PROCEEDINGS

of the

SECOND REGIONAL SEMINAR ON PSYCHOTROPIC MEDICATION 23—28 April 1973

Kuala Lumpur
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NEURO PSYCHIATRIC SOCIETY OF THE MALAYSIAN MEDICAL ASSOCIATION (1972/73)

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PREFACE

The Proceedings of the Second Regional Seminar on Psychotropic Medication, Kuala Lumpur, Malaysia, 23–28 April 1973.

As indicated by the name, this is the second of a series of seminars held in the South-East Asian region which have for their main theme the progress made in the field of drug treatment of psychiatric disorders. These series of seminars have been made possible by the generous sponsorship of Roche Far East Researhc Foundation, 1108, Princess Building, Hong Kong. The initiation of these series of meetings was to a large extent the brain child of Professor R. Kusumanto Setyonegoro, Chairman, Department of Psychiatry, University of Indonesia, Djakarta, Indonesia, under whose very able leadership the first and very successful meeting was held from 23-28 March, 1970. The proceedings of that meeting were published as a supplementary issue of Majallah Djiwa, the Indonesian Psychiatric Quarterly.

Although the main emphasis of most of the papers is psychiatric, especially related to the field of Psychotropic Medication, papers on other aspects of Psychiatry were also presented at this conference and there was a significant number of papers presented in Neurology and Neurosurgery. One of the four panel discussions was on "The Modern Treatment of Parkinson's Disease."

There are many reasons for this inclusion of the neurological sciences in this Seminar. The participating professional organization in the South-East Asian regions are mostly "neurospychiatric" societies rather than separate neurological and psychiatric organizations as such. While this arrangement may be due to deliberate choice in some situations, in other countries this is a very pragmatic expediency because of the relatively small number of professionals in the field of psychiatry and the neurological sciences. This arrangement is of course neither permanent nor is it going to be a continuing trend in the future. Even during the period of the organization of this meeting, moves have been made in certain areas to form separate organizations in some countries. However, while our neurologist and neurosurgeon colleageus are members of such national organizations, their participation in a meeting such as this can only have an enriching effect on the level and the nature of the deliberations.

The importance of such regional seminars cannot be over-emphasized. While most countries in the South-East Asian regions were historically colonies of various metropolitan powers in Europe, professionals in the field of psychiatry and neurological sciences in this region knew much more about what is going on in the professional scene in those metropolitan countries in Europe and what goes on in the United States better than what their counterparts in neighbouring countries are doing. Such seminars, therefore, provide a forum for the exchange of ideas between professionals working in similar fields in the countries of this region. These week-long meetings also afford a good opportunity for participating professionals to get to know their counterparts in neighbouring countries so that professional and personal relationship can be established and maintained. The organising committee regretted that a number of invitees were unable to come. On the other hand, the participation of the luminaries from the United Kingdom, Australia and Japan was most welcomed.

It was the consensus of the participants in the 1970 seminar in Djakarta that this series of seminars should be held once in every two or three years. This feeling was reaffirmed in Kuala Lumpur in 1973 and it is hoped that the Roche Far East Research Foundation will continue to support this enterprise, so that the interaction between professionals in the countries of the South-East Asian regions can continue.

During the seminar in Kuala Lumpur, discussions were held informally among some participants about the formation of the South-East Asian Federation of Neuropsychiatric Societies involving the professional organizations in Indonesia, Singapore, Philippines, Thailand and Malaysia. It is hoped that this organization will come into being soon to provide an avenue for continuous interchange of ideas between professionals in the region and it may be one of the parties involved in the organization of such seminars in the future.

The organising committee is grateful for the generosity of the Roche Far East Research Foundation of 1108, Princess Building, Hong Kong for its sponsorship of this seminar and wish to record their special appreciation to Dr. P. A. Buhr and Dr. S. S. Loh for their extreme patience, generosity and forebearance in helping us in the organization of this Seminar.

Eng-Seong Tan
Chairman
Organising Committee

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AUSTRALIA

By I. PILOWSKI

Professor, Department of Psychiatry, University of Adelaide, Adelaide, South Australia.

In Australia, the trend over the past few years has been towards regionalization of psychiatric services with specific hospitals taking responsibility for the mental health of circumscribed communities. New hospital facilities are usually attached to general hospitals and have become an integral part of the health delivery system. Many such general hospital psychiatric units exist and more will be developed. These units cope in the main with short-stay patients, using the techniques of crisis-intervention as well as psychopharmacologic methods.

At the same time, it is generally acknowledged that specialized units are required for the treatment of the intellectually retarded, psychogeriatric patients, adolescents, disturbed children and others. Progress in these areas is uneven due to financial strictures and shortages of trained personnel. The latter problem has to some extent, been met by the training of non-professionals in the field of community work. This has worked particularly well in South Australia where "Mental Health Visitors" have been trained since 1964. The training course lasts for six months, and was introduced initially because of an awareness that the early discharge of patients from psychiatric hospitals was imposing strain on the patients, relatives and other members of the community. It was felt that in order to reduce misunderstanding as a result of early discharge, it would be necessary to provide satisfactory follow-up services. In addition, the almost impossible task of finding sufficient qualified social workers made it quite obvious that some other method had to be devised in order to meet demands for community support. It should be mentioned that an experiment had been carried out in which a qualified psychiatric nurse had been attached to a Child Guidance Clinic as a supporting visitor to the children's family. Although she had no specific training, she worked closely with psychiatrists and social workers as part of the Child Guidance Clinic team, and it was found that she was a most valuable contributor.

Students are carefully selected for the training programme and are usually between the ages of 30 and 45. Warmth and personality stability as well as reasonable intelligence are also attributes which are sought. It should be pointed out that intelligence is not judged on the basis of educational background since, in some cases, there has been a lack of opportunity. Lectures are given on the nature and classification of mental disorders, description of clinical syndromes, interview techniques and developmental psychology. In addition to this, the trainees are taught relevant sociological principles and are taken on visits to various community agencies and facilities, as well as doing practical work. A most important observation is that mental health visitors function best if they remain part of a group and are given support and supervision. It is absolutely crucial that they have opportunities for sharing their experiences.

The Mental Health Visitor Scheme is only one example of a number of attempts which have been made in Australia to take psychiatry into the community. Where community nurses are available, we have been struck by the excellent use which has been made of them by general practitioners and patients. Of course, it is more difficult to provide psychiatric services in outlying communities which have severe transportation problems; but even in this area, excellent work is being done and units are being set up in country towns while, in others, arrangements are made for psychiatrists to visit on a regular basis. Where possible, attention is always directed to educating the professionals on the spot and not attempting the impossible task of dealing with all the community psychiatric problems from a hospital based service.

The move into the community has, of course, placed strains on existing hospital services and has produced feelings of insecurity in staff used to working in a hospital setting. However, attitudes are changing and there is little doubt that the age of the large mental hospital is essentially over. At the same time, of course, we may still see mental hospitals converted into groupings of autonomous units devoted to the care of special problems.

HONG KONG

By K. SINGER

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All commonly used psychotropic drugs are available in Hong Kong. A doctor's prescription is required and the drugs cannot usually be obtained under the counter since the Government is tightening up restrictions in this respect. All who require medication and cannot afford it are also able to obtain it at little or no cost for as long as is necessary from Government institutions. This is particularly helpful in the long-term maintenance treatment of psychotics from the lower social strata. It is probable, however, that a large proportion of patients still exists who have not come forward for treatment for various reasons.

Concerning trends of usage, I shall deal first with the practice among psychiatrists. As regards the antipsychotic drugs (neuroleptics), the phenothiazines are still the most commonly used. Chlorpromazine remains the first line drug for schizophrenia, especially when a sedative action is also required. Trifluoperazine is another first line drug for schizophrenia, particularly for paranoid and hallucinatory manifestations and dullness. Less commonly used phenothiazines are Thioridazine and Perphenazine. Fluphenazine in its long-acting form has been found useful in outpatients unreliable in their drug taking or who appear over-sedated with other phenothiazines. However, of late, there has been found a tendency for patients to relapse with its exclusive use. In the butyrophenone group, Haloperidol continues to find a place as the main drug in mania, and as a second line drug in schizophrenia particularly with paranoid-hallucinatory phenomena. The thioxanthenes have practically not been used in Hong Kong except for research purposes.

We come to the anti-anxiety drugs (anxiolytic sedatives), a term I shall use to include (a) minor tranquillizers and (b) hypnotics and sedatives.

The minor tranquillizers continue to be much used by psychiatrists, usually in combination with anti-depressants. Among the benzodiazepines, Chlordiazepoxide and Diazepam are the most commonly prescribed. Of the two, Diazepam is increasingly favoured for its stronger tranquillizing action. It is also increasingly used for rapid sedation and in epilepsy. Other benzodiazepines e.g. Oxazepam (Serepax) are much less used. Medazepam (Nobrium) however is somewhat more frequently used than the others as an alternative to Librium and Valium. Other minor tranquillizers including meprobamate are rarely used by psychiatrists. The hypnotics and sedatives comprising mainly the barbiturates are fairly widely used. Nitrazepam (Mogadon) is practically the only non-barbiturate drug in this group that is commonly used, mainly as a substitute for barbiturates which carry a greater danger of addiction.

As regards anti-depressants, the tricyclics, mainly amitryptiline, tend to be more frequently used than the MAOIs; however the latter continue to be used to a fair extent, in the neurotic or atypical depressive as well as in all other neurotic conditions, in combination with a minor tranquillizer. Almost the only MAOI used is Isocarboxazid (Marplan). Psychostimulants such as amphetamines are little used by psychiatrists, except occasionally in epilepsy and narcolepsy.

While Psychiatrists are aware that psychotropic drugs should be used only as part of a comprehensive treatment programme, there is a tendency to place much reliance on physical methods because of shortage of personnel. Also the local population expect to be given drugs and injections and are sceptical of other forms of treatment.

I shall say only a few words about the use of psychotropic drugs among general practitioners. The latter use mainly the anti-anxiety drugs, and these they use in abundance. One general practitioner informed me he had Librium in 8 different colours. The main minor tranquillizers used are Librium, Valium and Nobrium. Meprobamate is still extensively used. These drugs are used for treatment of anxiety, sleep disorders, and psychosomatic conditions. One has the distinct impression, though unsupported by factual data, that general practitioners are prescribing anti-anxiety drugs excessively and that abuse of these drugs is a large problem. Unlike in Western countries, there is little tendency to use anti-depressants or the major tranquillizers, mainly because of poor knowledge of mode of action of these drugs and a disinclination to get involved with the more serious psychiatric conditions.

It may be worth mentioning that we have not

found any significant differences from Western countries in respect of dosage, therapeutic response or side or toxic effects, except that the effective dosage tends to be about 80% of that used say in the United Kingdom; this is understandable because of the proportionately colour body weight of the Chinese. I mention all this in view of claims advanced in some quarters of large cross-cultural differences in psychotropic drugs dosage and response which are not solely determined by differences in prescribing tablets.

In conclusion, the main differences in the useof psychotropic drugs between Hong Kong and Western countries is found not among psychiatrists but among general practitioners. The latter in Hong Kong who are in the front line of defence, should play a greater role in the treatment of psychological disorders but before they do so, they should be better educated in the use of psychotropic drugs and in psychiatric practice generally.

INDONESIA

By B. SADONO

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The speed of scientific development in this modern age has reached such a stage where the most up-to-date information has not only become a pressing necessity but an indispensable basic need. Although medical authorities in Indonesia have worked out programmes for the nation's second Five Year Development Plan (1974–1979) and psychiatrists active in mental health planning have attempted to look into the future as far as 30 years ahead, the aim of this presentation is only to focus on actual facts in psychotropic medication which existed during 1970–1973.

Psychotropic Medication in Indonesia was only known in 1956, when Chlorpromazine was introduced. I wish to refer to a report which describes the status of psychotropic medication in Indonesia until 1970*

The number of psychotropic drugs now available has become numerous and is expected still to increase.

Drugs like **Librium (Chlordiazepoxide)** and **Valium (Diazepam)** stimulated the development of more systematic psychosomatic approaches among Indonesian physicians who previously were predominantly organically-oriented. Scientific literature provided by pharmaceutical firms was also helpful in this development. Although antidepressants were introduced much later, Amitriptyline (Laroxyl^{R}, Tryptanol^{R}, or Elavil^{R}) are now widely used. There is, however, still a relative unfamiliarity with the somatic manifestations of depressions especially among general practitioners and non-psychiatric specialists. LSD is not used therapeutically.

Although psychotropic drugs are not processed or developed in Indonesia, most drugs like *chlorpromazine, reserpine, meprobamate, chlordiazepoxide and diazepam* are imported as bulk materials. There are many pharmaceutical firms active in manufacturing tabletted form of such substances. No basic drug research is carried out in Indonesia; on the other hand, clinical drug trials were carried out in a number of medical centres:

a. Jakarta: under the auspicies of The Directorate of Mental Health, Ministry of Health, and The Department of Psychiatry, University

* The Indonesian population estimated at 120 million is served by 41 mental hospitals and Department of Psychiatry which are located in the main cities in Java, Bali, Sumatra, Kalimantan, Sulawesi and Irian Jaya.
There are 3 central state mental hospitals (all located on the island of Java), with an average bed capacity of 1,000. There are also about 20 regional state mental hospitals with an average bed capacity of 200, most of them on the other islands. A few general hospitals have psychiatric facilities. The Department of Psychiatry of the University of Indonesia, for instance, is part of the General Hospital in Jakarta.
The report also states that the number of certified psychiatrists in Indonesia is about 75 persons.

of Indonesia.

b. **Bandung:** under the auspicies of The Department of Psychiatry, University of Pajajaran.

c. **Jogjakarta:** under the auspicies of The Department of Psychiatry, University of Gajah Mada.

d. **Surabaya:** under the auspicies of The Department of Psychiatry, University of Airlangga.

e. **Medan:** under the auspicies of The Department of Psychiatry, University of Sumatera Utara.

A short summary of some results from these drug trials is given:

MAJOR TRANQUILLIZERS:

1. **Combination Therapy of ECT, Reserpine** and **Chlorpromazine.** With the aim ot find low-cost therapy, in 1964 a trial was done for the ambulatory treatment of functional excitement states.
2. **Thioridazine** *("Melleril"-Sandoz)*: An effective drug with mild side effects. Caution is mentioned when using high dosages (> 300 mg/day).
3. **Chlorprothixene** *("Taractan"-Roche)*: An effective drug for the treatment of psychotics. A recent trial in 8 mental hospitals in Java covering some 800 patients again reaffirmed this conclusion.
4. **Fluphenazine** *("Anatensol"-Squibb)*: A potent major tranquillizer. Caution mentioned when using high dosages (> 3 mg/day).
5. **Trifluoperazine** *("Stelazine"-Smith, Kline & French)*: This drug in many respects resembles fluphenazine. Optimal responses with psychotics can be obtained with 10–15 mg daily.
6. **Levomeprozine** *("Nozinan"-Specia)*: A major tranquillizer with beneficial effects for schizophrenics experiencing acute episodes. Side effects are rare and not severe; lowered blood pressure was mentioned as a side effect occurring during the first week of treatment. Average dosage : 50 – 150 mg daily.
7. **Haloperidol** *("Haldol". Janssen; "Serenace"-Searle)*: A major tranquillizers with mild-to-moderate side effects. Beneficial effects on paranoid symptoms and other types of distorted perceptions of thought (hallucinations and paranoid delusions). Average dosage: 1.5 to 4.5 mg/day.
8. **Thiopropazate** *("Dartalan"-Searle)*: A 'mild type' of major tranquillizer, nearly without side effects. Average dose: 20–60 mg daily.
9. **Perazine** *("Taxilan..-BYK-Gulden)*: A drug considered effective on disturbances of perception and thinking process in schizoprenia. Slight and transient undesirable concomitant effects are: drowsiness, finger tremor and decrease in blood pressure. Average daily dosage: 300–1200 mg.

MINOR TRANQUILLIZERS:

1. **Chlordiazepoxide-HCL** *("Librium"-Roche)* and **Diazepam** *("Valium"-Roche)*: The best known and most prescribed psycho-active drug by the psychiatric and non-psychiatric profession as well. Mostly used in neurotic conditions, relatively inactive for psychotic disorders.
2. **Benzodiazepine deratives** *("RO-3350 or Lexotan"-Roche)*: Good results for severe psychophysiological disorders. Lexotan seems to bring new hope in the treatment of obsessive-compulsive conditions and other severe neurosis which so far are highly resistant to drug-therapy. Side effects are not severe. Daily dosage: 9 to 30 mg.
3. **Lorazepam** *(WY-4036 or "Ativan-Wyeth)*: A potent anti-anxiety compound and welcome addition for the psychiatric practitioner. Generally, side effects are transient and human tolerance towards the drug is good. Dosage: 0.5 – 12 mg daily.
4. **Oxazepam** *("Serax"-Wyeth)*: An effective anti-anxiety agent. Daily dosage: 45 – 135 mg.
5. **Benzotamine HCL** *("Tacitin"-Ciba)*: For cases of anxiety. No serious side effects. Daily dose ranges: 15–90 mg.

ANTI DEPRESSANTS:

1. **Imipramine HCL** *("Tofranil"-Geigy)*: Effective for the ambulatory treatment of depressions.
2. **Chlorimipramine** *("Anafranil"-Geigy)*: Good results in the reactive, neurotic and atypical depressions. Side effects like insomnia, anorexia, excitement, nausea and vomiting disappear by reducing the dosage. Dosage ranges: 25–125 mg/day.

In addition to the drugs listed above, there are still some other psycho-active drugs which are not regularly available in the Indonesian market.

The increasing need for psychotropic drugs during 1970–1972 is illustrated by the figures supplied by The Directorate General of Pharmacy.

DIRECTORATE GENERAL OF PHARMACY

MAJOR TRANQUILLIZERS:	1970	1971	1972
1. **Chlorpromazine**			
Tablets	1,168,500	765,000	2,651,000
Ampoules	11,570	33,721	19,540
powder/kg	25	60	70
2. **Thioridazine** *("Melleril"-Sandoz)*			
Tablets	50,000	70,000	58,000
3. **Trifluoperazine** *("Stelazine"-Smith, Kline & French)*			
Tablets 1 mg	14,500	–	–
Tablets 5 mg	16,200	–	–
4. **Fluphenazine** *("Anatensol"-Squibb)*			
Tablets 1 mg	438,500	100,940	410,000
Tablets 2.5 mg	31,500	133,000	187,000
Tablets 5 mg	221,000	132,000	170,000
5. **Chlorprothixene** *("Taractan"-Roche)*			
Tablets	–	41,500	–
6. **Haloperidol** *('Haldol"-Janssen; "Serenace"-Searle)*			
Tablets ½ mg	–	594,000	1,111,500
Ampoules 5 mg	–	– –	2,600
7. **Levomepromazine** *("Nozinan"-Specia)*			
Tablets 25 mg	125,000	120,000	227,500
Ampoules	–	1,000	–
8. **Perphenazine** *("Trilafon."-Schering)*			
Tablets 2 mg	180,000	174,400	240,000
Tablets 4 mg	94,000	104,000	208,600
Tablets 8 mg	–	–	35,000
9. **Reserpine** *("Serpasil"-Ciba)*			
Tablets 0.1	7,500	162,500	–
Tablets 0.25 mg	60,000	100,000	–
Ampoules	150	–	–
Powder/kg	2	–	–

OTHER DRUGS AVAILABLE:

10. **Thiopropazate** *("Dartalan"-Searle)*
11. **Perazine** *("Taxilan"-BYK-Gulden)*

MINOR TRANQUILLIZER:			
01. **Chlordiazepoxide** *("Librium"-Roche)*			
Tablets 5 mg	32,000	100,000	750,000
Tablets 10 mg	99,000	–	–
Powder/kg	159,400	228,800	155
02. **Diazepam** *("Valium"-Roche)*			
Tablets 10 mg	55,000	–	–
Tablets 5 mg	217,500	120,000	200,000
Tablets 2 mg	549,000	1,600,000	1,200,000
Ampoules	4,500	37,672	–
Powder/kg	–	826,080	35
03. **Nitrazepam** *("Mogadon"-Roche)*			
Tablets	344,000	72,000	

		1970	1971	1972
04.	**Medazepam** *("Nobrium"-Roche)*			
	Tablets	276,000	184,000	3,000
05.	**Meprobamate**			
	Tablets	150,000	–	–
	Powder/kg	–	250	506
06.	**Oxazepam** *("Serax"-Wyeth)*			
07.	**Benzotamin** *("Tacitin"-Ciba)*			
08.	**Lorazepam** *("Ativan"-Wyeth)*			
09.	**Benzodiazepin** *("RO 5.3350" or "Lexotan"-Roche)*			

ANTI DEPRESSANTS:

01.	**Amitriptyline** *("Laroxyl"-Roche)*			
	Tablets 10 mg.	56,500	115,800	2,250
	Tablets 25 mg.	11,250	12,500	750
02.	**Protriptyline** *("Concordin"-MS&D)*			
	Tablets 5 mg.	80,000	10,000	–
	Tablets 10 mg.	90,000	10,000	20,000
03.	**Isocarboxazide** *("Marplan"-Roche)*			
	Tablets 10 mg.	–	12,500	–

OTHER DRUGS AVAILABLE

04.	**Imipramine** *("Tofranil"-Geigy)*		
	Tablets 25 mg.		
05.	**Chlorimipramine** *("Anafranil"-Geigy)*		
	Tablets 25 mg.		
06.	**Doxepin HCL** *("Sinequan"-Pfizer)*		
07.	**Mutabon M** (2/10) – Schering U.S.A.:	Perphenazine	2 mg.
		Amitriptyline	10 mg.
08.	**Mutabon D** (Schering U.S.A.):	Perphenazine	2 mg.
		Amitriptyline	25 mg.
09.	**Motival** (Squibb tablets):	Fluphenazine	0.5 mg.
		Nortriptyline	10 mg.
10.	**Amitriptyline** *("Elavil"-Frost)*		
	Capsules 10 mg.		
	Capsules 25 mg.		
	Amitriptyline *("Tryptanol"-MS&D)*		
	Capsules 10 mg.		
	Capsules 25 mg.		
11.	**Limbritol** *(Roche, capsules)*		
	Amitriptyline 12.5 mg.		
	Chlordiazepoxide 5 mg.		

POLICIES, DIRECTORATE OF MENTAL HEALTH, MINISTRY OF HEALTH:

1. **Hospitalization:**
   Ambulatory treatment must be emphasized as an alternative to hospitalization and sometimes equally effective method.
2. **Inter-relationship of Behavioural Sciences:**
   To obtain maximum beneficial effects, psychiatry must arrange working relationships with psychology, sociology, and anthropology.
3. **Isolationist Tendencies of the Mental Hospital:**
   This may indirectly involve attitudes to also exclude **psychiatry** from the mainstream of medical sciences. This should not be allowed to

occur.

4. **The Adoption of a Public Health Oriented Approach in Psychiatry:**
   This will enhance psychiatric coverage of the population and diminish psychiatry as an "exclusive service" for limited groups in the society.
5. **Integration of Mental Health Principles in General Medical Approaches:**
   This will allow greater psychiatric involvement at a public health level such as the appointment of consultant psychiatrists at community health centres, mental health refresher courses not only for general practitioners but also for non-medical professionals as well like: city planners, police officers, etc.

INFORMATION FROM VARIOUS AREAS:

In November, 1972, about 50 letters were distributed to various area-centres of mental health by the Directorate of Mental Health, Jakarta, with the following questions:

1. What psychotropic drugs are commonly used in your area, its estimated amount of usage, and what are your experiences?
2. Please comment on the effectiveness of these drugs and their comparative effectivity. Please submit your research data to complete your report; if possible with reprints of your publications.
3. What are your plans and expectations of the usage of psychotropic drugs for the future?
4. Your report should focus from 1970–1973.

