) WHO Expert Committee on Nursing Fifth report (32 pages)	3/6	0.60	2.—
348	(1967) Procedures for Investigating Intentional and Unintentional Food Additives Report of a WHO Scientific Group (25 pages)	3/6	0.60	2.—
349	(1967) Measurement of the Public Health Importance of Bilharziasis Report of a WHO Scientific Group (93 pages)	6/8	1.25	4.—
350	(1967) National Health Planning in Developing Countries Report of a WHO Expert Committee (40 pages)	5/-	1.00	3.—
351	(1967) Conference of Directors of Schools of Public Health Report of a WHO Inter-Regional Conference (24 pages)	3/6	0.60	2.—
352	(1967) WHO Expert Committee on Cholera Second report (28 pages)	3/6	0.60	2.—
353	(1967) Appraisal of the Hygienic Quality of Housing and its Environment Report of a WHO Expert Committee (54 pages)	5/-	1.00	3.—
354	(1967) Joint ILO/WHO Committee on Occupational Health Fifth report (19 pages)	3/6	0.60	2.—
355	(1967) The Use of Health Service Facilities in Medical Education Sixteenth report of the WHO Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel (36 pages)	5/-	1.00	3.—
356	(1967) Safe Use of Pesticides in Public Health Sixteenth report of the WHO Expert Committee on Insecticides (65 pages)	6/8	1.25	4.—
357	(1967) WHO Expert Committee on Malaria Thirteenth report (59 pages)	5/-	1.00	3.—
358	(1967) Teaching of Immunology in the Medical Curriculum Report of a WHO Expert Committee (46 pages)	5/-	1.00	3.—
359	(1967) WHO Expert Committee on Filariasis (<i>Wuchereria</i> and <i>Brugia</i> infections) Second report (47 pages)	5/-	1.00	3.—

No.		Price		
		s.d.	\$	Sw. fr.
360	(1967) Biology of Fertility Control by Periodic Abstinence Report of a WHO Scientific Group (20 pages)	3/6	0.60	2.—
361	(1967) WHO Expert Committee on Biological Standardization Nineteenth report (120 pages)	8/6	1.75	5.—
362	(1967) Requirements of Vitamin A, Thiamine, Riboflavine and Niacin Report of a Joint FAO/WHO Expert Group (94 pages)	5/-	1.00	3.—
363	(1967) Services for the Prevention and Treatment of Dependence on Alcohol and Other Drugs Fourteenth report of the WHO Expert Committee on Mental Health (45 pages)	5/-	1.00	3.—
364	(1967) Principles for the Testing of Drugs for Teratogenicity Report of a WHO Scientific Group (18 pages)	3/6	0.60	2.—
365	(1967) Epidemiological Methods in the Study of Chronic Diseases Eleventh report of the WHO Expert Committee on Health Statistics (31 pages)	3/6	0.60	2.—
366	(1967) Standardization of Procedures for the Study of Glucose-6-Phosphate Dehydrogenase Report of a WHO Scientific Group (53 pages)	5/-	1.00	3.—
367	(1967) Treatment and Disposal of Wastes Report of a WHO Scientific Group (30 pages)	3/6	0.60	2.—
368	(1967) Mosquito Ecology Report of a WHO Scientific Group (22 pages)	3/6	0.60	2.—
369	(1967) Arboviruses and Human Disease Report of a WHO Scientific Group (83 pages)	6/8	1.25	4.—
370	(1967) Pesticide Residues in Food Joint report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues (19 pages)	3/6	0.60	2.—
371	(1967) Research in Psychopharmacology Report of a WHO Scientific Group (39 pages)	5/-	1.00	3.—
372	(1967) Epidemiology and Control of Schistosomiasis Report of a WHO Expert Committee (35 pages)	5/-	1.00	3.—
373	(1967) Specifications for the Identity and Purity of Food Additives and their Toxicological Evaluation : Some Emulsifiers and Stabilizers and Certain Other Substances Tenth report of the Joint FAO/WHO Expert Committee on Food Additives (47 pages)	5/-	1.00	3.—
374	(1967) Prevention of the Re-Introduction of Malaria Report of a WHO Meeting (32 pages)	3/6	0.60	2.—
375	(1967) Chemotherapy of Malaria Report of a WHO Scientific Group (91 pages)	8/-	1.25	4.—
376	(1967) The Education of Engineers in Environmental Health Report of a WHO Expert Committee (26 pages)	4/-	0.60	2.—
377	(1967) Joint FAO/WHO Expert Committee on Nutrition Seventh Report (84 pages)	8/-	1.25	4.—
378	(1967) Joint FAO/WHO Expert Committee on Zoonoses Third Report (127 pages)	10/-	1.75	5.—
379	(1967) Control of Ascariasis Report of a WHO Expert Committee (47 pages)	6/-	1.00	3.—
380	(1967) Current Problems in Leptospirosis Research Report of a WHO Expert Group (32 pages)	4/-	0.60	2.—

WHO PUBLICATIONS

SUBSCRIPTIONS AND PRICES 1968

Global Subscription

The global subscription covers all WHO publications, i.e., the combined subscription "C" and, in addition, the *Weekly Epidemiological Record*, *Monograph Series* and any other occasional publications.

£38 \$125.00 Sw. fr. 385.—

Combined Subscriptions

Special prices are offered for combined subscriptions to certain publications, as follows:

Subscription

A <i>Bulletin, Chronicle, Technical Report Series, and Public Health Papers</i>	}	£13	\$42.00	Sw. fr. 130.—
B <i>World Health Statistics Report and World Health Statistics Annual</i>				
C <i>Bulletin, Chronicle, Technical Report Series, Public Health Papers, Official Records, International Digest of Health Legislation, World Health Statistics Report, World Health Statistics Annual, and World Health</i>	}	£28	\$90.00	Sw. fr. 280.—

WHO Distribution and Sales Unit will be pleased to submit a quotation for any other type of combined subscription desired.

Individual Subscriptions

<i>Bulletin</i> , vol. 38 and 39 (12 numbers)	£7 10s.	\$25.00	Sw. fr. 75.—
<i>Chronicle</i> , vol. 22 (12 numbers)	£1	\$ 3.00	Sw. fr. 10.—
<i>International Digest of Health Legislation</i> , vol. 19 (4 numbers)	£3	\$10.00	Sw. fr. 30.—
<i>Technical Report Series</i>	£4 10s.	\$15.00	Sw. fr. 45.—
<i>Official Records</i>	£4 10s.	\$15.00	Sw. fr. 45.—
<i>World Health Statistics Report</i> , vol. 21 (12 numbers)	£4 16s.	\$16.00	Sw. fr. 48.—
<i>Weekly Epidemiological Record</i> , 43rd year (52 numbers)	£4 10s.	\$15.00	Sw. fr. 45.—
<i>Vaccination Certificate Requirements for International Travel</i>	16/-	\$ 2.75	Sw. fr. 8.—
<i>World Health</i> , vol. 21	£1 4s.	\$ 5.00	Sw. fr. 12.—

Subscriptions can be obtained from WHO sales agents for the calendar year only (*January to December*).

* * *

Specimen numbers of periodicals and a catalogue will be sent free of charge on request.