There were about 50% responses to the enquiries. Some of the conditions described are listed below:

1. In general hospitals where treatment for the mentally ill is only supplementary, minor tranquillizers are more extensively used than major tranquillizers. As can be expected, there seems to be more neurotic than psychotic patients. The ratio of psychotropic drug usage is:
   - Minor tranquillizers : 55%
   - Major tranquillizers : 10%
   - Anti-depressants : 35%
2. Mental hospitals generally carry out clinical drug trials such as:
   1. The Navy Hospital, Jakarta, has done trials with Anatensol, Meleril and Serax;
   2. Medan Mental Hospital did trials with Anatensol and Melleril;
   3. Bandung Mental Hospitals with pyrithioxine *("Encephabol")*, Nozinan and Taractan;
   4. Surakarta Mental Hospital with Taractan.
3. Other detailed reports gave descriptions of local conditions or made specific suggestions:
   1. **Jakarta Mental Hospital:**
      (a) inexpensive drugs must be made available for the treatment of the chronically ill.
      (b) better standardization of locally-made drugs must be done.
   2. **Bogor Mental Hospital (West Java)**
      Regular usage of Stelazine, Largactil, Nozinan & Stelazine is done.
   3. **Magelang Mental Hospital** (Central Java):
      Demands for wider usage of psychotropic drugs like Chlorpromazine, Nozinan & Melleril, and especially recommends Chlorpromazine due to its modest price.
   4. **Bangli Mental Hospital** (Bali) :
      Reports that in Bali, drug preference is more determined by the availability of the drug rather than by its quality.
   5. **Banjarmasin Mental Hospital** (Kalimantan):
      Chlorpromazine is most suitable for the regions outside Java, it is cheap and yet effective.
   6. **Medan Mental Hospital** (North Sumatra):
      Chlorpromazine is commonly used in Medan.
   7. **The Navy Hospital,** (Jakarta):
      Reports that drug packings are not to be neglected hence domestic products should be more attractively packed.
   8. **Surakarta Mental Hospital** (Central Java):
      The best known drugs are Chlorpromazine, Melleril, Taractan and Stelazine.
   9. **Banda Aceh Mental Hospital** (North Sumatra):
      No drug trial carried out here due to lack of manpower, facilities and equipment.
   10. **Semarang Mental Hospital** (Central Java):
       No drug trials done.
   11. **Police Mental Hospital,** Jakarta:
       No drug trials done.
   12. **In general:**
       Chlorpromazine Melleril, Stelazine, Taractan, Valium, and Librium are some of the drugs most widely used. Most Mental Hospitals stress the importance of national and international meetings, workshops and seminars on psychoactive drugs such as Regional Seminar on Psychotropic Medication in Jakarta and Kuala Lumpur.

Integration of Psychotropic Medication in Public Health Centres.

The National Seminar on Mental Health held in Jakarta in 1971 observed that in Indonesia certain phenomena threaten the stability of the

community: narcotic, drug dependence, student unrest, unstable marriages, abuse of mass-media, unemployment (visible and disguised), breakdown of traditional life, changes of the traditional system of values and rapid social change. These complex social phenomena cause increased anxiety, frustration, stress and strain to which greater attention must be paid by those concerned with the health of the nation.

It was also observed that with the successful campaigns against communicable diseases within the next thirty years, psychiatry in particular, and mental health problems in general will emerge as subjects of much greater importance.

Although it was felt that drugs will never be able to bring about complete improvement of disordered human behaviour as such, it is considered that psychotropic medication will prove most beneficial in the treatment of the major psychoses, as well as some of the neurotic and behaviour disorders. It was also predicted that psychotropic medication will constitute a major stimulus for the development of psychotherapeutic approaches. Within this framework, the Seminar recommended that general practitioners should not only have greater theoretical knowledge and understanding of psychoactive drugs, but that they should be actively engaged and involved in the psychotropic medication procedures in Public Health Centres, and cooperate closely with consultant psychiatrists.

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JAPAN

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I. INTRODUCTION

Since 1970, the year of the First Seminar, there has not been any significant changes in psychotropic medication in Japan. The recent statistics indicate that the consumption of major and minor tranquillizers has not increased, except anti-depressants, especially amitritypline which has been slightly increased because of the introduction of the term "masked depression". It is considered that this unique term has stimulated most probably the use of anti-depressants by non-psychiatric doctors.

According to the governmental statistics, the annual increase rate of the number of psychiatrists, psychiatric hospitals, and the beds for the psychiatric patients in psychiatric and general hospitals was stable, and the rate of schizophrenia and other psychosis followed the same tendency.

In Japan, psychotropic medication has become very popular and has taken the lead in the treatment of mental disorders.

Based on different statistics, it is estimated that a schizophrenia patient may annually consume important major tranquilizers worth about Y90,000 (or US$ 330) and that about 1 – 2 million of the Japanese take minor tranquillizers daily.

II. Actual Status of the Psychopharmacological Therapy for Psychiatric and Psychosomatic Diseases

A. Schizophrenia

1. Management of Schizophrenia Symptoms

The pharmacotherapy of schizophrenia is almost standardized in Japan. The different types of antipsychotic drugs will be selected mainly according to the symptomatology which may be classified into two different aspects, i.e. positive states such as hallucination, delusion and psychomotor excitation, and negative states mainly recognized by autistic symptoms.

a) Management of Excitation

Generally, the treatment is started by parenteral administration (i.m.) of Chlorpromazine or Levomepromazine (25 – 50 mg, 2 – 4 times per day) or Haloperidol (5 – 10 mg, i.m. or i.v.). Recently, it is confirmed that i.m. or i.v. administration of Diazepam (10 – 30 mg) obtained favourable results and are even more effective than dosage increase of antipsychotic drugs.

When tranquillization appears in patients, parenteral administration should be switched to oral administration of antipsychotic drugs, especially Haloperidol and Chlorpromazine.

b) Management of Stupor

Perphenazine and Fluphenazine are used most frequently in the following ways.

- Perphenazine is administered by starting with initial dosage of 6 – 12 mg/day and increasing up to 20 – 30 mg/day.
- Fluphenazine is effective with daily dosage of 3 – 6 mg/day.

Administration of Diazepam slowly and intravenously also releases patients from the state of stupor.

c) Hallucination and Delusion

The use of butyrophenone derivatives (Haloperidol) Trifluperidol and Floropipamide) has recently become more familiar but Chlorpromazine is still more frequently used.

d) Diminution of Rapport and Reduction of Spontaneity

The phenothiazine which has the piperazine ring in side chain (Perphenazine 10 – 30 mg/day, Fluphenazine 1 – 5 mg/day) is most widely used. Carbipramine, which was originally developed in Japan, is indicated for this case and yields good results. However, the relapse in the acute phase may sometimes occur. These symptoms will most frequently appear in cases of chronic schizophrenia and are generally difficult to treat. However, several new antipsychotic drugs such as Clothiapine and Oxypertine claim special indication for these states.

e) Anxiety and Agitation

Anxiety state is frequently observed in schizophrenia, especially in its acute phase. In this case, the concomitant use of minor tranquillizers such as Diazepam and Medazepam with major tranquillizers such as phe-

nothiazine and butyrophenone is recommended.

2. Prevention of Relapse and Treatment for Remission.
   The necessity of drug therapy during the period of remission to prevent the relapse is generally accepted. Generally speaking, the relapse may occur 3 – 6 months after reduction or ceasing of medication. The continuous medication and the occurrence of tardive side-effects, epsecially tardive dyskinesia has been recently discussed.
3. Drug Association and Interaction
   The simultaneous use of two or more drugs with different pharmacological spectrums is frequently applied as a routine treatment of psychosis to obtain the potentiation of effects and/or to reduce side-effects. The use of Fluphenazine together with Levomepromazine is an example and the association of Chlorpromazine with Chlordiazepoxide may manage agitated patients better than Chlorpromazine alone. The confirmation of the interest of combination therapy has not been made yet while the problem on drug interaction has more and more attracted clinical doctors' attention. Therefore, we should pay more careful attention to the association of drugs in routine practice.

B. **Treatment of Mania and Depression**

In this field, two new topics are now discussed in Japan.

1. The treatment and the Possibility of Prevention of Manic Syndromes by Lithium Carbonate.
   Even Lithium Carbonate has not yet received governmental approval as a new drug. Large-scale clinical trials have been performed all over the country. The following are the conclusions and problems.
   a) Lithium acts rather slowly and effects may be obtained within 4–10 days for those who respond to Lithium.
   b) The specific anti-manic effects of Lithium was discussed but some authors reported that Lithium was effective also for the manic state of symptomatic psychosis or schizophrenia.
   c) It is agreed that Lithium removes the manic state naturally, contrary to the major tranquillizers which suppress the symptoms and produce so-called "drug-produced state of quiet."
   d) Blood (serum) concentration of Lithium ion and therapeutic effects.
      The optimum therapeutic concentration will be located between 0.4 – 1.2 mEq/1 according to the studies by Watanabe. The occurrence of toxic symptoms may be parallel with blood concentration of Lithium ion. The maximum safety level is around 1.5 mEq/1 and toxic level more than 2.0 mEq/1.
   e) The prevention of manic-depressive phase in cyclothymic psychosis by Lithium is now under investigation. However no conclusive evidence has been obtained. The long-range administration of Lithium should be done very carefully regarding the toxic side-effects.

2. *Drug Therapy of So-called "Masked Depression"*

Despite the hesitation of the psychiatrists, this new terminology is now widely used among the Japanese medical professionals. In almost all cases, the association of anti-depressants (mainly Amitriptyline) and minor tranquillizers (Diazepam and Medazepam) are applied to different kinds of psychotherapy including Morita therapy and hypnosis.

The choice and dosage of anti-depressants are the most important problems and the non-psychiatric practitioner prefers Amitriptyline to Imipramine. Due to possible adverse reactions of tricyclic anti-depressants, daily dosage of anti-depressants is determined as low as possible. In this respect, the combination of minor tranquillizers, especially benzodiazepine derivatives, seems to be useful. In certain cases, the administration of Medazepam alone has improved the depressive state.

For handling accompanying symptoms of depression, especially insomnia, the reasonable administration of hypnotics (Nitrazepam) is recommended.

In this connection, some practitioners who use the hypnotics as psychotherapy prefer Diazepam injection (i.v.) for the introduction of hypnosis.

C. *Drug Therapy of Neurosis and Psychosomatic Diseases.*

As mentioned in the introduction, it is estimated that 1–2 million of the Japanese (1–2% of population) consume minor tranquillizers of benzodiazepine derivatives per day. This means that each medical doctor (total: 113,214 in 1970) prescribes this kind of drugs for about 8 – 17 patients daily, and that if the case is limited to psychiatrists (total: 8,713 in 1970) about 100 – 200 patients are taken care by a psychiatrist

daily. As the latter seems too far from a fact, the drug treatment for neurosis and psychosomatic disease is handled not only by psychiatrists but all medical practitioners. Therefore, knowledge about psychotropic medication will be required more intensely by non-psychiatrists.

Two new benzodiazepine derivatives were introduced in Japan two years ago. One was Medazepam originated by Roche, and the other was Exazolam developed by Sankyo. According to the large-scale double blind trials of Medazepam against Diazepam, it was discovered that Medazepam was more effective on anxiety neurosis and phobia, and less effective on depressive neurosis. By symptoms, Medazepam was effective on anxiety and phobia and Diazepam on anxiety, depression and neurasthenia. In these double blind trials, the earlier onset of action of active drugs (Medazepam and Diazepam) was observed in comparison with placebo. The drugs were significantly more effective than placebo for 1 – 2 weeks after medication. Placebo group improved after 3 weeks of drug administration. Attention should be paid especially on the 2nd and 3rd week of medication, and doctors should at this period review again the efficacy and adverse reaction of drugs. The use of Meprobamate which was one of the most popular minor tranquillizers in the period of 1960's, was considerably reduced in Japan due to its adverse reactions.

III. *Use of Psychotropic Drugs by Non-psychiatrists*

As described in I. and II., the use of minor tranquillizers and anti-depressants spread among non-psychiatric practitioners in Japan. However, the use of major tranquillizers (antipsychotics) was mainly limited to psychiatrists. Generally speaking, psychiatrists were more interested in the efficacy of drugs and general practitioners were very anxious about the side-effects of drugs. When specialized drugs were used by non-specialized practitioners, the permanent safety of drugs should be assured.

Attention should be paid to psychotropic drugs which not only act on the specific function of the brain but might also modify the morphology, physiology and/or biochemistry of the whole body.

Most of the psychotropic drugs have an influence on the following systems and/or organs.

a) Central Nervous System
   - (i) Sleep, awake
   - (ii) Paradoxical reaction
   - (iii) Depressive reaction
   - (iv) Manic state induced by anti-depressants
   - (v) Manifestation of schizophrenic state
   - (vi) Acute exogenous type reaction
   - (vii) Paradoxical reaction
   - (viii) Convulsion
   - (ix) Others

b) Extrapyramidal Syndrome
   - (i) Reversible: akinesia, Parkinsonism and acute dystonia
   - (ii) Irreversible: tardive dyskinesia

c) Autonomic Nervous System
   - (i) Phenothiazine: Adrenolytic
   - (ii) Tricyclic anti-depressant: Antichlolinergic

d) Endocrine and Metabolic System
   - (i) Libido and potency
   - (ii) Menstruation disturbance
   - (iii) Lactation
   - (iv) Obesity and increase in body weight
   - (v) Diabetes mellitus
   - (vi) Liver and its appendages
   - (vii) Blood and hematopoietic organ
   - (viii) Skin and its appendages
   - (ix) Eye and other sensory organs
     - (a) Glaucoma
     - (b) Cornea and crystallina turbid
     - (c) Retina (pigmentary retinopathy)
   - (x) Cardiovascular organ
     - (a) Thrombosis, infarctus and phlebitis
     - (b) ECG
   - (xi) Effects on the foetus and reproduction system.

A careful and regular check of these systems organs is necessary when using psychotropic drugs in daily practice.

The effect of Major tranquillizers on extrapyramidal system and possible development of tardive dyskinesia becomes an important topic and antipyschotic drugs (Clozepine) which have no or few implications to extrapyramidal functions are now investigated.

The long-range administration of phenothiazine may act on the eye and may occasionally produce disturbance of the crystallina and cornea. Also, some phenothiazines cause retinitis pigmentosa.

The effects of tricyclic anti-depressants on the foetus and the cardiovascular system were also discussed.

The dependency liability and abuse of minor tranquillizers are continuously discussed. However, actual attentions are rather oriented to the relationship between the personality of the abuser

(host) and his social environment. This problem arises because amphetamine produces severe organic psychosis and abuse with very few physical dependency liability, while non-barbiturate hypnotics, methaqualon which produce endemic abuse in Japan has almost no dependency liability. There are only very few sporadic cases of marihuana abuse in Japan despite very frequent cultural exchange between U.S.A. and Japan.

The abuse of benzodiazepine derivatives has not been reported in Japan.

IV. *Discussion on the Testing Principle for the General Assessment of Efficacy and Safety of Psychotropic Drugs*

The following are recent topics of discussions on general problems of psychotropic medication.

1. Pharmacokinetics and metabolism.
2. Action of psychotropic drugs in normal subjects and in patients
3. Controlled trial for the evaluation of safety and efficacy
4. Studies on the dosage and duration of treatment.
5. Monitoring of the adverse reaction

The correlation between the efficacy and blood concentration of phenothiazines was studied by several authors. However, there is still no firm conclusion of the correlation. Tentative studies on the effect of anti-anxiety drugs (Diazepam and Bromazepam) in normal volunteers were performed by Ogawa et al. The results show that each drug acts differently on the subjects with higher anxiety level and on those with lower anxiety level.

The requirement for scientific evaluation of the efficacy and safety of drugs is now found in Japan. For the performance of this kind of trials, we are using Japanese originated rating scale because of the Japanese specific socio-cultural and language problems.

As mentioned in II. and III., the duration of administration of major tranquillizers is now under review in consideration of residual or long lasting effects after the long-range administration.

Since last year, Japan has been a member of the International Drug Monitoring System organized by the W.H.O. The methodology of intensive and passive monitoring for adverse reactions will be a problem in the near future.

V. *Conclusion*

Psychotropic medications have been already well established in Japan and psychotropic drugs are now widely prescribed not only by psychiatrists but by all medical practitioners. According to this tendency, more careful attention not only to the efficacy of the drug but also to the safety of drugs will be stressed. Therefore, for the assessment of the safety and efficacy, several problems on testing principles were discussed.

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Table 1

1. *Number of Doctors*

	1969	*1970*
Neuropsychiatry	8,251	8,713
Internal Medicine	56,174	57,654

2. *Number of Psychiatric Hospitals and Beds*

	1969	*1970*	*1971*
Psychiatric Hosps.	874	896	900
" Beds	177,567	185,162	188,395
General Hosp.	—	—	—
" Beds	60,625	62,103	65,067

3. *Number of Psychiatric Patients Actually Treated*

	1969	*1970*	*1971*
Schizophrenia	160,000	151,000	165,000
Other Psychosis	2,500	2,500	2,700

PHILIPPINES

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Psychotropic medications are in wide use in the Philippines, particularly in the Manila and Greater Manila areas. Both general practitioners and specialists prescribe them rather liberally to hospital and clinic patients. The only recent deterrent to this trend has been the issuance of a Dangerous Drug List by the National Bureau of Investigation, in an effort to curb drug abuse. To prescribe a drug which is on the list (and most tranquilizers, all hypnotics and sedatives are on this list), a physician has to write out a prescription in triplicate. One copy goes to the drug store, a second to the patient and the third is kept by the physician. The official prescription pads are issued only by the NBI. A doctor has to apply for their purchase. This seems to be a cumbersome procedure which discourages physicians from giving them unless urgently and specifically necessary. This means that the minor tranquilizers for tensions, anxieties, and less malignant psychological disorders have dropped in usage.

Before the above requirement was imposed, one pharmaceutical firm conducted a survey of prevalence of psychoneurotic conditions for a thirty-day period through inquiry from a sample of physicians. From this survey, it was found that the number of cases of psychoneurotic conditions who consulted physicians in the 30-day period totalled 73,058 for the whole Philippines. Computed on the estimated population of the Philippines (38 million), this would mean an estimated prevalence rate of 2,392.14 per 100,000 population.

In the same survey, 30.25% of the total cases were psychosomatic disorders. The rest were a mixture of either emotional disorders, as diagnosed by the general practitioner and other non-psychiatrists. The experience of most psychiatrists who come to see these patients is that the referring doctor, sensing some underlying psychological problem, prescribes a tension-relieving drug and sends the patient on to a psychiatrist. It is not at all uncommon to have such a patient report to the psychiatrist that he has tried a variety of the minor tranquilizers.

Psychiatrists are of course the principal prescribers of psychotropic drugs. For the malignant, usually hospitalized case, the favourite seems to be still the phenothiazines, particularly Thioriela-zine. An anti-Parkinsonian drug (Artane or Cagentin) is given together with the Phenothiazines. Of the minor tranquilizers, Librium and Valium, with Tensinyl a close second, appear to be the most widely used. Of the anti-depressants, there seems to be no clear trend as to which is the most widely used, although Tofranil appears to have a slight edge. It seems that each psychiatrist has his individual preference as far as anti-depressants go.

Patients and their families accept the use of tranquilizers (major and minor) fairly well. Only the side effects (dizziness, dryness of mouth) are bothersome. These preparations also tend to be somewhat more expensive and resistance by the patient to using them makes the family hesitate before buying them.

SINGAPORE

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INTRODUCTION

Prior to the advent of psychotropic drugs, the main medications used in Woodbridge Hospital were paraldehyde, barbiturates and morphia. About 1954, reserpine was simultaneously introduced with chlorpromazine. After a short period, reserpine was discontinued because of its slow action and its tendency to cause depression. Chlorpromazine was first used in Woodbridge Hospital in the preparation "Injection Largactil" in May 1954. The following month, Largactil tablets were introduced. Since then, chlorpromazine has become one of the standard psychotropic drugs in the hospital. A large number of other psychotropic drugs had been tried out from time to time but with a few exceptions, their use had not been sustained.

Table I

Tranquillizers and Anti-depressants

Drug	Date first used in Woodbridge Hospital
Inj. chlorpromazine	May 1954
Tab. chlorpromazine	June 1954
Tab. isocarboxazid	June 1960
Tab. prochlorperazine	July 1960
Tab. promazine	August 1960
Tab. thioridazine	November 1960
Tab. chlordiazepoxide	May 1961
Tab. trifluoperazine	April 1963
Tab. imipramine	April 1964
Tab. amitriptyline	November 1965
Tab. diazepam	December 1965
Tab. pericyazine	May 1966
Tab. haloperidol	May 1966
Cap. nortriptyline	August 1967

The use of psychotropic drugs in Singapore will be discussed under the following headings:

(i) Major tranquillizers
(ii) Minor tranquillizers
(iii) Anti-Depressants.

Table II

Major Tranquillizers

Drug	Consumption within Woodbridge Hospital per month
Tab. chlorpromazine	226,000 tablets
Inj. chlorpromazine	100 amps.
Tab. trifluoperazine	50,000 tablets
Tab. promazine	12,000 "
Tab. thioridazine	4,000 "
Tab. haloperidol	2,500 "
Tab.pericyazine	2,000 "

As can be seen from the above table, chlorpromazine is the most frequently used drug of this group, followed by trifluoperazine. Chlorpromazine is used mainly for psychotic patients who are excited, hyperactive, destructive and aggressive, and generally for patients suffering from Schizophrenia. The initial dosage is 100 mg. 3 times a day. The dosage is adjusted according to the response. The maximum dose ever used was 2,000 mg. a day. Chlorpromazine is not generally used for patients above the age of 60 for which promazine is used. Thioridazine is used for cases who develop hypersensitivity side effects of chlorpromazine (skin rashes, jaundice). Trifluoperazine is used mainly on withdrawn schizophrenics and for the suppression of delusions and auditory hallucinations. The standard dosage is 5 mg 3 times a day. Pericyazine is used mainly for young patients who exhibit "behaviour disorders" and Haloperidol is used when the patients show features of mania. At the moment, long-acting parental tranquillisers (fluophenazine) are being tried out and it is likely that they will be introduced as a standard drug in the near future.

In the Government out-patient psychiatric clinics, the pattern of usage of major tranquillisers is the same as that in Woodbridge Hospital. Among psychiatrists in private practice, the three drugs most commonly used are chlorpromazine, trifluoperazine, and thioridazine

Most of the better known major tranquillisers have been tried at Woodbridge Hospital at one time or another. The following are some of the major tranquillizers that have been tried out at Woodbridge Hospital, but whose use had not been sustained. Stemetil, (prochlorperazine); Trilafon, (perphenazine); Majeptil, (thioproperazine); Veractil, (methotrinaeprazine), Pacatal, (pecazine). Notensil (acepromazine), Anatensol, (fluphenazine).

At present the following drugs are being used on a trial basis: Triperidol (trifluperidol), Orap (primozide), Leponex (clopazine), and Modecate, (fluphenazine decanoate), Navane (thiothixene).

Minor tranquillisers

Minor tranquillisers are not used in large quantities for the treatment of in-patients of Woodbridge Hospital except that diazepam 10 mg. o.n. is frequently prescribed for patients requiring a hypnotic. This accounts for the large quantity of diazepam consumption per month as shown in Table III below:

Table III

Drug	Consumption per month (1972)
Diazepam	22,000 (5–10 mg) tablets
Chlordiazepoxide	4,000 (5–10 mg) tablets

In the psychiatric out-patient clinics, the minor tranquillisers are used much more frequently and the main drugs are chlordiazepoxide and diazepam. Among the less commonly used minor tranquillisers are Serax (oxazepam), Ativan (lorazepam), Nobrium. Among the private psychiatrists, diazepam is the most frequently prescribed drug.

Table IV

Antidepressants

Drug	Consumption per month (1972)
amitriptyline	9,000 tablets
imipramine	1,500 "
isocarboxazide	200 "
nortriptyline	100 "

The above table reflects the usage on antidepressants in Woodbridge Hospital. The first antidepressant drug introduced was Marplan (isocarboxazide) in 1960. It was superseded by imipramine in 1964 because of the possibility of serious side effects of MAOI. At present, amitriptyline is the most common antidepressant drug used in the hospital and the standard dosage is 25 mg. 3 times a day. In the private sector, the MAOI is rarely used. The 4 most common drugs used are amitritpyline, imipramine, trimipramine and nortriptyline.

Psychotropic Medication in General Practice

Although most of the better known psychotropic drugs are available in Singapore, the General Practitioners tend to rely on the more established, drugs. In a survey by TSOI and CHIA (1972), two-thirds of the doctors used Stelazine, Largactil, Stemetil, Melleril and Sparine for the treatment of Schizophrenia. 61% used tricyclic drugs and only 5% used MAOI (Marplan) for treating Depression. Most doctors used Librium and Valium for the treatment of Neurosis.

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SRI LANKA

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Since the last report in 1970, psychiatric facilities in the country have been increased by the establishing of more psychiatric units in general hospitals. Table 1 shows the number of patients admitted to psychiatric in-patient facilities and the number of consultations given at out-patient psychiatric clinics during the years 1954 – 71. It will be observed that there has been an increase

of 76% in admissions and 35.3% in out-patient consultations, during the 6 year period 1965 – 71. This has necessitated the use of increasing quantities of psychotropic drugs. Table 2 shows the issue of chlorpromazine and trifluoperazine – the two most commonly used drugs in government hospitals – in the years 1969–72. It will be seen that in these three years, the issue of chlorpromazine has increased by 270% and trifluoperazine by 227%.

This increase in the demand for drugs has not only been limited to psychotropic drugs. The use of drugs in the government hospitals as well as in the private sector has risen steeply in the past few years. In view of this, the Government with the aim of conserving its foreign exchange resources, has established a State Pharmaceutical Corporation, in which is vested the monopoly of the import of all drugs and the raw material for the manufacture of drugs. To achieve its objective of providing drugs at the cheapest cost, it is the avowed policy of the Pharmaceutical Corporation to limit drug identity to generic names.

This has led to a controversy in pharmaceutical and medical circles on the question of reliability of branded products versus non-branded products. The Pharmaceutical Corporation and the Pharmaceutical Manufacturers have taken extreme positions in this controversy. The medical profession, as represented by the Ceylon Medical Association, has taken an intermediate position (Editorial, 1972). It has pointed out that on account of differences in bio-availability, chemical equivalence does not assure clinical equality. It has therefore suggested a compromise solution, whereby in cases of drugs where therapeutic non-equivalence is suspected, products from reputed manufacturers are made available to the medical profession.

Table 1

Number of patients admitted and number of out-patient consultations 1954 – 72

Year	Admissions	O–P Consultations
1954–55	2,692	18,720
1959–60	14,057	35,577
1964–65	11,527	36,126
1971–72	20,336	163,704

Table 2

Issue of Chlorpromazine and Trifluoperazine to State Hospitals during 1969 – 1972

Drug	1969–70	1970–71	1971–72
Chlorpromazine	132.5 kg.	416.7 kg.	491.9 kg.
Trifluoperazine	11.1 kg.	20.2 kg.	36.4 kg.

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TAIWAN

By CHU-CHANG CHEN

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As Dr. Ming-tso Tsuang presented in detail the history of psychotropic medication in Taiwan in the First Regional Seminar on Psychotropic Medication held in Djakarta three years ago, I shall not describe this over again. This present report has been prepared with the cooperation of Dr. Min-min Tsuang who is a younger brother of Dr. Ming-tso Tsuang and is also a participant

in this Seminar.

In this report, I shall concentrate on the problem of how we apply psychotropic drugs in our daily clinical practice. So far as neuroleptics are concerned, we prescribe these drugs as one part of integrated therapeutic planning, and consider their efficacy in the total scheme of psychiatric treatment. If patients show mild psychotic symptoms, there is no doubt that out-patient treatment is advisable as the first treatment of choice. But even if patients show overt psychotic symptoms and have some financial difficulty, we still advise out-patient treatment. Thioridazine (Melleril) can be prescribed, because this drug shows few side effects and a relative absence of extrapyramidal symptoms (EPS)- in comparison with other neuroleptics. If patients experience delusions of persecution or lack of insight and refuse to take medicine, butyrophenone (Haloperidol) is administered in a solution which can be mixed with water, tea, or soup. Our hope is that these patients will accept other more adequate medication as their mental conditions gradually improve. Before a definite improvement takes place, they may suffer from EPS which gives the patient's family a good reason to place the patient on in-patient care for more intensive psychiatric treatment. If patients are cooperative in taking medicine on an out-patient basis, anti-Parkinson's medication can be given to prevent occurrence of EPS, which is quite intolerable for patients and induces some anxiety in their family. This can be done at the beginning of the out-patient treatment before providing larger doses of neuroleptics. If psychotic symptoms cannot be improved at all in a few weeks of out-patient treatment, in-patient treatment should be recommended in order to increase the dosage of medication, or add other drugs or electric convulsive treatment to intensify somatic therapy. When patients are very disturbed, dibenzothiazepine (Etumine) seems to be more effective in calming them down than chlorpromazine (Wintermin). If patients are inactive and withdrawn, trifluoperazine (Fluzine) is given to motivate them to take part in various kinds of ward activities because its relatively less sedative effect may not interfere with their initiative. When a dosage of medication is established, the frequency of medication can be cut down by increasing the amount of a single dose. Thus this allows a reduction in the amount of time nurses spend on drug distribution which can be utilized in a more extensive psychotherapeutic approach. Drugs with more sedative effect may be given at night, and the ones with less sedative effect may be administered during the day. This arrangement enables patients to participate actively in occupational and recreational therapies during the day-time. Injections of chlorpromazine, dibenzothiazepine, or butyrophenones will promote drug effect quickly to facilitate ward management, especially in an open ward, which can also contribute to development of melieu therapy. It is not necessary to give anti-Parkinson's medication at the initial stage of in-patient treatment before an appearance of actual drug effects can be observed. In order to diminish some troublesome procedure in drug-taking during an aftercare period, fluphenazine (Anatensol) in oil preparation is injected intramuscularly, because this single shot will reveal prolonged effects for about two weeks. Since patients are able to purchase medicines such as psychotropic drugs without a physician's prescription in Taiwan, patients on long-term treatment gradually become familiar with neuroleptics and obtain medicines by themselves without consulting psychiatric out-patient clinics. This practice saves them time and money. Patients who have financial problems, and have to take drugs for a long period of time, try to surmount their troubles by taking the cheapest way out, which does more harm than good. This kind of self-medication cannot be avoided, because a social medical insurance system has not been well-established in Taiwan. Unless a community mental-health programme is organized for psychiatric rehabilitation, this phenomenon cannot be improved in the near future.

Of the anti-depressants, imipramine (Tofranil) seems to be more effective for retarded depression and amitriptyline (Laroxyl, Tryptanol) for agitated depressions. Both drugs are generally more expensive than other psychotropic drugs. These medications become effective only after being administered continuously for more than two weeks. Moreover, they aggravate dryness of mouth and constipation. Therefore, we have to build up some sort of doctor-patient relationship and explain the treatment course of anti-depressants before we can start to give them these drugs. We do this in order to avoid any chance for discontinuation of treatment with depressive patients.

Chlordiazepoxide (Librium) and Diazepam (Valium) are the most widely used anxiolytics in Taiwan, while prochlorperazine (Novamin), one of the neuroleptics, is applied for relieving neurotic somatic complaints. A general trend of believing in the effects of herbs, especially for the treatment

of so-called "neurasthenia," still prevails in Taiwan. When anxiolytics are given to lower-class patients, we may tell them that these are effective drugs for stabilizing a nervous activity. This explanation is not psychologically oriented but tries to meet with the needs of the general public in that they want to get medication rather than to receive psychotherapy. Most patients feel that neurotic symptoms cannot be cured only by talking with a psychiatrist. Mental health education may modify the public concept of the mechanism of neurotic disorders and should be promoted by the team work of mental health personnel. However, these educational programmes will need our long-term consistent efforts.

Recently, we have been testing an effect of thiothixine (Navane) as an antipsychotic drug, and also doxepine hydrochloride (Sinequan) for the treatment of anxiety and depression.

We have not carried out any systematic psychopharmacological research during the recent years because of a shortage of staff members in our hospitals. However, we are planning to investigate effects of lithium carbonate in treatment of recurrent manic disorder or bipolar effective psychoses.

As one of the participants, in this seminar, I propose that we get together to design a workable research programme to compare the efficacy of different drugs in varied socio-cultural backgrounds. Since the sponsor of this Seminar is the Roche Far East Research Foundation, we could use one of their new drugs as a starting point to carry out this very needed international collaboration in the field of psychopharmacology. I hope that the Roche Foundation will consider this possibility and undertake this very meaningful study as a side product of this Seminar. It is my hope that this cooperative work will be carried out and reported in the next Seminar on Psychotropic Medication.

THAILAND

By PRASOP RATANAKORN

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Psychotropic drugs have gradually been brought to treat psychiatric patients in Thailand soon after the introduction of the phenothiazine chlorpromazine in 1952 and have increasingly been accepted as a method of psychiatric treatment among Thai psychiatrists. Since 1967, Thai psychiatry, introduced by the Division of Mental Health Services, has been moved to a new era, of Community Psychiatry, in order to cope with the rapidly increasing need for psychiatric services; psychotropic drugs have become a far more important method in treating psychiatric patients. They are used not only by most psychiatrists, but a fairly large number of physicians in other fields of medicine also administer them in conjunction with other medications.

The method of drug administration may vary among psychiatrists in different types of services and hospitals. One of the most preferable methods used in psychiatric hospitals is to combine an anxiolytic drug and an anti-depressant or a neuroleptic drug and an anti-depressant or even between two kinds of neuroleptic drugs which have different effects. This is for the purposes of reducing dosage and toxicities of each drug and obtaining a better therapeutic effect.

Almost all kinds of psychotropic medication are available inThailand. Most of them are from Western Europe and the United States. The use of long-acting phenothiazines such as fluphenazine enanthate or even fluphenazine decanoate has currently become more popular and it tends to play a more important role in the future because its long action can cut down the patients' boring routine of taking medication.

Anxiolytic drugs and anti-depressants are widely used by general practitioners and physicians in other specialities. But the outcome of the drug

treatment is not as effective as it is used by psychiatrists or psychiatrically-oriented physicians. This may be that the psychiatric diagnosis cannot be simply made by only physical examination, or psychiatric disorders cannot be treated by giving medications alone, and if the physicians are not well acquainted with indications, contra indications and side-effects of the drugs, the dosage prescribed may not be high enough to reach its therapeutic level or the drug chosen may not be in the right group. For example, some of them may use anxiolytic drugs to treat a psychotic patient, or some of them may not recognize depressive symptoms of the patient; therefore the drugs given will have no anti-depressants included, and so on.

Most psychiatric patients in Thailand accept psychotropic medication unless they are too sick to do so. However, no matter how good the psychotropic drugs are, the know-how in giving them is still of great therapeutic value for the psychiatric patients.

Psychotropic medication both major and minor groups have also been used widely in the treatment of drug addiction.

UNITED KINGDOM

By W. LINFORD REES

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Psychotropic drugs constitute the largest single group of drugs prescribed under the National Health Service in terms of both numbers of prescriptions and cost.

In 1971, 47.8 million prescriptions for psychotropic drugs were dispensed under the National Health Service in hospitals in England. General Practitioners issued prescriptions for 3,000 million tablets or capsules i.e. about 60 million a week. During the decade up to 1971 there was a 48.8% increase in prescribing for psychotropic drugs.

In 1971 prescribing for psychotropic drugs was subdivided as follows:

	M_2
Hypnotics	41%
Tranquilisers	38%
Antidepressants	5%
Stimulants and appetite suppressants	6%

During the preceding quinquerium 1965–1970 the trends were:

	M_2
Barbiturate hypnotics – decrease of	32%
Stimulants and anorectics – decrease of	43%
Non barbiturate hypnotics – increase of	166%
Tranquillisers – increase of	70%
Antidepressants – increase of	103%

The increase in prescriptions for all psychotropic drugs during this period totalled 8.1 million. In a survey of general practice prescribing over a period of one year, it was found that one in eight patients were prescribed psychotropic drugs. Twice as many women as men were prescribed psychotropic drugs and in both sexes, the number prescribed increased with age.

FACTORS INFLUENCING PSYCHOTROPIC DRUG PRESCRIBING AND PATIENT ACCEPTANCE OF DRUGS

1. **The Doctor**
   - (a) The most important factor is the introduction during the past two decades of efficacious drugs for treating depressive illnesses schizophrenia, anxiety states and other psychiatric disorders.
   - (b) Choice of a particular psychotropic drug by the doctor will depend on his personal experience with the drug, recommendations from consultants, fashion trends in prescribing and sales promotion.
2. **The Patient**
   - (a) Sanction and approval of certain

classes of drugs by Society at different times influence use and abuse of drugs. E.g. in the 1930's it was barbiturates; in 1950's pep pills, late 1950's and early 1960's tranquillisers and antidepressant drugs and in the 1970's combined preparation of anti-anxiety and antidepressant drugs.

(b) Prescribing fashions by doctors influence patient's expectations and demands.

3. **Pharmaceutical Industries**

It is mainly the result of research by pharmaceutical industries and the large amount of new psychotropic drugs discovered and developed. Pharmaceutical industries promote their sales by advertising, visits to doctors by representatives and by the work they do generally in public relations.

Cost of Drugs in United Kingdom

The total cost of drugs in the National Health Service for 1971 was £163 million; £140 million were earned by exports and £96 million by sale of household remedies. The total cost amounts to 0.5% of the National Income. Pharmaceutical industries spend £22 million a year on research.

In the United Kingdom, pharmaceutical industries spend 16% of their gross income in sales promotion which is less than the U.S.A. figure of 20%.

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VIETNAM

By TRINH VAN LANG

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The Psychiatric Hospital of Bienhoa, a unique big institution in Vietnam was built in 1918. Originally designed for 1,200 patients, it is now over-crowded with over 2,200. Before 1960, psychiatrists had little means, at their disposal, in their therapeutic arsenal, therefore custodial care and electric shock treatment were the only method for control of the behaviour of the patients.

With the introduction of Phenothiazines in 1962, a certain improvement in the atmosphere of the hospital was noted. An open-door system could be achieved for some wards. An occupational therapy centre and an out-patient clinic created shortly after, were the proof of the effectiveness of drug therapy.

Concerning the status of psychotropic medication, we would like to specify some particular problems:

1. Major tranquillizers often are available to control the over-active, to reduce and to reduce delusions and hallucinations, for example, with

   100–400 mg of Chlorpromazine per day (Largactil)
   200–600 mg of Thioridazine per day (Melleril)
   12–16 mg of Perphenazine per day (Trilafon)
   15–30 mg of Prochlorperazine per day (Compazine)
   10–30 mg of Trifluoperazine per day (Stelazine)
   3–10 mg of Fluphenazine per day (Moditen-Anatensol)
   3–10 mg of Haloperidol per day (Senarace)

   Side effects of the extra-pyramidal type are infrequent because moderate dosage is used. They are overcome by Trihexyphenidyle (Artane). Three cases of jaundice with chlorpromazine are reported.

2. Some acute psychotic patients need a high dosage of phenothiazines, thanks to which they can be discharged from the hospita

after a few weeks and resume their normal life. For the chronic patients, drug therapy helps to calm down the exuberance of a paranoid state or to stimulate the inhibited patients. With those who have persecutory delusions and consider the drug as an aggression to their personality, the usage of long-acting drug associated with brief psychotherapy and milieu therapy seems to be necessary.

3. The antidepressant agents such as Imipramine (Tofranil) or Amitryptiline (Elavil or Laroxyl) are used often against neurotic or reactive depression in association with anxiolytic drugs like Benzodiazepines (Librium, Valium, Carbamate, Meprobamate) to subdue anxiety and insomnia usually frequent in the depressive syndromes.
4. The minor tranquillizers occupy an important position in general private practice as well as in the out-patient clinics. More than half of the townsfolk know the name of the modern minor tranquillizers. We would like to emphasize the stressful situation as an essential factor of many autonomic disturbances. Most of the patients somatize their anxiety; cardio-vascular and other bodily complaints are highly frequent. Chlordiazepoxide (Librium) and Diazepam (Valium) prove to be the drugs of choice in freeing these patients from their distressing complaints. However, some of the neurotic patients do not react favourably to the drug because of this paradoxal phenomenon: the anxiety, instead of being reduced, increases considerably. They consider the drug as an external danger that threatens their ego and weakens their mechanism of defense. This state of tension calls forth an intensive psychotherapy.

In conclusion, we believe that psychotropic medicine becomes effective only in conjunction with other therapies (occupational therapy and psychotherapy) in an institutional as well as in ambulatory treatment setting. Lastly, we want to call your attention upon the war situation of our country, which makes us difficult to get regular medical supply. We must use any appropriate medicine available. So we cannot give accurate figures about the usage of psychotropic drugs in our country.

MALAYSIA

By M. SUBRAMANIAM

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Psychiatric treatment became a practical possibility in this country with the introduction of Psychotropic agents, a little more than ten years ago. It has been said with equal enthusiasm, that the freeing of our patients from traditional custodial functions accounted for most of the improvement, and physical treatment was merely a stimulant to a more liberal attitude towards freedom and therapy of patients.

However, those of us, who have worked in the pre-physical treatment days will agree with me that without modern physical treatment, custodial care, however humane, was absolutely necessary for many patients especially psychotics. The actual reduction of mental hospital size is dependent on many factors, most of them depending on decisions outside clinical authority and remarkably linked to what are thought to be priorities of medicine.

However the psychotropic drugs did demonstrate in a practical way in Malaysia, that out-patient department and community therapy was possible Psychiatric Units were opened up in several of the larger general hospitals.

We must understand our greater dependency on physical treatments than in more developed countries, because linguistic problems posed imponderables in the use of many methods of psychotherapy and related treatments. This great

dependency on psychotropic medication has of course produced some dangers in practice.

1) The individual treatment of the patient is generalised and this is not good medicine. It is naïve to think we can cure a Schizophrenic with phenothiazines alone. But what can 10 psychiatrists with 10 million people at risk do?
2) The long term risks of psychotropic agents become blurred in our heavy case loads, and are we senselessly maintaining therapy after its effective value has disappeared? Again a rider must be attached. I find that stoppage of medication often produces a relapse or with antidepressants, a withdrawl syndrome.

This is an experience based on thousands of patients I have seen after 14 years of psychiatry in this country; more often than not, I believe other factors act in combination to produce a relapse. However no extensive research has been done. Such research should be made and the results made known to us.

I have mainly emphasised the great value of psychotropic agents in Malaysia. I have also posed some nagging doubts in my mind which reflects real anxiety on my part. I know that most of the distinguished speakers will tell us about their clinical trials but what will be missing will be the great question 'how long do we expose patients to drugs'. In fact, I believe that this cannot be answered by the very few psychiatrists during the bulk of the work in down to earth units of the Government Medical Service due to lack of time.

Whether the situation will improve at the sites where most people are treated is in the ultimate analysis, an administrative decision, depending on whether society thinks it is a priority. I am told our division of mental health is going to tackle this situation. These problems are not peculiar to Malaysia. Yet because of this, the temptation to centralise will always be a force to reckon with.

"DRUGS AND BEHAVIOUR"

By I. PILOWSKI

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In this paper, I would like to discuss a particular aspect of the relationship between drug treatment and individual behaviour. My purpose is to discuss some of the findings related to the placebo response and the implications of the findings for drug therapy.

It has long been known, of course, that the placebo response plays an extremely important role in an individual's reaction to a particular drug. This was very well shown in a study by Park and Covi (1965) who carried out an investigation in which placebos were given to a series of 15 neurotic patients newly admitted to the out-patients department of the Henry Phipps Psychiatric Clinic. This is a service for adolescents and adults who cannot afford private care. The mean age of the sample was 35 years, with an age range from 19 to 67, with years only one patient over 50 years.

Each patient was seen on two occasions. On the first visit, the patient was fully evaluated and a placebo was prescribed. On the second visit, which took place one week later, two separate interviews were held to assess change and decide on further treatment.

At the initial visit, the patient was prescribed a placebo in a standard way. The psychiatrists told the patient that his problem had been discussed and it was decided that the possibility for further treatment would be made one week later. In the meantime, he was told that he would be given a pill which might help. He was told that many people were helped by, what was called, a sugar pill and that this was "a pill with no medicine in it at all". He was told "I think this pill will help you as it has helped so many others. Are you willing to try this pill?" The patient was then given a supply of the placebo which consisted of pink capsules and told to take one three times a day at each meal. He was also told to discontinue any other medication which he might have been taking.

The findings for this study were extremely interesting. In the first place it was found that neurotic out-patients were willing to take a placebo even when the inert content was disclosed. Fourteen of the fifteen patients took the pills and returned for the second appointment. All of the fourteen reported improvement, and there was, also, overall marked improvement according to the doctor and patient ratings on several measures. Of the fourteen patients, only eight stated at the second interview that they believed the pills were placebos and, of these, only three absolutely certain that this was the case. Six of the patients thought the pills contained drugs and two were absolutely certain that this was so.

These researchers concluded that "the formulation of placebo effect as a response to the belief active medication is prescribed involved too narrow a view. A more comprehensive assumption would be that the basic requirement is general belief that a situation defined this treatment, whatever its specific details."

This study is a most interesting and important one since it forces to acknowledge that the placebo effect is not a unitary phenomenon and is, in fact, a rather complex one.

It is also interesting to consider the effect of expectations from a placebo in psychiatrists and nursing staff. Loranger et al., (1961) gave placebos to 120 hospitalized psychiatrict patients Patients, psychiatrists and nurses were told that two drugs were being evaluated, one of which was a new tranquillizer and the other a new energizer. In actual fact, both drugs were inert. Uncontrolled and subjective methods of evaluation indicated that from 53 to 80% of the patients benefited from the new "drugs". When matched control groups and objective rating scales were used, it was found that a temporary improvement was caused by the tranquillizer but not by the "energizer". This study, the authors felt, "dramatically illustrates the dubious value of studies which do not employ double-blind and other controlled procedures". In addition to this, of course, it also indicated that the precise nature of the placebo response.

There is, of course, considerable interest in understanding the personality correlates of the placebo response. One study aimed at elucidating this question was carried but by Gelfand et al., (1965) These workers noted that a number of writers had suggested that the placebo phenomenon

could be viewed as one example of the social influence or persuasion process and that, therefore, one might expect that personality variables which correlated with general persuasability should also be related to placebo responsivity. One variable found to be negatively related to persuasability is self-esteem and it was, therefore, also hypothesized that low self-esteem would be associated with high placebo responsivity. Other workers found that placebo reactors were more likely to give socially desirable responses in an interview situation and that they were more likely to identify themselves as regular churchgoers and interested in church affairs. It has certainly been suggested by a number of writers that faith is an important element in placebo responsivity. Against this background, Gelfand et al. studied 25 paid volunteer female college students, aged 18 to 30. The placebo testing procedure involved the induction of pain using an ultra-sonic therapy unit. Subjects were told that the apparatus would cause warmth to the ball of the thumb at first, followed by a feeling of pain. They were told to indicate when the warmth turned to pain and then to remove their thumb from the apparatus when the pain became too uncomfortable. There were four trials before the inert substance was taken, followed by another three trials. The subjects were given a self-esteem test and a social desirability questionnaire. In addition, they filled in a religious belief-behaviour questionnaire after the experiment.

The result of this study indicated a positive relationship between placebo responsivity and religious behaviour and belief, but no relationship between any of the self-esteem measures and placebo responsivity. A significant finding was that religiosity and social desirability scores were related to the pain tolerance but not to the pain threshold placebo measure. It was felt that this supported previous work which indicated that pain threshold is more highly loaded with physiological and with psychological components, whereas pain tolerance is more highly loaded with psychological than physiological components.

Another study of considerable interest to the question of personality variables in the placebo response involved the investigation of the relationship between this response and suggestibility and hypnotisability. This study was carried out by Evans who studied two groups, each of 12 male volunteer undergraduates who were selected from the upper and lower 5% of the distribution of susceptability to hypnosis. Definite changes in objective and subjective performance were found following the ingestion of placebo in a modified double-blind study. The placebo response did not discriminate between subjects who were susceptible or insusceptible to hypnosis and there were no strong relationships between measures of placebo response and measures of suggestibility. Thus, the suggested relationships between the placebo response and in the suggestibility of hypnotic susceptibility were not supported.

The studies which have been described make us conscious of the powerful effect of the doctor/patient relationship and the need to be aware of placebo factors in the course of pharmacologic treatment. Not only has it been shown that patients respond to inert substances but Vinar even described a patient who had become drug dependent on a placebo. Schapira showed that the colour of tablets played a significant role in the patient's response. They found that symptoms of anxiety were most improved with green tablets, whereas depressive symptoms responded best to yellow tablets. These colour preferences did not reach levels of statistical significance, except in the case of phobias as rated by the physicians' assessment.

Attention should also be drawn to the fact that not all placebo responses are positive ones. Lesse pointed out that negative placebo responses can occur, particularly in patients who had previous experience of similar drugs or have been associated with others who have taken these drugs and have reported untoward effects.

In conclusion, one may say that the placebo response is a much neglected aspect of drug therapy. Its complete elimination from every day treatment is not only impossible, but probably also undesirable. What is required is a proper understanding of the nature of the placebo response in order to make the better use of the placebo effect possible. Forrer has pointed out that "the placebo effect is a psychosomatic resultant of psychological processes which have become unconsciously attached to therapeutic endeavours. Symbolising as it does to the patient the gratification of infantile needs, the placebo can serve to relieve functional components of discomfort and disability. Placebos should be acknowledged as a potent force of our therapeutic armamentarium."

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INTRODUCTION

Because the pathophysiology of mental illness has not been made clear yet, psychotropic drugs are studied mainly for their possible therapeutic effects on the symptom and behaviour of men, especially patients. The predictive value of animal study is still uncertain. However, recent advances in the study of animal psychology and ecology may bring us useful information on the presumed effects and safety of new drugs. These studies also may contribute to the drug trial in men. Furthermore, if unexpected events should happen during the clinical trial, it would be necessary to "feed back" to the animal studies to clarify the cause. For this reason, the basic knowledge of clinical psychiatrists on the effects of psychotropic drugs on animal behaviour will be more and more required for the initial clinical trial of the safety and effects of new drugs.

For the interpretation of animal studies, the following two types of classification are tentatively made, based on the ecological and psychological aspects of behaviour.

1. Drug action on individual or group behaviour.
2. Drug action on conditioned or non-conditioned behaviour.

According to this classification, some known effects of psychotropic drugs will be mentioned.

1. *Individual and Group Behaviour*

Most laboratory experiments were performed in isolated environment which differed sometimes from the usual living conditions of animals. Recently, Utena studied the effects of amphetamines by chronic administration to a group of Japanese monkeys and observed that the effects of drug on the intoxication symptoms varied according to the rank of each monkey in the colony. Furthermore, it is well known that the acute toxicity of amphetamine in isolated mice is ten times lower than in grouped mice. The relation between the two different species of animals, such as cats and mice, is common knowledge, and administration of a tranquillizer to the predatory cat suppresses its natural rat-killing behaviour. Recently, Ueki et al. studied the mouse killing behaviour (muricide) of rats after the administration of T.H.C. (active substance of marihuana). The aggressive behaviour of a cynomologus monkey towards the experimentor was used to test the taming effect of minor tranquillizers which reduced aggression without impeding the spontaneous psychomotor activity.

2. *Conditioned and Non-conditioned Behaviour*

When we interpret the behavioural change in animals induced by drugs, the nature of basic behaviour should be at first analyzed. For this purpose, the classification into two different natures of behaviour, non-conditioned and conditioned, seems to be one of the most simple and convenient ways.

a) *Non-conditioned behaviour*

This included natural, instinctive behaviour acquired through heredity, and artificially induced (by men) behaviour. The pathologi-

cal criterion on normality and abnormality is the same as human clinical psychology.

i) *Normal behaviour*

The C.N.S. stimulants and depressants influence the spontaneous motor activity of animals when administered in certain dosages. However, it is almost impossible to interpret the action of drugs by phenomena only, because amphetamines and LSD may inhibit the ambulation of animals. In this respect, the after-effect of drugs should be carefully evaluated. Very often, so-called hang-over or rebound phenomena may be observed in the case of hypnotics, analgesics and alcohol after the disappearance of the drugs from the body.

The effects of psychotropic drugs on the feeding behaviour is well known. Amphetamine and related psychostimulants reduce appetite, and chlordiazepoxide increases the food intake and body weight of animals when administered continuously. The sedative effect and polyphagia in animals after the administration of minor tranquillizers seem to be interesting in connection with specific pathology of Klein-Levin's syndrome (Hypersomnia-bulimia, i.e. periodic somnolence and morbid hunger).

The effects of psychotropic drugs on sexual behaviour were reported several times in human beings. We have not yet had enough information on whether these effects are direct or indirect. Most drugs may be influential on libido and/or potency in human sexual behaviour. Recently, there have been recurrent observations on increased sexual activity after L-dopa treatment in Parkinsonian patients. The sexual behaviour and brain monoamine were studied recently in animals. Parachlorphenylalanine (PCPA), which is a specific inhibitor of 5HT synthesis without affection on catecholamine, produces compulsive sexual activity in male rats, cats and dogs.

The homosexual mounting behaviour in rats can also be induced by the administration of L-dopa with peripherally acting decarboxylase inhibitor Ro4-4602. PCPA not only induces homosexual mounting behaviour, but markedly increases the percentage of male animals exhibiting copulatory behaviour with females in estrus. The effect of PCPA is not only prevented by castration but strikingly potentiated by teststerone (Tagliamonte 1972)

The effect of psychotropic drugs on the sleep cycle, especially on the slow and paradoxical sleep, was reported very frequently in animals (Jouvet et al.). In this connection, the rebound phenomena of paradoxical sleep suppressed while the drug is effective were discussed in connection with hang-over phenomena and possible relation with drug dependency. However, there are still no conclusive findings.

ii) *Abnormal and pathological behaviour*

It is still almost impossible to produce or obtain any psychopathological phenomenon in animals which is similar to human beings. However, many efforts have been made to examine the drug effects on the abnormal behaviour of animals for the purpose of obtaining more specific and sensitive tests to be used in the screening of new drugs.

Some examples are cited as follows:

–Hereditary characteristics abnormal behaviour.

There are not so many reports on the findings of pathological phenomena in the same species of animals, i.e. hereditary neuro-psychiatric diseases. The audiogenic epilepsia in mice and the dancing mice (manic psychomotor excitation) will be one of the examples. The discussion on the existence of spontaneous schizophrenia-like state in monkeys is of permanent interest among the specialists, but most of all the hypothetic interpretation.

The species' specific abnormal behaviour (mainly interpreted by men) will be observed quite frequently. The photic epilepsy in African baboons was used for the screening of new anticonvulsants. The taming effects of benzodiazepine derivatives on the aggressive cynomologus monkeys are very well known.

– Chemically induced pathological behaviour

The most difficult problem is to produce permanent abnormal behaviour, even after the direct effect of chemical substance disappears.

Nakajima H. and Thuillier reported in

1957 on the dancing-mice produced by short-term administrations of iminodipropionitril. The symptoms were similar to hereditary dancing-mice. This phenomenon lasted during the whole life of the mice.

The effects of major and minor tranquillizers, hypnotics, hallucinogens and amphetamine on these mice were studied and classified according to the actions which corresponded well with the clinical classification of Delay.

Ueki reported the long lasting abnormal behaviour of rats in isolated condition (muricide and catalepsy) induced by short-range administration of T.H.C. and studied the action of different psychotropic drugs.

The considerable amount of research on abnormal behaviour produced while the drug is active has been reported.

Catalepsy induced by neuroleptics and bulbocapnine is well known and used for the screening of anti-depressants and anti-parkinsonism drugs.

– *Physically induced pathological behaviour*

The rats whose limbic systems (septal, olfactory and amygdaloid) are destroyed have been used frequently for the screening of tranquilizers. The external noxious stimuli may modify animal behaviour. The fighting behaviour of mice by foot electroshock has been used also for the screening of tranquillizers.

– *Abnormal behaviour induced by special situation*

Generally, when mice and rats living in groups are isolated individually for some time, the aggressive fighting behaviour to others will appear. This is used for the screening of tranquillizers.

b) *Conditioned behaviour*

Most integrated human behaviour is conditioned; but in the case of laboratory animals, the spontaneously conditioned behaviour does not always exist.

Therefore, the effects of drugs are studied in the following two directions.

– Effects on the formation of conditioning
For example:
  * Learning procedure
  * Drug intake behaviour (In this case, the drug is used as a kind of reward, i.e. reinforcement of conditioning).

– The effect on conditioned behaviour, especially in operant avoidance and escape.

The interpretation of the results obtained by animal conditioning experiments is sometimes different, especially on human conditioned behaviour formed in quite different procedures. Therefore, the analysis and interpretation of the data for clinical applications should be done extremely carefully.

CONCLUSION

The effect of psychotropic drugs on animal behaviour will supply useful and interesting information for the clinical evaluation of the safety and efficacy of drugs. However, it should be noticed that most of the results obtained in animals have only relative predictive value for human studies in the case of psychotropic drugs. Therefore, the needs of adequate and well-designed clinical studies should be more emphasized. In this regard, the comparative value to reference drugs (not only inactive control and positive control, but also negative control) will bring clinicians very useful suggestions for the application of drugs to human beings.

By ENG-SEONG, TAN

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In the last two decades, the introduction of psychotropic drugs which are pharmacologically potent and effective has changed the practice of psychiatry radically from what it used to be. It is

difficult I am sure, for the younger ones among us who have come into psychiatry during the era of psychotropic medication to imagine what the practice of psychiatry was like when, even at the best centres in the world, with the most eminent professors available and the best facilities at one's own disposition, all that psychiatrists had to offer was psychotherapy or long drawn-out psychoanalysis for neurotic disorders for patients who can afford the time and the expense, and institutional custodial care for the psychotics whose behaviour was socially unacceptable and therefore embarrassing to their relatives.

Modern Psychiatric Therapy

Although the millenium has not arrived yet when the aetiology of the major psychiatric disorders are known and radical cures are available most probably in the form of pharmacological substances, naturally occurring or synthetic, the options for therapy available to a young resident in psychiatry to offer his patients today is something that is vastly different from what they were twenty-five years ago when all one had to offer were electro-convulsive therapy, insulin shock-therapy and a couple of pharmacological compounds of dubious efficacy. By the same token, it is very difficult to imagine what the practice of psychiatry was like at the turn of the century. All one had to use on disturbed patients were the bromides and a few other sedatives. Of course there were the strait-jackets of leather or canvas and there was the padded-cell to fall back on in the last resort.

While taking a historical perspective, it is cogent to point out that the use of drugs to control the behaviour of human beings is not new to this part of the world. It is common knowledge that maidservants or *amahs* of this part of the world who were left with the charge of unruly offsprings of upper and upper middle class families often resorted to substances like opium to keep the exuberance of their young charges within bounds. But at the more therapeutic level, the Ayurverdic physicians of India have been using the leaves of Rauwolfia Serpentina for the treatment of mental disorders for several centuries now. The use of this substance in the management of psychiatric disorder was brought to the attention of the medical world by Dr. R. A. Hakim of Ahrnabad, India, when he presented a paper on this subject for which he was awarded a gold medal in 1953. Nathan S. Kline took this up and was able to demonstrate in a successful therapeutic trial on psychiatric patients in a state hospital in the United States. (Noyes & Kolb. 1958).

Social Changes

This wide availability of drugs in the last two decades, often referred to as the "pharmacological explosion" has influenced not only the behaviour but also the attitudes and life patterns of human beings both directly and indirectly. These drugs provide the relief, if not the cure for man's physical and psychiatric ills. The availability of the wide range of antibiotic drugs has completely changed the pattern of morbidity and mortality in many societies. This has many far-reaching sociological effects. The age structure of the population in the developed countries has changed significantly. People survive to an older age and therefore, the middle-aged and the elderly constitute a much larger proportion of the population than before, and social facilities and social institutions, therefore, have to be changed accordingly to cater for this sector of the population. The sexual behaviour and sexual mores of people in many societies have changed radically as a result of the availability of the oral contraceptives For young people in urbanised societies sexual activity now becomes a practical proposition without the threat of the possibility of an unwanted pregnancy. This has of course been equated with promiscuity and decried as decadence by moralists, but decadence or not, oral contraceptives provide an answer of sorts to the problem of over-population.

The Drug Dependent Society

With the whole array of pharmacological compounds available, indeed one can even say that there are several alternative drugs available for each particular purpose. The life of human beings, one gets the impression, become so dependent on the use of drugs. Working in a university community, in a situation where great emphasis is laid on the passing of examinations, one sees students near examination time taking tablets so that they can keep awake to study and then taking tablets to go to sleep, in an attempt to counteract the effect of the stimulant tablets taken earlier and then waking up by the alarm clock to take other tablets in order to be able to stay awake again at lectures the following morning. It is no wonder that many of these students become drug-dependent. Just as the trade name "Aspirin" has become a household word to people now in their forties and fifties for the whole range of ills, anything from a headache that results from a disagreement

with one's spouse through the fever and vigor of a urinary tract infection so also now, to people in their late teens and twenties, the trade names of "Librium" and "Valium" have become household words in their own right as agents for the relief of any distress ranging from anxiety about the outcome of one's application for a job to the dejection following a failure in an important examination. Indeed Carstairs (1969) says that "....everyone nowadays expects to be happy. Pills have come to be regarded as a means of doing away with everyday anxieties and pains....". Indeed modern man will be quite lost and unable to cope if he finds himself in a situation where these pharmacological compounds become unavailable. Even inactive compounds are used e.g. Deer Horn and Essence of Chicken.

The Drug Dilemma

In a way one cannot help pointing a finger at oneself, the physician, for this state of affairs. Very often, a family doctor in his busy practice with his long line of patients waiting outside his consulting room to be seen, finds it a much easier way out than taking a little bit more time to talk to his patients, to resort to the use of anxiolytic drugs to help to tide the patients over various crises. Indeed, doctors often feel that the prescription of a drug for the patient is mandatory when in fact lending a sympathetic ear to the patient's problem for half an hour might be more efficacious in helping him to cope with it. Smith, (1966) in a study of drugs prescribed for hospitalised patients found that an average of eight drugs are routinely prescribed for hospitalised patients without infections while those with infections could be prescribed as many as 42. But on the other hand, in the practice of psychiatry, one is very often confronted with a schizophrenic patient in a state of relapse and the evidence is very clear that the relapse has come about as a result of this patient neglecting to take his medication. Indeed the physician has very carefully steered a course between the Scylla of over-prescribing and Charybdis of not prescribing at all. Imlah (1970) states, "Every doctor has a list of patients who wants drugs but should not have them, and another list of those who need drugs but do not take them."

There is, of course, the other school of thought which is very wary of the use of drugs, particularly in the control of human behaviour. Szasz (1957) stated that use of tranquillisers in the treatment of disturbed psychotic patients is nothing more than using "chemical strait-jacket" rather than using a canvas or leather one. Huxley (1932) visualised in his "Brave New World" a society not very distant in time when the behaviour of the population can be controlled by the mass administration of various drugs through the water supply. This indeed is a frightening prospect which evokes rather paranoid fantasies of some of the population of every country to the extent that even the fluoridation of the water supply, a measure against dental caries in children, a fact for which there is strong scientific evidence to support, is regarded with suspicion and rejected in terms such as a measure in "compulsory medication". These are the very same people who have no compunction whatever to reach out for the bottles of Aspirins or Valium when they are in the least way distressed by any work problem they are faced with any day of the week. Such a controversy over the fluoridation of the water supply rages at this very moment in this country and every few weeks one sees a spate of letters from readers in the local newspapers on this subject arguing the issue despite repeated assurances from the authorities.

Which for what?

Going on to a personal level, one feels that while the availability of psychotropic drugs is a boon to the practice of psychiatry, one has to be aware on the other hand that the vast array of compounds that are being produced and being marketed leaves one with a problem of which drug to choose and for what condition. Indeed keeping up with the journals on the reports of drug trials alone is a major occupation in itself. Indeed, there is evidence to show that many physicians have given up on this and depend on the representatives of various drug firms who visit their offices ever so regularly to digest this information for them. (Wilson, 1963).

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"PSYCHIATRIC DRUGS AND THE GENERAL PRACTITIONER"

By I. PILOWSKI

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A widespread feeling exists that General Practitioners prescribe greater quantities of psychotropic drugs than patients actually require. In Australia, for example, the figures recently released indicate that minor tranquillizers are the commonest form of prescription written for patients. At the same time, doctors working in intensive care units in general hospitals, are extremely aware of the fact that depressed patients are prescribed large quantities of extremely dangerous drugs, as a result of their experience of the treatment of patients following suicide attempts. In this paper, I would like to consider some of the factors which influence the doctors' prescribing habits and some of the consequences of this behaviour.

General Practitioners are clearly individuals working under considerable pressure. The time which they are able to devote to individual patients is limited, and in this short encounter, they are expected to evaluate a patient's psychological, social and biological functioning. For this task they are often ill-prepared. For many years, medical schools have emphasized the biological aspects of medicine at the expense of the psychological, and as a result, the doctor emerges equipped only to evaluate biological dysfunction and to dispense non-psychological types of treatment.

Against this setting, we have a situation in which practically every patient seen by a General Practitioner suffers some form of emotional distress, and a substantial percentage suffer from conditions which are essentially psychological.

The factors which might result in unsatisfactory prescribing habits are fairly obvious in the case of certain General Practitioners. As indicated above, these habits may be due to poor training which, in turn, generate negative feelings towards patients with conditions which the doctor is ill-equipped to understand and treat. In the face of patients with psychological problems, the fully-trained doctor becomes anxious and defensive and may show his hostility to the patient overtly or covertly. In some cases, doctors, are quite out-spoken about their feelings, and may tell patients that they cannot believe that they have anything the matter with them. Others may not express this belief verbally, but indicate by their manner that the patient is unwanted and that he is being given a prescription essentially to terminate the interview.

The use of prescription writing as a means of terminating interviews is an extremely common and, perhaps, an understandable habit. There is no doubt that by the writing of a prescription the doctor wishes to indicate that he is not rejecting the patient but continues to be concerned for him and is attempting to alleviate his problems in some way. Too often, however, the patient is well aware that the tablets are not given with any sense of conviction and he feels rejected and misunderstood. It is not unusual, in fact, for the patient not to take the tablets at all.

In this regard, it is interesting that doctors often rationalize their need to prescribe tablets by saying that patients expect to be given something. That this is a rationalization, is supported by the fact that many patients coming to psychiatrists, complain that their doctors have given them tablets rather than explore their problems, and it has been quite obvious, in listening to such patients, that they were fully aware of the fact that the prescription of psychotropic agents was not the answer to their problems. This probably explains why such patients often neglect to take their tablets as directed.

The other side of the coin, as it were, is the tendency to under-prescribe in general practice. It is not uncommon to find that a patient has been prescribed psychotropic drugs over a long period of time, but in rather minimal doses. The psychiatrist working in a hospital setting, finds it surprising that such small quantities of an antidepressant or a tranquillizer could have been prescribed for the diagnosed condition, and has difficulty in understanding why the General Practitioner should expect this dosage to be of any help. It is interesting to reflect, on the reasons for prescribing such small doses. Clearly, one explanation may be, that the doctor fully realises that the patient does not have the sort of condition which might be expected to respond to the psychotropic agent, but rather than prescribe a completely inert substance, somehow assuages his feelings of guilt, by giving the patient a tablet which has at least

some minimal potency. A further possibility is that General Practitioners have become aware of troublesome side-effects when patients are given psychotropic agents in a community setting. It is a common observation that out-patients are far more likely to report side-effects when given antidepressants or tranquillizers when compared to in-patients. This probably explains the high drop-out rates from drug trials carried out with out-patients. Therefore, the General Practitioner's tendency to prescribe low doses may reflect an awareness of the ways in which these agents affect patients who are treated outside hospital while engaged in their normal occupations and activities. It is difficult to believe, however, that at these low doses, there may be some factor which results in effectiveness equivalent to higher doses given in the in-patient setting.

What then is the answer to the General Practitioner's dilemma? How is he to cope with the enormous numbers of patients coming to his surgery in the time which he has available? There is obviously no single solution. A step in the right direction would seem to be the trend towards General Practitioners working in group practices, supported by social workers and other community workers who are able to counsel and support patients experiencing substantial psychosocial stress. The General Practitioner himself, can improve the situation by sharpening his skills related to the assessment of psychosocial factors in all illnesses and his capacity to engage in crisis intervention activity when this is appropriate. Graduates emerging from medical schools now are clearly better equipped for this task than were the counterparts a decade or two ago. With the improvement of counselling skills in General Practitioners, and their enhanced capacity for working in crisis situations, I feel one can be optimistic about the future and predict that psychotropic drugs will be prescribed in the general practice situation with increased accuracy and appropriateness.

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The introduction of psychiatric drugs to the general practice of medicine is of particular importance to South-East Asian countries.

There is a shortage of trained psychiatrists everywhere, but this shortage is acutely felt in developing countries. No training programme will in the near future be able to turn out adequate numbers of psychiatrists, to meet the demand for trained workers. This situation is increasingly aggravated by (a) rapid social change with its concomitant increase in incidence of mental disorders and (b) the population explosion.

Seen in this context, we can conclude that the use of psychotropic drugs in general practice, which can be regarded as the integration of mental health principles in public health, is not only a feasibility, but a *necessity*.

The involvement of the General Practitioner has a number of practical consequences:

(1) it will necessitate the development of more intensive and extensive programmes both on an undergraduate as well as on a post-graduate level. In this respect, it is also deemed necessary to extend such programmes to other residency trainings such as pediatrics, gynaecology and other branches of medicine.

(2) the curriculum of the programme should focus on topics such as the effects and side-effects of psychotropic drugs and the integration of those drugs in psychotherapy.

(3) the competence and limitations of the non-psychiatrist in dealing with psychiatric patients, and when to refer to the psychiatrists.

It goes without saying that the implementation of such programmes necessitates also the develop-

ment of psychiatric consultation services which again entails the development of more and better psychiatric training and hospitalization facilities.

Doubts have been expressed by some psychiatrists lest the General Practitioner might take psychiatric patients away from their practice. These doubts have no grounds as has convincingly been proven in many places; also in Jakarta where a heightened awareness on the part of the General Practitioner has led to an increase in referrals to the psychiatrist.

By H. ISLER

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Psychotropic medication has always been known. Food intake can, in a sense, be the psychotropic medication, and all of us have on occasions personally experienced this truth. In many cultures alcohol is the layman's psychopharmacopeia, and it is greatly effective in the majority of cases. In western cultures, it can often be said that the psychiatric cases seen by doctors are those who are beyond the help of alcohol intake. It appears that the layman's psychopharmacopeia, ie. alcohol and nicotine, have been instrumental in buffering the stresses of the first industrial revolution in Europe and the United States. It would seem that present approaches to the hoped-for containment or eradication of toxic habits such as these should be based upon a more comprehensive understanding of the role of these and of the more "modern" consumption habits.

Now we must focus our attention upon psychopharmaceutical agents used by doctors. Up to Delay and Deniker's introduction of Chlorpromazine in 1952, the doctor's psychotropic drugs were mainly sleep-inducing agents such as the millennia old opiates, with the exception of Reserpine which had been made known to Western medicine by Sen and Bose's paper in 1931 as a psychotropic agent.

The pre-neuroleptic psychotropic drugs had mostly been used by General Practitioners to sedate their neurotic or psychosomatic cases *"ut aliquid fieri videatur"*, and their role in psychiatric hospitals had not been very important. With the introduction of the first true neuroleptic, the psychiatrists became nearly the sole proprietors of effective psychotropic medication. But in the same decade, the minor tranquillizers were introduced, and they immediately found their way into general practice. Within months from their introduction, the consumption of minor tranquillizers by outpatients began to exceed the consumption in psychiatric hospitals. At the same time, the necessity to continue neuroleptic treatment after discharge led to increasing involvement of general practitioners in the use of neuroleptics and the same happened when antidepressive; agents were introduced.

By now non-psychiatric doctors were dispensing the bulk of psychotropic medication practically everywhere in the world. This is also a consequence of the relative scarcity of psychiatrists. i.e. nine in Malaysia, a hundred in Indonesia as opposed to the overabundance of patients with emotional, psychological and psychotic disorders.

It is quite obvious that adequate training and information concerning psychotropic medication is more urgently needed for General Practitioners and non-psychiatric specialists than for psychiatrists. It is no use to complain about General Practitioners giving inadequate dosages of antidepressive drugs, muddling up the clinical picture, or to demand that they leave antidepressant and major tranquillizer treatment to the psychiatrists. There is nobody to relieve the General Practitioner from the need to attend to such problems (unless somebody should prefer to introduce barefoot doctors for that purpose). But there is an obvious trend towards indiscriminate dispensing of psychotropic drugs in developing countries as well as in the western industrial countries. If we are to believe, for a change, what the drug representative

tells us when we ask them, it would appear that many General Practitioners do not know the difference between an antidepressant and a minor tranquillizer, while they use the difference between the prices as a guideline for their psychotropic treatment.

I feel that their quandary can be explained, at least in part, as a result of affluence of both brands of drugs and candidates for psychotropic treatment. In Volume, 3, Number 1, January 1973, of the DIMS (drug index for Malaysia and Singapore) there are thirty tranquillizers and three hypnagogic and four antiemetic tranquillizers, five amphetamines, seventeen antidepressives, five gastrointestinal sedatives which are also called spasmolytics, based upon tranquillizers, six antiallergics containing tranquillizers, one anabolic agent containing tranquillizer, five anti-obesity agents containing amphetamines and even tranquillizers, and these are altogether seventy-five brands of psychotropic drugs that are now available in the country. On the other hand, the percentage of patients with psychological or emotional or psychotic disorders in General Practice is very high everywhere in the world where people have given up the habit of dying early from undernourishment and infections and infestations. In some western countries, thirty to fifty percent of patients in general practice have been found to belong to these categories. This kind of development is often wrongly classified under "civilization disease" and hopefully correlated with increased stresses and strains from modern ways of life. I think it is more an effect of survival. If you live longer, you will experience more frustrations and have more emotional catastrophes which you cannot cope with for want of compensatory boons. This kind of development is bound to increase in Malaysia all along with improving living conditions being the direct consequences.

Where there is no means of warding off the future increase of psychosomatic patients because the art and science of emotional hygiene has not even yet been invented in contemporary industrial society. The only way to streamline this situation would be to make it simpler for the non-psychiatric doctor to use psychotropic medication.

Since most of the brands are really redundant to the General Practitioner, and since he simply cannot lose much by not using the very newest products before they have acquired a good place in hospital medicine, we should propose a simple list of *needed* psychotropic drugs with which all general practice patients can be satisfactorily served unless they develop an allergy or an acute severe psychosis.

This list, if derived from my own experience with psychosomatic patients in neurological practice, would contain:

1. The neuroleptic or major tranquillizer, Chlorpromazine, for continuation of the treatment of psychosis after discharge or as an initial treatment of acute psychoses before admission.
2. The minor tranquillizer, Chlordiazepoxide, for anxiolytic treatment of outpatients.
3. The minor tranquillizer and muscle relaxant, Diazepam, for quick sedation, relaxation and sleep induction.
4. The more sedative antidepressant, Amitriptyline, for depressions with marked vegetative involvement.
5. The more stimulating antidepressant, Imipramine, for the treatment of more apathetic depressions and those depressions which do not respond to Amitriptyline.

I think that such a guideline would be a first step towards a more rational treatment of emotional and psychiatric problems in General Practice. It should, of course, be followed by methodical and very brief training of all non-psychiatric doctors in the specific art of General Practitioner Psychiatry, notably in the psychotherapeutic approach.

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As you know, this is an exhaustive subject and to be comprehensive is to fail to illuminate important issues. I have decided therefore to emphasize one facet of General Practice which hitherto has not had academic exposure in this part of the world, and even elsewhere, has mostly been taken for granted, and whose psychiatric implications with General Practice cannot be over-emphasized.

General Practice is the oldest of the medical disciplines while Psychiatry is relatively new and Psychotropic drugs newer still. In this context you might wonder what psychotropic drugs were available to the General Practitioner some 40 years ago, let alone, the Psychiatrist. True sedatives, hypnotics and narcotics were available, but certainly none of the wide range of anxiolytics and antidepressants as we have them today, yet the General Practitioner was not completely unarmed. He had one wonder drug which he used with great skill and still uses today. This drug is not in the books; you will not find it in any of the Pharmacopoeias, but like any drug it can be subjected to pharmacological analysis. This drug that I refer to is none other than the doctor himself. The most commonly used drug in General Practice is the doctor himself and the most important psychotropic drug in General Practice is again the doctor himself. What is this "doctor" drug? Is this a new dimension in thinking? It has for too long been equated with bed-side manners which is a dangerous half-truth. The "doctor" drug I refer to is the sum total of his personality, the dynamic dialogue that occurs in history taking, the professional touch with which he examines the patient, the authority with which he pronounces his diagnosis, gives counselling and comfort and finally, the confident air when dispensing the bottle. All these add up to this all important drug "the doctor". The "doctor" naturally like any drug, has its dosage, mode of administration, duration of action, acceptability, tolerance, addiction and expiry date in some,too! These are more than metaphorical expressions. The successful General Practitioner is one who, all things being equal, is able to prescribe himself in the right dosage, at the right time, for the proper duration and without any side-effects. Having expounded this concept, this real everyday dispensation of the "doctor" drug that goes in every surgery in town, I should like to turn to the more mundane pen, paper, and pill stuff, leaving the even greater importance of the "doctor" drug in psychiatric situations to fertile. Freudian minds.

A host of psychotropic drugs are prescribed by the General Practitioner daily, but not all of these (unlike as in the case with psychiatrists) are for psychiatric needs. A sizeable portion of these are for non-psychiatric conditions. The phenothiazines make the best anti-emetics and are excellent for vertigo, a first choice for hiccoughs, and a wonderful uterinal muscle relaxant. The muscle relaxant effect of Diazepam are harnessed by the General Practitioner for use in his spastics, myalgias, basal ganglia lesions and obliquely in status epilepticus. Amituptilline and enuresis are by-words among General Practitioners. In this manner, the list becomes quite endless.

Looking at the other side of the coin is the use of psychotropic drugs, by the General Practitioner for psychiatric situations. Here we find him quite free with their use because he is pressed for time. This is unfortunate to some extent in that though he is ideally poised to play the role of the dynamic psychiatrist, he has become, by force of circumstances, a convenient cross between the dynamic and the organic psychiatrist. In his choice of drugs he has often been found to reflect, in a large measure, the prescribing habits of the regional psychiatrists with whom he has rapport.

In summary, therefore, I would like to emphasize that the most important psychotropic drug in General Practice is the doctor himself and an understanding of the pharmacology of this "doctor" drug is as important, if not more so, than that of the various psychiatric sample bottles and pamphlets that adorn our consulting tables.

"MODERN TREATMENT OF PARKINSON'S DISEASE"

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Many clinical trials extending over periods of up to 12 months and concerned with several thousands of patients have clearly established that l-dopa is the most effective drug at present available for the treatment of Parkinson's disease (Brogden, Speight and Avery, 1971). This report is concerned with the long-term effect of l-dopa and attempts to ascertain if the early therapeutic success is maintained, lost or enhanced, and if treatment with l-dopa can arrest or retard the natural progression of the disease.

A previous study of 51 patients suffering from idiopathic paralysis agitans, who had taken l-dopa for 12 to 20 months, showed that a progressive improvement of most disabilities occurred during the first 12 months of l-dopa therapy (Selby, 1973). Not only did the number of patients who responded to the drug increase after four to six months of continuous treatment, but there was an even greater shift from a slight to a moderate or marked degree of improvement. This trend was most obvious for relief from akinesia and rigidity, where the proportion of patients showing marked improvement more than doubled as treatment continued beyond four to six months, but marked alleviation of tremor also rose from 21% of patients at the six months stage to 37% after 12 months treatment.

Improvement in gait, on the other hand, occured mainly during the first six months of treatment, although some of the most severely affected patients learned to walk independently only after this period of time.

The progressive recovery from specific disabilities is reflected again in the restoration of independence for daily activities and in the assessment of the patients' overall improvement. The proportion of greatly improved patients rose from 27% at the four to six months stage to 40% at the final assessment.

It is interesting to speculate on the mechanisms for such a continuing and progressive recovery in a significant proportion of patients. As a working hypothesis some "disuse atrophy" of the cell body or axon, or more probably of the synaptic vesicles which contain the transmitter substance could be considered. Is it conceivable that dopamine derived from therapeutic administration of l-dopa could result in a gradual restoration of such functioning vesicles? Such a hypothesis can be reconciled with the common appearance of l-dopa induced involuntary choreiform movements which may be due either to a relative excess of dopaminergic transmission or to the accumulation of a metabolite of dopamine which has an effect on synaptic transmission. It is relevant to this argument that these involuntary movements develop earlier and are more severe in patients who show a spectacular response after only a few weeks treatment with l-dopa.

There was also a significant shift towards lower doses of Larodopa after the first six months of treatment; whereas only 18% of patients took less than 3,000 mg, per day during the first six months, these relatively low doses were used by 34% of patients after 12 to 20 months. Dosage requirements in excess of 4,000 mg. per day fell from 45% of our cases at six months to 28% after 12 months. In many, but not all cases this reduction in the dose of l-dopa was demanded by the appearance of drug-induced dyskinetic movements. In some instances these dyskinesias subsided only at sub-optimal dosage levels with a consequent recurrence of some Parkinsonian symptoms. Some of these patients were then helped by the addition of Amantadine to the smaller dose of l-dopa.

The series of 51 cases reviewed above is included in a larger group of 80 cases of idiopathic paralysis agitans who have now taken l-dopa for two to three years. Detailed and regular observations on these patients have shown that their long-term response to l-dopa therapy follows one of four distinctive patterns.

Group I. These patients were severely disabled, and many gave a history of rapidly progressive Parkinson's disease before treatment with l-dopa was begun. Improvement was slow to appear, tended to increase during the first six to twelve months of treatment, and was then maintained at a moderate, but satisfactory level. After 18 months to two years some signs of a slight progression of the disease were noted, mainly a decline in voice volume and speech, a slight deterioration of gait and postural equilibrium, and a mild progression of rigidity. An

increase in the dose of l-dopa is of limited benefit only and normal levels of dopa in the serum and of its metabolites in the urine show that there is no disorder of metabolism of the drug (Liberman et al., 1972). The majority of these patients never develop drug-induced abnormal movements, and this may be an indication that they have a poorly responsive dopaminergic system. The severity of their Parkinson's disease before l-dopa therapy implies more advanced structural changes, perhaps with fewer available synaptic vesicles, or alternately some abnormalities at the uptake sites. The late recurrence of some Parkinsonian symptoms appears to be due to the natural progression of the disease and not to the development of drug resistance.

Group II consists of patients who were only moderately disabled when treatment was begun. Although they may have had Parkinson's disease for several years, progression of thier illness was slow and most were able to care for themselves. Their response to l-dopa was clearly evident during the first six months, though moderately slow to appear, and progressive improvement occurred over 12 months and was then maintained with little or no decline after two to three years. They showed either minimal or no drug-induced abnormal movements and were easily maintained on a stable dosage without adverse side-reactions. These patients evidently have much less structural damage of the nigro-striatal dopaminergic pathways and a sufficient number of intact synapses. The relatively benign nature of their Parkinson's disease before they were treated with l-dopa has been maintained and it may be predicted that future progression will be very slow.

Group III is also concerned with patients with only a mild to moderate disability, which did not progress rapidly at any stage of their Parkinson's disease. Tremor was usually a prominent symptom. The characteristic feature of this group is a rapid and spectacular improvement during the first two to three months of treatment with l-dopa at relatively low dosage levels. During early review examinations virtually no signs of an extrapyramidal disorder can be detected. Soon afterwards involuntary movements appear, often a twisting of the limbs and painful dystonic postures of the feet and toes. These drug induced dyskinesias may be quite violent and usually demand a reduction in the dose of l-dopa to sub-optimal levels. These patients are extremely sensitive to the smallest changes in dose, which has to be regularly and carefully adjusted. They fare best on frequent small doses of l-dopa, of the order of 100 to 250 mg. every one to two hours.

These clinical events can hardly be explained on the basis of structural lesions in the extrapyramidal system alone. Some anomaly in either the uptake or breakdown of dopamine must be an important causal factor. Peripheral decarboxylase inhibitors administered together with l-dopa have no influence on the incidence and severity of these dyskinesias. They may be related to O-methylated derivatives of dopamine, as Ericsson (1971) reported that treatment with a catechol-O-methyl transferase (COMT) inhibitor, N-butyl gallate, not only reduced the abnormal movements, but also enhanced the desired therapeutic effect of l-dopa.

Group IV. A small number of patients experienced marked diurnal fluctuations (oscillations) in performance, which may be quite dramatic and include periods of hypotonia and "akinesia paradoxica" (Barbeau, 1971). They appear only rarely during the first few months of treatment, but tend to develop after 18 months to two years. Patients are quick to recognize a decline in their voice, mobility and gait which may occur regularly at a specific time of day and can persist for up to three hours.

In our series of patients no relationship between the occurrence of these "oscillations" and the severity or rate of progression of Parkinson's disease could be established. There is, however, a definite and direct relationship to the appearance of drug induced abnormal movements. The administration of peripheral decarboxylase inhibitors in addition to l-dopa may reduce the degree of these fluctuations and alter their timing, but does not abolish them. They can usually be minimised by a slow and cautious reduction in the dose of l-dopa and by the administration of smaller doses at more frequent intervals.

Anomalies in the absorption of l-dopa or in the rate of metabolic turnover of dopamine appear to be the most likely cause of these striking oscillations in the patient's well-being and physical capabilities. Muenter and Tyce (1971) distinguish

two types of response to treatment with l-dopa:

(a) long duration response of three to five days.

(b) short duration response of one to five hours.

They found that the short duration effect was not apparent in mild cases, but became progressively more obvious in some of the more severely disabled patients. Absorption of l-dopa from the gastro-intestinal tract tends to become more rapid during the first few months of treatment.

Stroka et al. (1972) have recently reported a careful metabolic study of a patient with marked diurnal fluctuations in performance. The plasma levels of dopa during "good periods" were 1850 μg/1., compared with 20 μg/1. during "bad periods", and the average three-hour urinary excretion of dopa and its metabolites was five to ten times greater during "good periods" than during "bad periods". Decarboxylase inhibitors altered these ratios only to a minor degree, although the patient subjectively felt a little better. These observations suggest that the rate of absorption of l-dopa from the gastro-intestinal tract must be a major factor in the causation of fluctuations in the patient's clinical state.

Side Effects:

The incidence of gastro-intestinal side effects, such as anorexia, nausea and vomiting declined after the first few months of treatment. These symptoms recurred in a few patients after a missed meal, during an intercurrent illness, or when drug-induced abnormal movements or oscillations in performance demanded frequent administration of l-dopa independent of meals. Postural hypotension did not appear for the first time after 12 months or more of l-dopa therapy, nor did it become more severe in thoe patientss where it was recorded from the beginning of the trial. In a few of the very elderly patients some defects of memory and concentration were reported, but the more striking changes in critical function, including a decreased attention span, constructional apraxia and frontal lobe-like disturbances described by Barbeau (1971) have as yet not become obvious in our patients.

No late changes in the peripheral blood, liver and renal function, serum calcium and uric acid were found, nor were there any adverse effects on electrocardiograms.

CONCLUSIONS

In less than one half of our patients who have taken l-dopa continuously for two to three years a slight deterioration of speech, gait, postural equilibrium and manual dexterity occurs, whereas recurrence of tremor is unusual. In a few cases of unilateral Parkinsonism, mild rigidity, tremor and akinesia appeared in the limbs which were not affected when treatment with l-dopa was begun.

A comparison of the rate of progression of paralysis agitans treated with anticholinergic drugs alone before the discovery of l-dopa with the fate of the patients reported in this study justifies the conclusion that treatment with l-dopa retards the natural progression of Parkinson's disease to a very significant degree.

Dopamine deficiency is clearly not the primary cause of Parkinsonism, but is merely a result of a pathological process which, beyond the invariable loss of pigmented cells in the compact zone of the substantia nigra, is still an enigma. Treatment with l-dopa cannot arrest this pathological process, but can diminish its effects by restoring dopamine also to the newly involved synapses; in this manner the natural progression of the disease is greatly retarded.

In a proportion of patient anomalies in the absorption of l-dopa from the gastro-intestinal tract, or in the metabolic breakdown of dopamine in the brain produce striking clinical manifestations, which do not appear to be due to specific structural changes in the "extrapyramidal" pathways, and do not influence the course of the disease.

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Since introduction of l-dopa, the general trend of treatment of Parkinson's Disease has changed and progressed a great deal. However, it remains still as a symptomatic treatment, and is not a causative one. Any treatment at present cannot prevent or stop the start or the progress of the disease, which is now being confirmed by the neuropathological study of the patient's brain who had been under long-term l-dopa treatment.

As well recognized, l-dopa has the most remarkable effect on akinesia and on rigidity and much less on tremor. If we show this in the statistical data of 133 cases of idopathic parkinsonism in two and half years from early 1969 to July, 1971, rigidity is improved very markedly and moderately in about 81.4%, though tremor was influenced in about 55%. At present, the number of cases in our series of l-dopa treatment is over 500, but these statistical ratio of effect do not differ much in the larger experiences. Of course these values may be changeable, depending on different groups of patients at different clinical stages, clinical presentations and at different stages of general physical and mental incapacitation.

Rigidity and akinesia are considered to be caused by dopamine deficiency due to a pathological lesion of the nigrostriatal tract. Experimental lesion within this tract produces parkinson-like muscle stiffness and slowness of movements in animals. The injection of harmaline (3, 4-dihydroharmine), which is the blocker of monoaminoxidase, produces rigidity of muscles in animals with shivering-like shaking. An intravenous injection of l-dopa reverses these effects.

Rigidity is tentatively interpreted as the result of the release of the activity from inhibitory control by the nigrostriatal system, though the final explanation is still not available. These pallidal hyper-activity producing rigidity may be conducted to the thalamic ventrolateral nucleus (VL), for which the stereotaxic surgical lesion has a definite effect either by pallidotomy, ansotomy or by VL-thalamotomy. Anticholinergic synthetic drugs such as trihexyphenidyl is also well known to be effective in influencing this symptom.

Akinesia had been really the most difficult and untreatable symptom in Parkinsonism by both pharmacological and surgical methods, until the l-dopa therapy became available. The most important progress of introduction of l-dopa therapy exists in its clear and definite effect on akinesia, usually being accompanied by the remarkable improvement of ADL of the severely incapacited patients. The cause of idiopathic or primary severe akinesia accompanied by slight rigidity in the disease, such as slowness of movement, inability of initiation of movements, frozen gait or difficulty of speech or of handwriting, is now clarified as due to the result of dopamine deficiency in the striatam. Effect on such akinesia, idiopathic and secondary, was observed, dramatically in 55.6% and markedly 25.8%.

The secondary akinesia due to high-grade muscular rigidity can also be well alleviated by routine l-dopa therapy, paralleling a diminution of rigidity.

Tremor, however, responded in only about half of the cases. These well-improved cases were usually the cases with moderate tremor coexisting with marked rigidity. The cases of tremor only, or of violent tremor with much slighter rigidity has less possibility of being alleviated by l-dopa. For this condition, trihexyphenidyl therapy or the stereotactic-neurosurgery is indicated.

Deteriorating psychic symptoms such as paranoid, hallucinatory experiences or a general lowering of mental capacity including mild disturbance of consciousness may occur with l-dopa therapy and therefore this form of therapy is contraindicated.

Depressive moods of psychoneurotic states observed in the Parkinsonian patients are sometimes reduced by this therapy. Autonomic symptoms may also improve.

Side-effects of l-dopa therapy are also important from both clinical and theoretical points of view. The gastrointestinal side-effects (about 52% of the above series of cases), insomnia or slight lowering of blood pressure can be easily controlled or avoided by the use of other drugs, such as anti-emetics or cardio-vascular stimulants. But about 30—40% of such side-effects should inhibit the further use of l-dopa. The most troubling and sometimes disturbing side-effects are psychic (13.6%) and choreo-dystonic movement, especially in the peroral and neck area (7.5%). For the purpose of minimizing the dosage of l-dopa, the use of peripheral inhibitor of

dopa-decarboxylase is now seriously being examined.

Considering the whole clinical picture of each individual patient, the varied combination of different therapeutic devices as referred above, should seriously be considered and evaluated. However, despite of these side-effects l-dopa is of significant importance in therapy. The value of anticholinergic medication and stereotaxic-neurosurgery has not taken second importance if the patient's total clinical picture is very carefully analysed and considered.

In the author's clinic, hemi-parkinsonism with moderate tremor and rigidity was treated more effectively by stereotaxic-neurosurgery and the bilateral cases by pharmacological means using l-dopa with concomittant anticholinergic medication.

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Parkinson's disease belongs to a group of extra pyramidal disorders embraced by the term Parkinsonism, which covers a clinical syndrome of hypokinetic and hyperkinetic symptomatology. The cardinal features of Parkinsonism are Tremor, rigidity and bradykinesea, which are present in varying degrees in a particular patient associated with, at times, with such features as speech and swollowing difficulties, hyperhidrosis, hypersalivation, occulogyric crisis and psychological disturbances. The clinical details will not be discussed here and my remarks will be directed towards the treatment.

Until such time as the aetiology and pathogenesis of the Parkinson's disease are defined clearly, the treatment remains as supportive, symptomatic and palliative. It is only in patients with symptomatic parkinsonism resulting from the use of such drugs as phenothiazine derivatives or occurring in association with specific disease process that the treatment of the causative agents may result in the improvement of the symptoms otherwise Parkinsonism is a progressive syndrome.

As you all are well aware that the treatment of Parkinsonism is mainly medical, that is, drug treatment associated with psychotherapy and physiotherapy. In the last 3 decades, the neurosurgical treatment has also become established in the management of patients with Parkinsonism and my remarks are mainly directed towards this aspect of the treatment.

As far as the surgical treatment is concerned, until 1940, the attention of the neurosurgeon, dealing with the involuntary movements, was focussed on the mortor cortex and pyramidal tract. Bucy and his co-workers had stated that the surgical alleviation of the involuntary movements was dependent upon the production of paralysis on damage to pyramidal tract or to corticospinal pathways. They held this view in spite of the work of Russel Meyer in 1940, who had shown that open surgery on pallidofugal pathways was capable of reducing tremor without producing paralysis, but the open operation carried mortality rate of 15.7%, but his work was the herald of the basal ganglion surgery in the management of the Parkinsonism. His report was followed by work of Fenlon (1953), Guiot and Barion (1952), who showed that lesion produced in the globus pallidus alleviated the tremor. Cooper (1953) observed that unilateral resting tremor and rigidity was abolished in a patient following ligation of anterior choroidal vessel. Subsequently by his observations on fifty-five patients following this procedure, he concluded that ligation of this vessel resulted in the lesion of bentro lateral region of thalmus, globus pallidus, pallidofugal and cerebellofugal pathways and thereby controlled the tremor and rigidity. In 1955, Hassler pointed out the importance of the ventro lateral neucleus of thalmus in management of Parkinsonism. Subsequently Speigal et al (1963), Fager (1968) and others suggested lesions in the subthalamic region, believing that relatively small lesions in this site where the fibres are most concentrated, would prove more effacadious and less prone to complications.

While the anatomical sites for surgical lesions were being defined, sophisticated and safe methods for making such lesions were being developed. In 1947 Speigal and Wycis, developed technique of

stereotactic surgery for use in man and in 1954, they reported their experience with stereotactic methods for producing lesions in the ansa lenticularis in cases of Parkinsonism. Since then many types of stereotoxic instruments have been devised and at the first international congress of the neurological science in Brussells in 1957, Parkinson's disease and its stereotactic treatment were discussed in detail. In the course of years, the technique has been modified and perfected, and has now become generally accepted in the management of Parkinsonism and other extra pyramidal disorders, intractable pain and epilepsy.

The technical details and various methods of producing lesions are not described here. The basic principle of the surgical management is the production of precise, well controlled, discrete and predictable lesions in the pallido thalamic complex without the production of sensory or motor defecit. As of the cardinal features of Parkinsonism, tremor and rigidity are most amenable to the surgical procedures whilst disturbance of gait and posture, if not due to tremor and rigidity, usually do not show improvement. Similarly other akinetic symptom are not alleviated by the surgery. Furthermore, in some despite total abolition of tremor and rigidity that patient may become increasing bradykinetic, during the ensuing years.

To ensure possible benefits to the patient of stereotactic surgery, especially now when there have been advances in the drug therapy, long term results of the operation have to be considered. Various long term follow-ups (Cooper 1969, Van Manen 1970 and others) have shown that there is a significant relationship between pre-operative status of the patient and results of the surgery. Gillingham et al (1960) have shown, in consecutive series of 131 patients, that results in the first 60 unselected cases were less successful than the subsequent 71 selected cases. Various reports have shown that the results of surgery are dependent on age, severity of neurological symptoms, disability, presence of hypertension and diabetes. The published reports suggest that with satisfactory criteria for selection of patients and standardization of the technique, the tremor and rigidity can be controlled in 90 per cent of good risk patients. Furthermore when the tremor and rigidity has been abolished for more than one (Cooper 1969) to three months (Van Manen (1970) the results are expected to be permanent. No one denies the benefits of surgery in the management of Parkinsonism, but there is a risk of morbidity and mortality, though less than 1% in skilled hands, even in good risk patients. Although it is possible to classify the patients for surgery on a clinical basis, there are great many individual factors which will influence the decision whether a patient should or should not undergo surgery. An ideal candidate for surgery is a young person with unilateral tremor and rigidity with minimal or no hypokinetic symptoms, who is still actively employed or can go back to work following surgery, but on the other hand should one recommend surgery in view of the possible morbidity and mortality. Should one wait till progression of disease makes him totally dependent on others in spite of the drug therapy. I think one has to consider these philosophical questions in the light of continuing advances in drug therapy specially the use of L-Dopa and Amantadine. But not all patients respond to this therapy and therefore neurosurgery still has an important role to play in management of the patients with Parkinson's disease.

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Recent Progress in Medical Treatment and its Pharmacological Basis.

Parkinsonism or Parkinson's Syndrome or the shaking palsy is commonly regarded as a degenerative disease of later life, manifesting primarily with akinesia or bradykinesia, rigidity and tremor. The common pathological findings, as described by Lewy in 1921, include atrophy and destruction of nerve cells in the zona compacta of the substantia nigra which, on naked eye examination, appear smaller and less uniformly pigmented than normal. The other pigmented nuclei in the locus caeruleus, the dorsal nucleus of the vagus and the substantia innominata of Reichert and the globus pallidus habitually show lesions. Lesions in the corpus striatum and the cerebral cortex are minimal.

Anatomical and Neurophysiological Basis of Parkinsonion Symptoms and Signs.

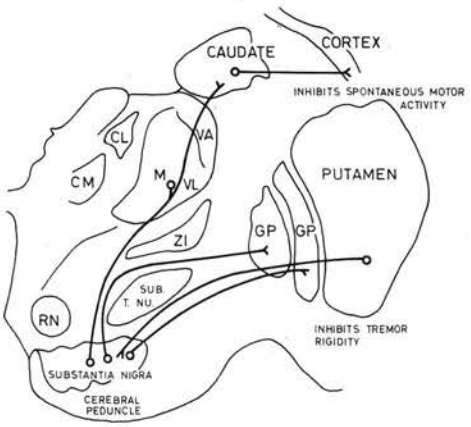
The extrapyramidal nuclei include:—

1) the corpus striatum, by which is meant the caudate nucleus and putamen,
2) the globus pallidus,
3) the substantia nigra and
4) the subthahlmic nucleus of Luysi.

These nuclei are interconnected to each other by afferent and efferent tracts and have, in turn closed circuit connections with the cerebral cortex, thalmus, brain stem and spinal centres.

Experimentally and surgically, it has been shown that lesions of the globus pallidus or its thalmic connections via the Forel's fields reduce rigidity and, to a lesser extent, tremor. Therefore, it is possible that rigidity and tremor are secondary to pallidal overactivity and this, in turn, is inhibited by nigro-pallidal connections directly and nigro-striatal connections indirectly. In Parkinsonism, with loss of neurons in the zona compacta, this nigral inhibition of the globus pallidus is lost and thus the development of rigidity and tremor. Further, the loss of nigro-reticulospinal pathway leads to a decrease of inhibitory influence on the gamma loop, leading to rigidity and akinesia.

Fig. I TRANSVERSE SECTION OF BASAL GANGLIA



CL Central lateral intralaminar nucleus
CM Nucleus centrum medianum
RN Red nucleus
SUB. T. NU. Subthalamic nucleus
M Ventral lateral nucleus —medical part
ZI Zona Incerta
VL Ventral lateral nucleus
VA Ventral anterior nucleus
GP Globus pallidus

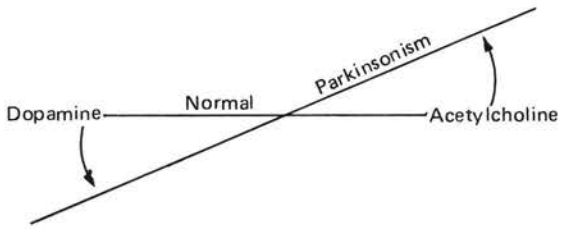
It has further been shown that the striatum normally has a depressant effect on spontaneous motor activity of the cerebral cortex. (This is possibly the explanation for the chorea and hyperactivity seen in Huntington's chorea, in which disorder, the primary pathology is striatal degeneration). The substantia nigra, in turn, has an inhibitory effect on the striatum. Thus, the loss of nigral inhibitory influence in Parkinsonism leads to increase of striatal inhibitory effect on the motor cortex, resulting in akinesia or bradykinesia.

The above anatomical and neurophysiological considerations help to explain a possible hypothesia for the cardinal signs and symptoms of Parkinsonism, namely, akinesia, rigidity and tremor.

Pharmacological Basis of Parkinsonism

The pharmacology of Parkinsonism is based on two basic principles. The first is that acety-

choline and dopamine have antagonistic effects on the neurons of the striatum and that normal striatal function depends upon a delicate balance between these two neurotransmitters. The second is that a shift of this balance in favour of acetycholine or disfavour of dopamine tends to produce the symptoms of Parkinsonism.



Belladonna alkaloids have been used in the treatment of Parkinsonism for over 75 years. Feldberg, in 1945, suggested that the usefulness of atropine and the atropine-like drugs in the treatment of Parkinsonism was based upon the central anticholinergic effects of these drugs. It has also been shown that cholinergic drugs like Prostigmine (or Physostigmine) will aggravate the symptoms in a Parkinsonian patient.

Carlsson, in 1959, showed by histochemical fluorescent technique that the striatum is rich in dopamine. He further showed that the dopamine is not within the cell bodies of the striatal neurons but is located within a dense meshwork of nerve terminals, the cell bodies of which are the neurons of the substantia nigra.

Poirier and Sourkes, in 1965, showed that the destruction of the substantia nigra results in loss of dopamine in the ipsilateral striatum. This nigro-striatal pathway has its cells of origin in the substantia nigra and its termination in the striatum. These neurons contain dopamine which they release upon the receptor neurons of the striatum.

Hornykiewicz, in 1966, showed that the physiologically important lesion in Parkinsonism is destruction of the nigro-striatal dopaminergic neuronal system, whereas the striatal neurons themselves are relatively well preserved. Subsequently other workers showed that the cerebrospinal fluid and the urine of Parkinsonian patients contain lesser concentration of HVA (Homovanillic Acid) and DOPAC (3-4-Dihydroxyphenylacetic Acid), which are the metabolic and products of dopamine metabolism.

Using intravenuous L-Dopa, Birkmayer and Hornykiewicz, in 1962, demonstrated a decrease in akinesia in 20 Parkinsonian patients. In the same year, Barbeau, using oral L-Dopa, described short lasting but definite improvements in both tremor and rigidity. Subsequently, Cotzias in 1967, Melvin Yahr in 1968 and McDowell in 1970, well substantiated the use of L-Dopa in Parkinsonism. Thus, the pharmacological basis of treating Parkinsonism is based on either restoring dopaminergic activity by replacement therapy or inhibition of its breakdown, or preventing excess chlonergic activity. Incidentally, some authors, including McGeer and Barbeau, believe that the tremmor of Parkinsonism is due to an imbalance of the serotogenic-histamine system.

Drugs Elevating Concentration of Dopamine:

1. L-Dopa
2. Amantadine (Symmetril)
3. Apomorphine
4. Alpha-Methyl Dopa Hydergine
5. MAO Inhibitors (Iproniazid, Imipramine, Desipramine)
6. 5-04 Tryptophan.

Drugs Decreasing Effective Concentration of Dopamine:

1. Reserpine – leads to depletion of brain dopamine + serotinin.
2. Phenothiazines – interferes with action of dopamine on receptor sites.
3. Pyridoxal Phosphate – potentiates peripheral decarboxylase activity and decreases central dopamine concentration.

Anti-Cholinergic Drugs:

1. Artane
2. Cogentin
3. Pagitane
4. Kemadrin
5. Akineton

Anti-Histamines:

1. Benadryl
2. Disipal
3. Phenoxene

Drug Therapy of Parkinson's Syndrome:

I. *Atropine-like Drugs*

This group of drugs, which include Artane, Cogentin, Pagitane, Kemadrine and Akineton, is one of the most commonly used anti-Parkinsonian drug groups. Essentially, they act by inhibiting cholinergic activity on striatal neurons. I am not going to elaborate on these drugs except to say

that they should not be used on patients with glaucoma and enlarged prostate. The side effects of these atropine-like drugs include headache, giddiness, blurred vision, mydriasis, dry mouth, epigastric distress and nausea, and confusion, agitation and psychosis. Atropine-like drugs can be used with dopaminergic drugs.

II. *Anti-Histamine Drugs*

This group which includes Benadryl, Disipal and Phenoxene is used empirically and is known to be more effective on tremmor than rigidity or akinesia. The side effects, other than their sedative properties, is less significant. The anti-histamines also work by producing cholinergic block.

III. *Amantadine Hydrochloride (Symmetril)*

Amantadine Hydrochloride (AH) is a 10 carbon cage amine. It first came into clinical use as a prophylactic agent against A2 influenza. Schwab et. in 1967, first used AH in Parkinson's Syndrome after one of his patients reported remission of her symptoms while taking the drug to prevent influenza. According to Schwab's report, 66 percent of the patients, out of163, showed subjective or objective improvement of akinesia, rigidity and tremmor. Patients usually noted improvement within 3 days of starting AH. Improvement was especially reported in hand-writing, dexterity, walking, balance and general mobility. They also had a sense of well-being. Results or improvement did not correlate well with age, sex or aetiology of Parkinson's Syndrome or previous Stereotaxic Surgery. Abrupt withdrawal of the drug seemed to aggravate the symptoms in several patients. Side effects are mild and include drowsiness, constipation and slurring of speech. AH is usually given in a dose of 100 mgm, twice a day. Further increasing the dosage has not been shown to improve the symptoms. In about 20 percent of patients, the drug's effect may undergo a partial decrease after 2–8 weeks of medication. This is believed to be due to exhaustion of the presynaptic dopaminergic pool. AH acts by mobilising existing stores of dopamine and inhibiting presynaptic re-uptake of dopamine. It thus increases available dopamine to the dopaminergic striatal neurons. Because of Amantadine's dependence on the dopaminergic system, patients who do well on Amantadine do well on L-Dopa and vice versa. Both drugs can be given simultaneously to the same patient. Unlike L-Dopa, AH is effective in drug induced Parkinson's Syndrome.

IV. *Larodopa (L-Dopa)*

The first report on L-Dopa treatment in Parkinsonism was published in 1961 By Birkmayer and Hornykiewicz who observed improvement of akinesia by slowly injecting 25–150 mgm. of L-Dopa intravenously. Subsequent reports of L-Dopa were not encouraging because the authors gave too low a dosage. In 1967, Cotzias did an extensive study and found striking improvement of Parkinsonian manifestations in 50 percent of 16 patients administered 3–16 Grm. of L-Dopa daily. He and his associates were the first to recognize the necessity of giving large doses. However, they subsequently recognized transient granulocytpoenia in some of the patients. They also found that the L-Dopa was more effective with less side effects than the D-isomer.

The rationale for the treatment with L-Dopa has been discussed earlier under pharmacology of Parkinsonism. L-Dopa ameliorates the symptoms of Parkinsonism by reinstitution of dopaminergic inhibition of the striatal neurons. The dosage of L-Dopa varies from patient to patient, and in the same patient at various times. Essentially, patients should be started on the lowest possible divided dosage, i.e. 125 mgm. qid., and this should be gradually and intermittently increased every 3rd to 5th day to the maximum dose that ameliorates symptoms or produces toxic effects. In my experience, most patients seem to do well on 3–4 Grm. of L-Dopa in divided doses.

The time of response and the degree of response seem to vary from patient to patient. As a rule, patients show some response within 2–3 weeks of starting on L-Dopa and akinesia is the first symptom to respond, followed by rigidity and finally by tremmor. Shuffling, associated movements, posture, festination, articulation, facial expression, dysphagia, lacrimation and salivation, all show progressive regression. Compelling evidence now exists that a large fraction of patients with Parkinson's Syndrome show striking and sustained improvement when treated with L-Dopa. L-Dopa can be administered with standard anticholinergic drugs or Symmetril. Failure to respond to L-Dopa is related to degeneration of striatal dopaminergic receptors. Patients who fail to respond to large and prolonged doses of L-Dopa are not likely to respond to Amantadine because both these drugs require functional dopaminergic receptor neurons.

The side effects of L-Dopa include:–

1. Nausea and vomiting
   – transient
2. Anorexia
   – transient
3. Postural hypotension
   – may be alarming.
4. Cardiac dysrhythmia
   –
5. Psychic manifestations
   – restlessness
   – heightened nervous tension
   – nocturnal hallucination
   – insomnia
   – toxic delirium
6. Transient effects
   – sense of body warmth
   – hyperhydrosis
   – excessive nasal discharge
   – pupillary dilation and widening of palpebral fissure.
7. Dyskinesias
   – grotesque facial grimacing
   – exagerated chewing
   – twisting and torsion of tongue
   – rhythmic closing and opening of eyes
   – head bobbing
8. Laboratory
   – positive coomb's test
   – leucopaenia
   – raised SGOT and BUN.

Of all the side effects, postural hypotension, Cardiac dysrhythmias and dyskinesias are the most troublesome. The dyskinesias are probably due to denervation hypersensitivity of striatal neurons, i.e. in unilateral Parkinsonism on L-Dopa, the uninvolved side does not show any dyskinesia. Treatment of the side effects, essentially consists of lowering of L-Dopa and reinstituting therapy in graduated doses.

Pyridoxal Phosphate (Vitamin B6) should not be given to patients on L-Dopa because it potentiates peripheral dopa-decarboxylase activity and, therefore, there is increased dopamine peripherally with its attendant side effects with decreased dopamine centrally. In severe cerebral toxicity due to L-Dopa, large doses of Vitamin B6 can act as an antidote.

L-Dopa has been shown to be effective in the treatment of chronic manganese poisoning, in which disorder the predominant symptoms are dystonias or Parkinsonian symptoms. Although the pathological lesion in chronic manganese poisoning is unknown, it is believed to be a dopaminergic deficiency disorder.

It appears that the introduction of L-Dopa in the past decade has opened a whole vista of neurochemical approach in the treatment of hitherto untreatable neurological disorders.

CONCLUSION

The date and observations reviewed above are in agreement with a comprehensive theory of the neuropharmacology of Parkinson's Syndrome. The most consistent lesion is degeneration of the cell bodies of the zona compacta of the substantia nigra. The result is a loss of dopaminergic input into the ipsilateral striatum. This loss of dopaminergic influence on the striatum is now felt tc be the principal factor in the production of Parkinsonian symptoms. Dopamine and acetycholine have antagonistic effects on the striatal neurons and the loss of dopamine in Parkinsonism leaves the acetycholine unantagonised. This is the rationale for the therapeutic use of anticholinergic drugs. L-Dopa ameliorates the symptoms of Parkinsonism by reinstituting dopamine inhibition of striatal neurons. Amantadine acts by blocking pre-synaptic re-uptake of dopamine and thereby prolonging its effects on striatal neurons.

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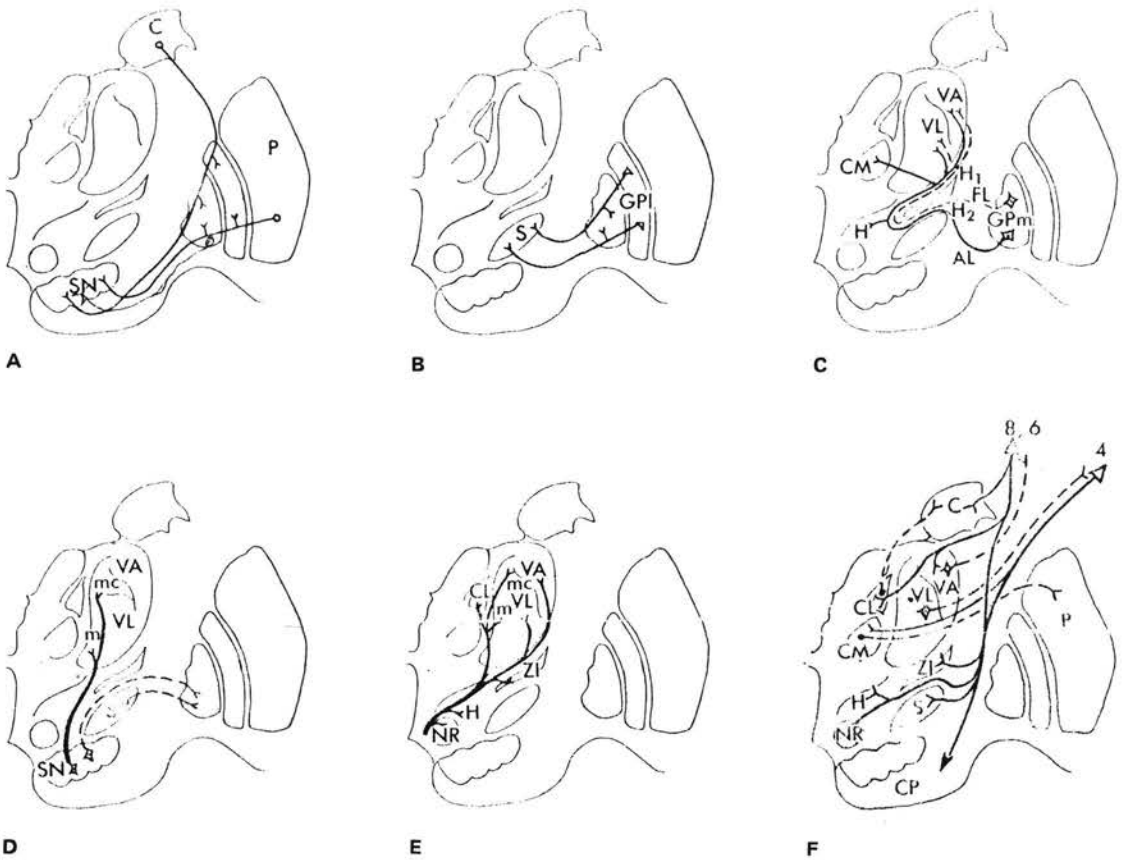
Figure II



A to F, Transverse sections depicting: A, striatonigral connections; B, connections of the lateral pallidum; C, connections of the medial pallidum; D, nigrothalamic and pallidal connections; E, brachium conjunctivum–diencephalic connections; F, thalamocortical, thalamostriatal, and corticodiencephalic connections.

KEY FOR ABBREVIATION USED

AL – ansa lenticularis
C – caudate nucleus
CL – central lateral intralaminar nucleus
FL – fasciculus lenticularis
CM – nucleus centrum medianum
CP – basis pedunculi
GPL – globus pallidus, lateral segment
GPM – globus pallidus, medial segment
H, H1, H2 – H-fields of Forel
IC – internal capsule
NR – red nucleus
P – putamen
RF – reticular formation
S – subthalamic nucleus
SN – substantia nigra
VA – ventral anterior nucleus
(mc – magnocellar part)
VL – ventral lateral nucleus
(m – medial part)
ZI – zona incerta

"CLINICAL TRIALS"

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INTRODUCTION

There are many pitfalls in the path of investigations attempting to assess the efficacy of new drugs in the treatment of psychiatric disorders.

Among some possible sources of error are:—

1. The tendency of many psychiatric illnesses to improve spontaneously.
2. The role played by factors other than the pharmacological action of the drug in producing improvement, such as:-
   (a) the possible effects of suggestion and the therapeutic effects of the trial regime per se, particularly arising from the greater interest and time devoted to patients participating in the trial;
   (b) the effect of personally important factors in the environment of the individual which may influence the tendency to improvement or exacerbation during the trial period.
3. The possible influence of bias in selecting patients for a particular treatment and control procedure.
4. The influence of enthusiasm, bias and "halo" effects in rating clinical changes when the nature of the treatment undergoing trial is known.
5. The failure to obtain accurately matched treated and control groups in order to obtain clinically and prognostically similar groups for comparison.
6. The inadequate dosage of the drug not given for a sufficiently long period of time.
7. The effects of "carry over" when inert tablets are given after administration of active treatment.

Sir Austin Bradford-Hill, the father of clinical trials, stated in his classical book on medical statistics: "The clinical trial is a carefully and ethically designed experiment with the aim of answering some precisely framed question." He added, "in its most rigorous form it demands equivalent groups of patients concurrently treated in different ways."

Choice of Design for Clinical Trials

The following are some of the designs available for clinical trials:—

1. Matched-pair trial.
2. Cross-over trial.
3. Combination group trial for a combination of these methods.

Matched-pair Trials

The matched-pair trial is a controlled clinical trial carried out on pairs of patients, each pair consisting of patients identical in all relevant factors. One patient is given the treatment under evaluation and the other patient is given the alternative treatment or procedure. The relevant factors include constitutional attributes, form and severity of psychiatric disorder. Ideally, the pair should be comparable in clinical status and prognosis.

As it is probable that most psychiatric illnesses are heterogeneous disorders, even if we succeed in obtaining clinically identical pairs of patients of similar prognosis, there is no certainty that the pairs are sufficiently similar for scientific comparison, for they may differ in some important and relevant constitutional, biochemical, psychological or other attributes.

The Cross-over Trial

Here the patient serves as his own control and is exposed to more than one treatment, and it is assumed, with certain qualifications, that any differences between responses to two treatments within one patient are due to actual differences between the treatments.

The method has certain disadvantages, for example, the condition being treated must not be cured by the first treatment, otherwise the second treatment will have no opportunity of showing its worth. Similarly, the patient should be as severely ill at the start of the second treatment as at the start of the first treatment. Also, the effects of the first drug should have completely disappeared before the second treatment is started.

There is some evidence to suggest that the first treatment tends to have a greater effect due to suggestion and expectation. On the other hand, the second course of treatment has an advantage for there would be a greater tendency to a spontaneous recovery.

In view of the possibility that any clinical

change occurring during the trial period might be due to a spontaneous improvement or to factors unrelated to the pharmacological action of the drug, it is essential that the treatment and control procedures be given in different sequences in order to ensure that any factor which might influence the patient's clinical state would have the same chance of being coincident with both treatments.

If there are two treatments, for example, there are two possible treatment orders AB and BA. If there are three treatments, there are six treatment orders, ABC, ACB, BAC, BCA, CAB, CBA. Treatment orders should be allocated at random using device such as random number tables.

The great advantage of a cross-over trial is that it controls relevant factors within the patient and also environmental or non-pharmacological effects operating during the trial procedure.

Group-comparative Trials

In this design, different treatments are given simultaneously to similarly constituted groups of patients. The disadvantage of this method is the difficulty of recognising all possible relevant factors which might accidentally bias one or other group with regard to factors which could influence the outcome during the trial period, and this is one of the commonest reasons for failure in this type of trial.

It has the advantage of being the most practical type of trial and is not restricted either by the order in which the patients arrive for treatment or by the prevalence of the disease.

Apart from clinical characteristics, it should be similar in both groups in other important factors, such as severity and duration. It might be necessary to take age and sex into account if they are clearly relevant. Thus, if age and sex are relevant factors, there would be four 'random number' dispensing lists one for each of the four sub-groups defined by male-old, male-young, female-old and female-young. This is known as a stratified randomisation with stratification for age and sex to produce balanced groups.

Mixed Design

The disadvantages of matched pairs and comparative groups can be minimised by combining each with a cross-over design.

Criteria for Inclusion in the Trial

Precise criteria must be set out to which patients must conform before acceptance into the trial. These criteria may include clinical features and restrictions as to age and sex distribution, and also the presence or absence of previous treatment, and the duration of illness.

Criteria for Exclusion in Trials on Psychiatric Disorders

These psychiatric disorders include Schizophrenia and the affective disorders. Exclusions would include those with organic disease, including organic brain disease, and criteria relating to age, duration of illness, etc.

Methods of Assessing Change during the Clinical Trial

The following questions may be asked:-

1. By whom is the assessment to be carried out.
2. Is it to involve patient assessments or assessments by nurses or by the physician
3. If so, is it going to be one physician or two physicians making assessments independently?

A large variety of methods of rating clinical state are now available, for example, the Hamilton rating scale, the Beck rating scale, the Taylor manifest anxiety scale, and the Present State Examination (Wing).

When assessments are to be made, one has to decide how long and how many times before the beginning of the trial, how frequently during and after the completion of the trial, they should be made.

The form of measurements may be interval, nominal, or ordinal.

In the evaluation of the results, parametric statistics, such as the "*t*" test are suitable for interval measurements, and Chi-squared for nominal measurements. A variety of tests are available for ordinal measurements including the Rank sign test, the Mann Witney 'U' test, the Wilcoxson matched pairs, test, etc.

The numbers of patients required for clinical trials will depend on the degree of efficacy of the treatment under trial compared with the control procedure. However, graphs have been published by Clarke and Downey (1966) which help to estimate the number of patients required providing one can assess roughly how the trial group might respond. Similar tables are supplied by Maxwell (1968). The use of the sequential design may minimise the duration of the trial.

Side-Effects

It is important to note the side-effects occurring during the trial. It is particularly important to note the complaints which were present before the trial

started in order to avoid incorrectly attributing them to side effects of the drugs.

Side-effects which are spontaneously reported are likely to be more valid than those which are reported in response to direct questioning. If direct questioning is used, it should be standardised, for example, "Have the tablets disagreed with you in any way?

Drop-outs

It is important that full records be kept of all drop-outs together with reasons, for the effective evaluation of the drug and details included in the published report.

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Psychotropic drugs have changed radically the management of mental illness. However, a number of problems that have yet to be resolved have given rise to the situation where the difficulty of defining the pathophysiology underlying the various labels of mental disease coupled to the host of largely symptommatic medications, has resulted largely in empirical use of drugs. This should not be taken that empirical drug use has no place in modern medication – rather it must be viewed in the light that such a situation needs even greater care in evaluation of the drug therapy. The drug trial as a pointer to the efficacy or otherwise of a particular medication for a specified condition is, therefore, an important prelude to the widescale introduction of the drug.

Case for a Local or Regional Drug Trial

Practically all the psychotropic drugs used today originate from the laboratories of countries outside Asia and have been introduced into the market based on laboratory and clinical evidence obtained in a different context. The question in deciding whether there is a case or not for a drug trial in the local or regional context is not so much as to whether the drug is useful in the defined mental illness but rather how effective it is. To delineate the drugs of use to the region would require first hand knowledge and experience with their use; hence uncritical acceptance of the findings of others from a different time and a different setting need not necessarily hold. There are a number of considerations that would make the drug trial desirable especially for new medications.

The ethnic differences may be reflected in a difference in the pharmacodynamics of the drugs used due to metabolic or other differences. Cultural differences may lead to logistic difficulties of drug acceptance and continuance of treatment and the complication of taking native remedies at the same time as the psychotropic medication. For similar reasons pointed out, untoward effects may be manifest that had not previously been noted and these may be of such magnitude that would make the medication unacceptable medically or by the patient.

Competitive marketting on the part of the drug manufacturers has led to the production of a

large number of drugs and increased sophistication in marketting techniques make it difficult for the average user to distinguish between a pharmacological advantage or a gimmick with little therapeutic value. Only a properly carried out trial will prove the claim of therapeutic supremacy under the conditions as are existing in the area. Cost considerations are also important in countries which are relatively poor so that it would not be possible for such communities to indulge in the frivolities of drug prescription on the basis that the drugs may be of some value. A more positive approach based again on proven usefulness of the drug is the needed guide.

Some Problems of the Drug Trial

A brief survey of the various drug trials carried out in the region indicates that while a certain interest is seen, there are indications that there could be further improvement in the approach used. Some of the deficiencies include poor design, uncontrolled studies, inadequate assessment of the effects of drug therapy, conclusions based on impressions and without proper statistical analysis and uncertainty as to the purpose of the trial.

There may be a number of reasons for the above deficiencies.

There may be the attitude that since the drugs have met with success in other conditions, it was of little importance to validate it again and even if persuaded into doing so, a trial is done more as an exercise.

There could also be a genuine interest in the drug trial but the absence of trained personnel in planning, execution and evaluation of the project may result in a poorly-conducted trial. Where there are inadequate number of professionals and a relatively large number of patients, pressure of other more pressing medical care requirements make attention to drug trials of low priority.

The Development of Drug Trials in Psychotropic Medication

Drug evaluation in psychotropic medication is not an easy subject because of the peculiar circumstances that are attendant on the problem. However there are challenges not insurmountable with effort and even more important than taking them on as an academic exercise, this must be an accepted approach to psychotropic medication where there has yet to be found an adequate laboratory model reliable enough to predict the pharmacological properties of these drugs in man. Only in man himself can there be adequate study of the value of psychotropic drugs.

A more critical assessment of reports on psychotropic medication would serve as a useful starting point. A careful selection of the most promising ones for the purpose and a properly handled drug trial will give the best approach through the rapidly expanding and increasingly complex subject.

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INTRODUCTION

The evaluation of drug efficacy might be determined only after clinical trials. In the case of psychotropic medications, since there are no concrete and direct correlation between the animal studies and human trials, the role of the clinical trials, might be the most important for drug evaluation.

The establishment of trial conditions is also considered to be special because the drug should be tried in mentally suffering patients whose physiological, biochemical and morphological pathology is not yet unknown. Particular ethical problems exist for executing the trials in mentally handicapped persons whose legal responsibility is sometimes different from normal subjects.

To justify the clinical trials under these peculiar conditions, the purpose of the study, should be first defined clearly. According to the well defined purpose of the study, an adequate and well designed planning should be established. Furthermore, as there exist no objective physical or chemical parameters for the evaluation, double blind controlled trials are frequently required in all study phases. The needs for the implementation of studies in this case should be carefully analyzed.

The different purpose of clinical studies will be mentioned in this report, and then important checking items for the planning of the studies will be enumerated. In consideration of the above-mentioned matters, the ideal testing principle of the implementation of double blind controlled trials will be explained.

1. *Purpose of the Study*

Prediction and warning from pharmacologists and toxicologists on efficacy and safety – Documentation and evaluation

Before starting the clinical trials, the examination of preclinical data by clinical staff together with pharmacologists and toxicologists is of utmost importance. The assessment of the predictive value of the animal studies should be carefully evaluated. It should be reminded that this procedure is necessary not only for the future planning of clinical trials but also for the important ethical procedure of the trials in men. The initial determination of dosage schedule with the consideration of the possible adverse reactions should be made during the documentations.

2. *Determination of phamacokinetic and metabolic pattern in men*

The pattern of absorption, metabolism and elimination of administered drugs in men is often different from that in animals. The need for this study at the very early phase of clinical trials is stressed because the data should be referred back to animal studies to choose the animal species, the metabolic patterns of which are similar to human. The large-scale extended studies on safety and efficacy are to be performed by using these species of animal along with human clinical studies.

The phamacokinetic and metabolic pattern of drugs may in certain cases be different among the human races with different ethnological origins.

This is the so-called Phase II study and its implementation will be combined usually with tolerance studies.

3. *Tolerance studies – Initial sounding on the drug action (beneficial and non-beneficial) in healthy volunteers (including initial setting of dosage and administration.*

It is recommended that the trials will be performed in healthy volunteers and the dosage should be increased until a certain effect (beneficial or non-beneficial) can be obtained. However, since unexpected events have happened several times, this principle cannot always be applied.

In the Phase I study, the use of healthy volunteers has been recommended. However, it is sometimes obliged to use the patient from the first stage of the trials, especially in the case of major tranquillizers with the small dosage of which extrapyramidal symptoms are expected to appear.

The reaction type and sensitivity to the psychotropic medication between healthy persons and patients are often different.

It is seriously discussed now whether the normal subject should be used for the trials or not. The double blind trials in this phase are frequently needed for the subjective evaluations of reactions especially in the case of normal healthy volunteers.

4. *Determination of pharmacological spectrum and possible adverse reactions in patients (including determination of optimal dosage in patients).*

This is the so-called Phase II study. The purpose is to evaluate and confirm the preclinical predictions. The data obtained in this phase of the study will not be enough to support the usefulness of drugs in terms of efficacy and safety. The purposes of Phase II and III studies should be clearly defined because many of clinical practitioners have misunderstood them. The information obtained in this study will sometimes lead us to "feed back" to animal studies for reconfirmation. The information of Phase II study will be used as the basic sources for the planning of the Phase III trials.

5. *General assessment of efficacy and safety in patients.*

– *Large-scale controlled trials*
– *Long-range administration trials (Long-range safety study).*
– *Nature and frequency of adverse reaction*

To assess the efficacy and safety of new psychotropic drugs, the adequately planned and well designed controlled trials comparing with conventional drugs are required on the double blind

basis to avoid the different kinds of bias in doctors and patients. In the Chapter III, the basic principles and activities to be considered for the implementation of studies will be mentioned.

Most of the psychotropic drugs will be taken by patients relatively for a long period of time. Therefore the long-range administration study, if possible, for more than 6 months with the regular check of subjective adverse reactions, physical examinations and laboratory examinations are necessary. The residual and after-effects of drugs such as tardive dyskinesia, drug dependency liability (psychological and/or physical) and other general physical and psychological conditions during and after the medication should be verified by this study.

In this phase, the evaluation of the nature and frequency of adverse reactions comparing with the standard drugs and/or placebo will be performed. When the adverse reactions which are qualitatively special or unusual in addition to high in frequency are observed, the "feed back" to the animal studies will be necessary for verification.

The interpretation of the adverse reactions which are probably originated from exaggerated therapeutic actions is very delicate and difficult for analysis: The examples of this type of reactions are extrapyramidal syndrome of neuroleptics, somnolence and muscle relaxant activities of minor tranquillizers and anxiety attack and manic conversion of antidepressants.

6. *Monitoring on adverse reactions – Intensive and passive monitoring*

7. *Review on efficacy of drugs*

Not only in the case of psychotropic drugs but also in all drugs, the continuous review on safety and efficacy should be carried out reasonably even after the commercialization and during the whole life of drugs. The WHO is now organizing the International Monitoring System and the Japanese Government obliges pharmaceutical companies annually to report the adverse reactions for 3 years after the New Drug approval.

The review of the efficacy of the existing commercial drugs is being conducted mainly in the U.S. and Japan.

The technique for the intensive and passive monitoring and the role of the monitoring centre (on the hospital basis or the national basis) are studied now by the WHO group as well as health authorities and industrial groups respectively.

The attitude to evaluate the adverse reactions detected by every monitoring system and technique is still very much diversified. However, the international efforts on this matter are now started for the quick retrieval and evaluation of information.

II. *Planning*

When the purpose of the study is determined, the adequate planning should be made for each drug considering the available preclinical and clinical data on hand.

The following are the important items to be considered for planning.

1. Subjects: Healthy volunteers or patients, sex, age, ethnological aspects, patients' history, severity of disease, acute or chronic state, etc.
2. Number of subjects:
3. Establishment of dosage and administration schedule
4. Ethical considerations – consent of trial subjects.
5. Observation parameters (objective and subjective)
   - Physical and biochemical parameters.
   - Rating scale
6. Comparative or non-comparative trials
7. Controlled trials, especially simultaneous comparison under randomly allocated condition
8. Open or blind (single and double) study

In principle, children, childbearing women and aged persons should not be included in the trials before the Phase II study.

The number of patients in each trial will be determined empirically and also roughly estimated statistically in the case of the controlled trials. However, the number of patients estimated by statistical calculation will generally be more than actually available number for the trial due to the fact that it is statistically or empirically impossible to decide the reasonable number of patients. Therefore, certain compromise might be made between the statistical and practical aspects.

The procedure of obtaining the consent from trial subjects is extremely difficult. This will vary from country to country, and according to the type (or phase) of studies, consent will be required case by case, orally or with a written form.

The observation parameter for the efficacy and subjective adverse reactions is mainly made based

on the psychological questionaire, i.e. the rating scale.

Generally, the doctor's questionnaire (Dr's rating scale) and the patient self rating scale will be applied simultaneously for the evaluation of minor tranquillizers. The nurse's rating scale may be useful for the evaluation of antipsychotic drugs in case of the hospitalized patients.

Certain practitioners still prefer the comparison of new drug experiences with the former treatment history or experiences. However as a trustful way, the simultaneous comparison should be justified with regard to the scientific attitude of trial. At the same time, the allocation of drugs to patients should be made at random as well as trial drugs and standard drugs. In this case, the double blind study will be needed to avoid the bias of doctors and patients.

In psychotropic drug studies, the treatment period for double blind studies should be limited because long lasting double blind studies disturb practically and ethically the management of patients. Generally, the effects of drugs will appear within a few weeks if the drug is effective.

For the safety studies, a rather long administration period will be required and in this case, the open studies are generally applied. The adverse reactions observed during the double blind study should be compared with those in the open study, and the rational medical interpretation of the reactions must be made finally. The predictive value concerning the adverse reaction data obtained during the double blind trials might be different from that of the open study.

III. *Implementation of Double Blind Controlled Studies*

As already mentioned, the need of double blind controlled trials is justified for most of the psychotropic drug studies, especially for the evaluation of usefulness.

The following are the activities of the trial team consisting of medical doctors, biostatisticians and medical monitors of pharmaceutical companies (when the trial is requested by industries) which are necessary for the planning, execution, data processing, evaluation of data and follow-up after the completion of double blind studies.

1 – Planning

1 – 1 Hypothesis

1 – 1 – 1 Medical hypothesis

Drug A may be more effective than Drug B. This hypothesis will be valid in _____symptoms which will appear in_____ disease but may not be true in_____ symptoms of the disease.

1 – 1 – 2 Statistical hypothesis and evaluation principle

1 – 1 – 2 – 1 Null hypothesis H_0 A = B

Alternative hypothesis

H_1 A > B (one tailed)

or

H_1 A ≠ B (two tailed)

1 – 1 – 2 – 2 Hypothesis on distribution of observed or statistical value

1 – 1 – 2 – 3 Determination of rejection region and critical value – Determination on probability

1 – 1 – 2 – 4 Determination of the rule of test

Reject H_0:

Observed value (or statistical value) $\geq$ Critical value

1 – 1 – 2 – 5 Observation (i.e. implementation of experiment)

1 – 1 – 2 – 6 Test for verification of hypothesis (statistical work)

– If the observed data correspond to the rule 1 – 1 – 2 – 4, the result is not accidental under H_0 but inevitable under H_1, ie.. rejects H_0 in the degree of risk α. This is also expressed as follows; the difference between A and B is significant with the significance level α. α means the probability of misjudging A to be B when A ≠ B is a fact.

Probability α : type of 1 error (error of overstating)

* If the data do not fit the rule 1 – 1 – 2 – 4, the result accepts H_0. A and B are not significantly different. When H_0 is accepted by misjudgement despite the fact that H_1 should be accepted, error of overlooking is made. The probability of error of overlooking is β.

Probability β : type of II error (error of overlooking)

1 – 1 – 2 – 7 Interpretation of the statistically stated conclusion

– Significant difference

Medical interpretation of observed difference

*– Non-significant difference
To check the value of β against the difference δ which might be the medical problem. In this case, the evaluation of detection power, i.e. probability $(1-\beta)$ should be necessary.

* In the case of drug evaluation study, generally β cannot be considered because the one tailed test will be used usually for data evaluation. (For example, Chi-square test)

1 – 2 Study design

1 – 2 – 1 Group comparative trials

1 – 2 – 1 – 1 Simple randomization

B C A C B B A (randomized)

1 – 2 – 1 – 2 Stratified randomization

Stratum 1 B C A C B B (randomized)

Stratum 2 A C C B A C (randomized)

1 – 2 – 2 Matched pair trials

1 – 2 – 2 – 1 Matched pair

A B A
B A B

(randomized)

1 – 2 – 2 – 2 Randomized blocks

B A C
C B A
A C B

(randomized)

1 – 2 – 2 – 3 Cross over trials

	1st Treatment	2nd Treatment
Patient 1	A	B
" 2	B	A

	1st Treatment	2nd Treatment	3rd Treatment
Patient 1	A	B	C
" 2	B	C	A
" 3	C	A	B

Reference: Maxwell, C.: Clinical Trial's Protocol, Stuart Philips (1969).

1 – 3 Drugs
1. Test drug
2. Standard or reference drug(s)
3. Placebo (inactive)
4. Quality control of trial drug(s)
5. Rule and restriction on accompanied general treatment.

1 – 4 Dosage and administration
1. Dosage fixed – flexible
   flexible – fixed
   fixed
2. Duration of trial and aftercare of trials.
3. Necessity of wash-out

1 – 5 Trial institution
1. Hospital (Psychiatric and/or general)
2. Clinics (out patients)
3. Multi-clinical study

1 – 6 Trialists
1. Experience in the specialized field
2. Group study
3. Role of paramedical personnel (nurse, psychologist, etc.)

1 – 7 Patients selection
1. Stratification and exclusion (children, aged patients, childbearing women, etc.)

1 – 8 Randomization and allocation
1. Collaboration of biostatisticians
2. Role of 3rd party controller for keeping trials fair

1 – 9 Rating of effectiveness
1. General improvement rate (G.I.R.)
2. General severity rate (G.S.R.)
3. Symptoms rating scale
4. Patient self rating scale

Quantification of scale

1 – 10 Adverse reaction
1. Comparison with placebo and/or standard drug
2. Laboratory data

1 – 11 Drop-out and discard case (Setting the rule for follow-up and handling).

1 – 12 Handling of unexpected adverse reaction during trials

2 Execution of trials

2 – 1 Confirmation and follow-up or recording process

2 – 2 Confirmation and stock of drugs and distribution to patients (Role of pharmacists)

2 – 3 Confirmation of random allocation of patients for trials

2 – 4 Confirmation of drugs intake by patients.

2 – 5 Follow-up of dosage schedule for each patient.

2 – 6 handling and treatment of adverse reaction

2 – 7 Follow-up of drop-out cases and handling of discard cases (replacement).

3 Evaluation of data
3 – 1 Documentation before key-open
Confirmation of fairness of trials
Blindness
Random allocation
Constancy of rating
3 – 2 Data processing
3 – 3 Medical interpretation of statistical data
1. Significant level
2. Meaning of applied statistical technique
3 – 4 Pooling of data
4 Follow-up of patients after trials
1. Relapse
2. Residual effects
3. Long-term effects
4. Recovery of non-used drugs

The planning is the most important step for trials. The collaboration with biostatisticians and pharmacists will be required for this purpose. Although doctors do not have to be biostatisticians by all means, they should be able to understand the meaning of statistics, especially how to translate medical hypothesis into statistical hypothesis, and accordingly should design the trial.

In the checking items, 1 – 1, and 1 – 2, the short explanation on the statistical hypothesis and the type of experimental design are shown. Even though the statistical difference between the new drug and the standard drug (or placebo) is demonstrated, the final medical interpretation on the difference should be explained.

In the case of clinical trials, the handling of β is almost impossible.

Generally, the placebo is used in Phase I study and the active control drugs (i.e. standard or difference drugs) in Phase II and III studies.

The standard drugs should be selected from already commercialized and widely used drugs according to the target indication and the method of trials.

The quality control (appearance, color, odor, taste and dosage of active drugs, content of active ingredients and disintegration time of pharmaceutical form in artificial stomach or gastric juice) should be verified by the third party if possible.

The drugs to be used occasionally for the general accompanied treatment such as hypnotics, gastrointestinal remedy, analgesic-antipyretic, etc. should be standardized to avoid the interaction with the trial drugs.

The dosage schedule will be designed according to the previous experiments, target indications, the nature of drugs and the study setting.

The fixed/flexible schedule is used mainly for the minor tranquillizer evaluation.

The wash-out of formerly administered drugs will be sometimes required before the trial and in the case of cross-over design. However, the wash-out is not absolutely necessary if the treatment period is sufficiently designed.

The multiclinical studies are now frequently organized for the purpose of obtaining enough number of patients and gathering the actual and realistic information. In this case, the planning meeting plays an important role.

The trialist should understand and be accustomed to the controlled trials, and be trained for the rating with the neutral attitude. In this connection, preliminary validity test on the rating attitude of trialists may be required in the case of group or multiclinical studies.

The stratifications of patients seems to be quite difficult and the matched pair design based on the sequential analysis used for psychotropic trials has been discussed frequently as regards the validity of the methodology.

It is required to appoint the controller(s) who randomized the trial drugs and patients, keeping the key table and checking the fairness on the trial design, execution and data processing.

For an evaluation, the general improvement rate (G.I.R.) evaluated by doctors (and patients) may be the most useful information to assess the efficacy of drugs. This rate may be measured by the final judgement by trialists using the terms of improvement, non-improvement or aggravation.

General severity rate (G.S.R.) may be less valuable and despite of its difficulty for evaluation because the starting point of severity in each patient may be different due to the difficulty of stratification of patients.

Quantification of rating scale is an insoluble problem. There are different kinds of proposals. We are using the most suitable way which will fit in each trial design.

The adverse reactions should be carefully checked and rated. Usually, the comparison will be made on 30% of confidence level when compared with placebo, and on 5 – 10% level of confidence when compared with standard drugs. We observe sometimes the adverse reactions (also in laboratory data) in a placebo group.

The follow-up of drop-out cases is very important and these cases should not be omitted when the data is evaluated statistically.

How to judge the effects of drugs in drop-out cases is also an important problem. The most

severe attitude is to include the drop-out cases in the not improved ones when the follow-up of patients is impossible.

The discard case which is usually caused by inattention of trialists as regards the selection of patients should be avoided as much as possible.

When adequate and well designed planning is established, the trials are to be executed based on the rules established previously.

When we evaluate the obtained data, it should be kept in mind that the fair and reasonable medical interpretation is extremely important. Recently, a lot of trialists have suffered from a peculiar disease, the so-called "Significantitis" and often forgotten the medical interpretation.

The follow-up of the trials is also important. When the hypothesis is not proved, the judgement on the necessity to repeat the trials should be attentively considered.

By M.F.R. WATERS

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Controlled clinical trials are designed to ensure that comparisons of different treatments are as precise as informative and as convincing as possible. The basic techniques of such trials have been well developed and widely publicised in the last 30 years. Nevertheless, many trial reports, certainly in the sub-speciality of leprosy, and I suspect in other branches of medicine, reveal important faults in planning, methodology and analysis. The following generalisations are based on experience gained in eleven controlled trials and seven pilot trials carried out at the Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Malaysia, over the past 14 years.

The Protocol

For any trial to be successful, careful planning is required, including the production beforehand of a detailed protocol. This should clearly and concisely summarize the entire plan of the trial, including the aims and objects, drug regimens to be followed and their duration, the number of patients required, including their selection and allocation, the examinations and investigations to be performed before and during the trial, the methods and frequency of assessments, any special investigations required in view of the known or anticipated toxicity of trial drugs, the policy for interruptions in treatment and intercurrent disease, and wherever possible the tests to be carried out to ensure that trial drugs are in fact being taken and absorbed (Waters, Rees and Sutherland 1967).

Patient Selection

Careful selection of patients is essential. We have found it better to keep to a defined group of patients despite any resulting delay in intake, rather than broaden the basis for admission. For example, recent work from the Leprosy Research Unit and its collaborators has shown that there are four distinct and different mechanisms of peripheral nerve damage in leprosy (Pearson, 1972). Thalidomide is very effective treatment for one, but only one, of the four (Sheskin, Magora and Sagher, 1969; Sheskin and Sagher, 1971; Waters, 1971 b), namely the immune complex complication (Wemambu *et al.*, 1969) known as Erythema Nodosum Leprosum (ENL). In drug trials in leprous neuritis, to include all cases without regard to aetiology would be highly misleading. Precision in psychiatric diagnosis, related as it usually is to well-recognized symptom complexes rather than to proven aetiologies, may well be more difficult. However, careful analysis of individual as well as group assessments should be considered; the discovery of anomalous results in a proportion of patients might provide new insights into the classification and perhaps even the aetiology of mental disease.

Control Regimens

The choice of the control regimens depends on the condition under investigation. In some diseases, current standard therapy is required, e.g. dapsone (DDS) in untreated leprosy or penicillin in General Paralysis of the Insane (GPI). In others, placebo tablets may ethically be given. Wherever possible, both trial and control drugs (or placebo) should be used in identical preparations, thereby allowing the "double blind technique" to be employed. This is always desirable, but is particularly important in psychiatric studies where so many of the assessments have perforce to be relatively subjective. Reputable drug firms are most co-operative in the supply of identical placebo and trial drug capsules or tablets, and will also manufacture unusual (and to the patient, unrecognizable) preparations of standard drugs, if these appear psychologically desirable to avoid bias on the patient's part (Pearson and Helmy, 1973).

Methods of Allocating Patients to Treatment Groups.

What is invariably essential is the random allocation of patients to the two (or more) treatment groups being compared, in the knowledge that this method will yield series of patients whose condition is similar at the start of treatment; any differences between the series, whether in known or unknown factors of prognostic importance, will be small and within chance limits. We have found that the most satisfactory practical method of allocating patients to groups is to have a sequence of numbered opaque sealed envelopes prepared in advance by a statistician each containing a slip bearing the serial number, and a predetermined treatment allocation corresponding to it. When a suitable patient is admitted to the trial, the patient is assigned to the next free serial number, the appropriate envelope is opened, and the patient is placed in the treatment series indicated. When the response to treatment is known or believed to be affected by a characteristic of the patient (such as race, age or sex) or of the disease (such as a measure of its severity), the device of "stratification" should be employed at the allocation stage. It is usual to arrange the random allocations so that totals of patients in each treatment series remain closely similar as the intake proceeds for otherwise quite large differences might arise by chance, for example as a result of seasonal weather effects: psychiatric breakdown may be precipitated by a pre-monsoon heat wave, and ENL neurities by the stress of a rainy or cold season.

After allocation, the management, observation and assessment of all patients must be closely similar, so that any differences in response can be ascribed with confidence to the difference in treatment.

"Cross-Over" Trials

Where a disease condition persists for many months with little alteration in its severity, an alternative trial design is to use the patient as his own control (Sheskin, 1965; Sheskin and Sagher, 1971; Waters *et al.*, 1967). This method is not applicable where the treatment is believed to effect radical cure, e.g. antibiotics in bacterial meningitis, penicillin for GPI or Vitamin B12 for subacute combined deneration of the cord, but it is particularly attractive in the study of psychotropic drugs. We have ourselves used it widely in ENL trials, and the methodology utilized in a study of the effect of thalidomide in severe ENL is shown in Figure 1 (Waters, 1971a). The trial consisted of four 4-week periods, and during each the severity of the ENL was assessed by the total weekly prednisolone requirement (in mg) just sufficient to suppress the principal symptoms and fever of the reaction. An initial (control) period was followed by a second, in which, depending on random allocation, either thalidomide or identical placebo tablets were prescribed, the reverse treatment being given in the third period. A fourth (or final control) period was included to confirm that the ENL remained at, or returned to, approximately the same degree of severity as in period 1, i.e. spontaneous worsening or remission was excluded. Although the trial was double

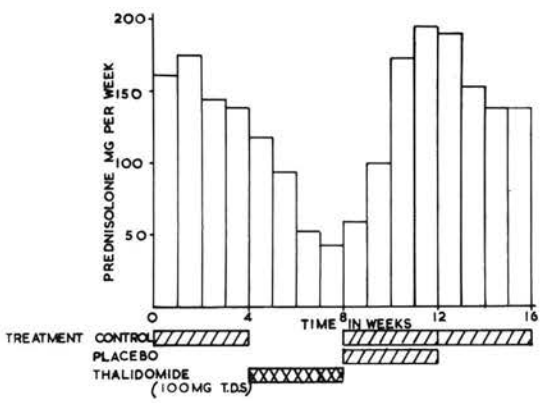

Figure 1: Double-blind trial design, 16-week schedule, for the effect of thalidomide (300 mg daily for 4 weeks) on prednisolone dosage in severe chronic erythema nodosum leprosum; representative result from an individual patient (Waters 1971a).

blind-indeed no one in Malaysia knew the tablet code until it was completed – two difficulties were encountered. First, the dates of the different trial periods were known to the doctor prescribing the prednisolone and theoretically bias in prescribing could have occurred at period change-over dates. In two more recent trials (Pearson and Helmy, 1973; Waters and Helmy, 1973) we have succeeded in making the dates of the individual trial periods effectively double-blind by utilizing treatment periods of two different durations, randomly allocated and known only to the drug dispenser. The second difficulty was that some patients complained of sleepiness during either period 2 or 3. The problem of both patient and doctor bias developing because of recognizable trial-drug side effects is less easily overcome, and is a major difficulty in studies of many psychotropic drugs.

Assessments.

Unless double-blind techniques are being employed, all assessments should be performed by Independent Assessors. This is usually simple to arrange for most objective assessments, e.g. nerve conduction velocities and voluntary muscle tests in neuritis, or serial EEG reports in epilepsy, but is frequently difficult in psychiatric assessment where patients may exhibit resentment and/or aggression against an 'outside' (independent clinical) assessor. In the more subjective clinical assessments, for both psychiatric and organic conditions, definitions of the different grades of severity used in scoring a sign or symptom should invariably be given. To state baldly, for example, that, "Anxiety was assessed according to four arbitrary" (and undefined) "grades of severity", makes a trial both unreproducible by, and the results less acceptable to, other workers.

Finally, controlled clinical trials are time consuming and exacting procedures. Before embarking on one, it is welll to ensure that the aims and objects specified are likely to be achieved by the trial design utilized, taking into account knowledge already gained of the properties of the trial drug from one or more pilot trials performed in a similar, if smaller, and equally carefully – selected group of patients. I have known one carefully conceived and executed controlled trial produce a negative result, solely because the dosage of the trial drug was too small to produce significantly the therapeutic effect under investigation (Pettit, 1967).

SUMMARY

From experience gained in the Leprosy Research Unit, Sungei Buloh over the past 14 years and from 11 controlled and 7 pilot trials, certain aspects of controlled drug trial design are discussed. It is recommended that a full written protocol should be produced before the start of any trial. The need for careful patient selection and of random allocation of patients to the different treatment series is emphasized. Certain practical difficulties encountered in double-blind trials using the patient as his own control ("cross-over trials") are discussed.

ACKNOWLEDGEMENTS

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CONCEPTS OF ILLNESS AND CHOICE OF TREATMENT

(A preliminary communication of a study on concepts of illness and choice of treatment among the people of Sri Lanka).

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INTRODUCTION

Concepts of illness and the preferred methods of treatment in a community are governed by a complex of interacting factors. These have to be understood by the practitioner not only for the purpose of helping the sick individual but also to effect counter-propaganda against beliefs and practices which militate against the acceptance of rational medicine.

It is observed in developing countries where strong traditions of indigenous medicine prevail, that efforts at introducing scientific medicine is hampered by varying degrees of resistance. To a considerable extent, this resistance is due to well established popular concepts of indigenous medicine which run counter to the concepts of modern medicine.

In Sri Lanka, the ill person has the opportunity of seeking assistance from three different sources, each of which is based on a different conceptual system. The oldest system of medicine originates from a magico-religious philosophy of life which leans heavily on demonology and to a lesser extent on astrology, Hinduism and Buddhism. The Ayurvedic system of medicine was introduced about 2000 years ago and this is based on the humoral theory of disease. The latest in the field is scientific medicine((western medicine), which although introduced about a century ago, was not generally available to the majority of the population up to the last few decades.

PRESENT STUDY

Objectives

The present study was undertaken with the following objectives:

(a) to determine the aetiological factors (concepts) which the patient (or informant) believed were responsible for his illness and to ascertain the factors correlated with such beliefs, and

(b) to determine the preferred methods of treatment and factors correlated with such choice.

Method

The sample consisted of 241 patients who entered the study from the following sources:

(a) 56 randomly sampled consultations from a suburban general practice,

(b) 63 consecutive admissions to 4 medical wards in a general hospital,

(c) 62 consecutive consultations from a psychiatric clinic in the out-patients department of a general hospital, and

(d) 60 randomly sampled admissions to a mental hospital.

Two criteria were applied in the selection of patients. First, the consultation should have been the first occasion on which the patient sought treatment for the present illness from any of the above sources and second, the duration of the present illness should have been at least two weeks, except for general practice where the minimum duration was taken as one week.

Study-Group

The study-group consisted of a general practitioner, two medical officers-in-psychiatry and a psychiatrist.

Data-Collection

A schedule was prepared by the study-group to collect the relevant data. This was completed by the interviewer soon after the clinical examination of the patient. In case the patient was below the age of 15 years or for any reason was considered incapable of responding adequately to the questions in the schedule, an informant who had intimate knowledge of the patient's illness was interrogated to complete the schedule.

A reliability trial was undertaken on 20 first-attenders to a psychiatric clinic of a general hospital. This established a high degree of correlation in the collection and recording of data between the members of the study-group.

RESULTS

In the presentation of data, respondent refers to the person who was interviewed to complete the schedule. Thus the concepts presented in this

section and the characteristics correlated with concepts and methods of treatment, refer to that of the respondents, irrespective of whether they be patients or informants.

Illnesses

The total sample consisted of 241 patients. When illnesses were classified into 3 broad groups of illnesses, there were 84 psychotic patients, 57 neurotic patients, 88 medical patients and 12 patients whose diagnosis was in doubt. The total number of psychiatric patients (psychotic + neurotic) was 141.

Concepts

The concepts stated by the respondents were classified under (a) demonological – which included demoniacal possession and charms or spells cast by an enemy, (b) unfavourable astrological influences, (c) disorder of humors, (d) organic affliction (other than disorder of the humors), (e) emotional disturbance, (f) other, and (g) no concept stated.

Respondents often claimed more than one aetiology for an illness; for 241 illnesses there were 485 concepts stated.

Concepts by Diagnostic Group

Respondents claimed a demonological concept most frequently in psychotic illnesses followed by neurotic illnesses. A good proportion (34%) also stated a demonological concept for medical illnesses.

About a third of respondents stated an astrological concept or humoral concept, in roughly equal proportions for the 3 groups of illnesses.

An organic aetiology was expressed mainly for physical illnesses followed by neurotic illnesses and medical illnesses. in that order. In reverse order, was stated an emotional origin for illnesses.

Concepts by Educational Level of Respondents

Belief in demonological, astrological and humoral concepts tended to drop sharply on reaching a Grade 10 level of education. This decline was less marked for psychiatric illnesses than for medical illnesses.

An emotional aetiology was infrequently stated at the lower levels of education.

Concepts by Income Level of Respondents

Demonological, astrological and humoral concepts were claimed less by respondents in the 2 highest income groups. This difference was less marked for psychiatric illnesses than for medical illnesses.

Treatment

Magico-religious methods of treatment were sought mainly in psychiatric illnesses – especially in psychotic disorders. However, they were also used in a considerable proportion of medical illnesses.

When the expenses incurred in the various forms of treatment were compared, it was observed that the magico-religious methods of treatment were the most expensive for the patient. Treatment by the witch-doctor was particularly exorbitant.

CONCLUSION

The general conclusions which can be drawn are:

(1) traditional concepts of illnesses and traditional methods of treatment are very much in vogue, especially in psychiatric illnesses,

(2) there is a tendency to abandon these concepts and methods of treatment with increase in education and income beyond a certain critical level.

(3) the magico-religious methods of treatment are more expensive to the patient than Ayurveda or modern medicine.

THE RATIONALE OF TREATMENT OF MALADAPTATION SYNDROME

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Under the present socio-economic and political structure, a man cannot be divorced from the society. In fact, it is difficult to conceive of a man in the modern age as an independent existing unit. He has to conform to certain rules and regulations, which dictates his behaviour pattern, and demands certain contributions and he has no choice other than to face dire penalties.

However, man, contrary to a popular saying, is not born gregarious. The newborn baby accepts no company. Gregariousness is induced culturally, and in the process of cultural induction, a man has to make constant adaptations. Failure in adaptation makes itself manifest in many ways, and passively, it takes the form of "ill-health" of a protean nature, which may be broadly grouped as maladaptation syndrome.

Theoretically, adaptation is a result of the interaction of two parties – the environment and the organism. A hostile environment, or an unadaptable organism or both in combination are necessary to cause maladaptation.

Hitherto, it is assumed that the treatment of maladaptation is a combination of drug therapy, psychotherapy, and social readjustment, but the fact that the disease manifestation is protean, and the incidence generally accepted to be rising must mean that as yet we are not treating the "disease" effectively.

In general, treatment of a disease is dependent on the accurate knowledge of the epidemiology, and the therapeutic skill. In maladaptation, however, although much has been said, little is known in a systematised manner. In order to arrive at some rationale of treatment, an analysis is made of 400 consecutive cases seen in a private consulting practice of an internist. This results in a pick up of 104 cases, which fit the label of maladaptation. The following report is based on an analysis of some of the relevant aspects of these cases.

These cases are divided into two broad groups – one that continues to receive medical supervision, 'repeaters' and one that very quickly wanders off and ceases to come up, 'non-repeaters'. We may oversimplify the case by assuming that the first group represents people who accept medical guidance readily, have trust and faith in their doctors, and are willing to keep up with the supervision, presumably because they are getting some benefit. In contrast, the other represents the treatment failures, and the sceptics who are ready to change their mode of medical care, presumably because they do not get satisfaction. It can be seen that the numbers are about equal – 51:53. (A previous unpublished study of mine showed that the success rate of non-psychiatric consultant in the treatment of maladaptation cases was 50%, a figure similar to the present study, whereas that of the private practitioner in general practice and that of the psychiatrist were 70% and 25% respectively).

These cases are analysed with regard to age and sex, the nature of the complaints, and the duration and quality of medical care received.

Table I shows that these cases are predominantly Chinese showing more a selection due to sociological reasons rather than a reflection of differential racial incidence. For example, Malays tend to seek much less of western medical care. An Indian prefers cheaper institutional facilities, and those classified as others include a large number of foreigners, whose stay in Singapore was brief such as tourist etc.

Table II shows that whereas the sex distribution is about 1 : 1 in non-repeaters, the repeaters show a strong female bias. The peaks in females of both groups are in the fifth decade, whereas in the male, one has no peak, and in the others, this occurs in the fourth decade. This permits many interesting speculations, such as that the male is more difficult to satisfy, and has no peak periods for the onset of maladaptation, whereas the menopause may be a significant factor, as in fact has been the belief among doctors for a good long time (Menopausal syndrome).

Table III shows that a significant number of these patients (32% – 51%) has physical anomaly, and of these anomalities, only about half of them are trivial. The incidence of physical disease is more in the group which continues with medical

care. It is of interest to note that cardiac diseases form the majority, more than can be accounted for by the relative incidence of diseases. This may mean that the campaigns on prevention of cardiac diseases have contributed to the increased awareness and fear resulting in a rise of maladapted cases among cardiac cases.

Table IV shows that mental subnormality has an insignificant role to play in maladaptation diseases.

Expectedly, psychiatric illnesses are few (4% – 8%), and the majority of the manifestations are anxiety, depression or both in combination (Table V). Also as expected is the high proportion of cases with multiple complaints (Table VI).

The next three tables are of particular interest in showing the economic significance of maladaptation diseases. They cause prolonged morbidity, and make the patients seek medical aid much more. Specialist services and hospital facilities are likewise much utilised without much evidence of benefit. The use of psychiatrist appears to be confined to only those cases who are frankly psychotic. This could be due to a number of factors at work; included among them may be mentioned the following:

1. The general reluctance of the medical profession, and the maladapted patients (at least in this series) to avail themselves of psychiatric service. Perhaps, psychiatry has yet to convince the medical profession that it is able to make significant contribution towards the treatment of non-psychiatric maladaptations.
2. Some cases may have been sent to psychiatrists earlier, and being improved, would not show up in this series. In other words, these cases could represent failed psychiatric cases in part. Comparison with series by general practitioners, psychiatrists, and specialists in other disciplines would yield interesting information.
3. The small number of psychiatrists available would militate the psychiatrists towards psychotics, who would occupy their time in almost toto, with little to spare for other conditions.

If we assume that the principle of treatment is the early restoration to normal health, then this series has told us that treatment has been on the whole unsatisfactory. Perhaps, our present technique of drug therapy with little psycho-therapy, amateurish or professional, is inadequate, and the real solution lies elsewhere.

Table I Race

Repeaters	51 (49%)	Non-repeaters 53 (51%)
Chinese	46 (90%)	45 (85%)
Indian	3 (6%)	1 (2%)
Malay	2 (4%)	1 (2%)
Others	0 (0%)	6 (11%)

Table II Age and sex

		Repeaters		Non-repeaters	
< 15 years	M	0		0	
	F		0		1 (4%)
16 – 20	M	2 (13%)		1 (4%)	
	F		2 (6%)		7 (25%)
21 – 30	M	2 (13%)		4 (16%)	
	F		6 (17%)		9 (32%)
31 – 40	M	2 (13%)		11 (44%)	
	F		6 (17%)		5 (18%)
41 – 50	M	3 (22%)		6 (24%)	
	F		10 (28%)		22 (7%)
51 – 60	M	4 (26%)		2 (8%)	
	F		9 (24%)		3 (11%)
> 60	M	2 (13%)		2 (8%)	
	F		3 (8%)		28 (53%)
Total	M	15 (29%)		25 (47%)	
	F		36 (71%)		

Table III Physical Signs.

Repeaters			Non-repeaters	
No physical sign	25	(49%)	36	(68%)
Physical Sign:				
Significant	13	(25%)	9	(16%)
Insignificant	13	(25%)	9	(16%)
Cardiac	15	(45%)	4	(22%)
Respiratory	3	(10%)	2	(11%)
C.N.S.	5	(15%)	4	(22%)
G.I.	5	(15%)	3	(17%)
Other	5	(15%)	5	(28%)

Note – some cases belonged to more than one system.

Table IV I.Q.

Repeaters			Non-repeaters	
Normal	48	(94%)	53	(100%)
Subnormal	3	(6%)	0	–

Table V Maladaptation Types

Repeaters		Non-repeaters
Psychiatric cases:		
Schizophrenic	2	1
Affective	1	1
Others	1	0
Total	4 (8%)	2 (4%)
Psychosomatic:		
Anxiety	24 (56%)	30 (57%)
Depression	17 (39%)	10 (19%)
Hysteria	1	8 (15%)
Malingering	1	1
Others	0	4 (7%)
	43	53

Note: Some cases belonged to more than one category.

Table VI Number of complaints

Repeaters		Non-repeaters
One complaint	8(15%)	15 (28%)
2 complaints	17 (73%)	16 (30%)
> 2 complaints	6 (12%)	22 (42%)

Table VII Duration of complaints

Repeaters		Non-repeaters
< 1 month	3 (6%)	4 (8%)
1 month – 1 year	11 (21%)	18 (34%)
1 yr – 5 yrs	21 (41%)	14 (26%)
> 5 yrs	16 (32%)	17 (32%)

Table VIII Number of doctors seen

Repeaters		Non-repeaters
1 doctor	5 (10%)	4 (8%)
2 doctors	15 (29%)	23 (43%)
> 2 doctors	31 (60%)	26 (49%)

Table IX Use of special services

Repeaters		Non-repeaters
Specialist	28 (49%)	22 (42%)
Hospital	23 (45%)	15 (28%)
Psychiatrist	3 (6%)	4 (8%)

TYPES OF NEUROSES AND THEIR TREATMENT

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I INTRODUCTION

We have many theories on neurosis. Neurosis is a disturbance due to a problem in interpersonal relationships. In principle, interpersonal relationships are mixtures of culture-bound parts and intercultural parts; therefore, there are various theories of neuroses. There are not only varieties of theory but also differences in the manifestations of neurotic symptoms under arculturation. WHO has been adopting an integrative conceptual typology of neurosis in the International Classification of Diseases as seen in Table I. However, in my opinion ICD is a classification for statistics and is not necessarily suitable for the treatment of a neurotic patient.

Table I

Psychoneurotic Disorders (310–318) ICD

- 310. Anxiety reaction without mention of somatic symptoms.
- 311. Hysterical reaction without mention of anxiety reaction
- 312. Phobic reaction
- 313. Obsessive-compulsive reaction
- 314. Neurotic-depressive reaction
- 315. Psychoneurosis with somatic symptoms (Somatization reaction) affecting circulatory system
- 316. Psychoneurosis with somatic symptoms (somatization reaction) affecting digestive system.
- 317. Psychoneurosis with somatic symptoms (somatization reaction) affecting other systems
- 318. Psychoneurotic disorders, other, mixed, and unspecified types
  - 318. 0 Hypochondriacal reaction
  - 318. 1 Depersonalization
  - 318. 2 Occupational neurosis
  - 318. 3 Asthenic reaction
  - 318. 4 Mixed
  - 318. 5 Of other and unspecified types.

Most of the many theories of neurosis were proposed and systematized through the experiences of the excellent founder who had the deepest insight about his few cases. For instance, today, we cannot understand neurosis without the theory of psychoanalysis of S. Freud. But, nevertheless he had published a great deal of his books and as is well known, had presented only five case reports in all his work as seen in Table 2. His psychoanalytic theories such as the mechanism of symptom-formation of neurosis, process of unconsciousness, infantile sexuality, resistance and transference were based on his case reports. Nevertheless, many people believe that his theories can deeply elucidate the mind of human beings but do not accept all his theories. He divided neuroses into the two types of actual neurosis and psychoneurosis as seen in Table 3. The former has no relationship to psychic conflict and is due to a waste or intoxication of sexual substance. By contrast, the latter has conflict in the processes of the unconsciousness. Many researchers rejected this theory. Also, Freud gradually stopped using the concept of actual neurosis after the presentation of his famous article "inhibition, symptom and anxiety."

Table II

Case Reports by S. Freud

1. Case of Dora (1905) (1901)
   Fragment of an Analysis of a Case of Hysteria
   (Comparison between mechanism of dream and hysteria)
2. Case of Little Hans (1909)
   Analysis of a Phobia in a Five-Year Old Boy
   (oedipus complex infantale sexuality)
3. Case of Rat man (1909)
   Notes upon a Case of Obsessional Neurosis
   (structure of obessive-compulsive neurosis infantile sexuality)
4. Case of Schreber (1911)
   Psychoanalytic Notes Upon Autobiographical Account of a Case of Paranoia (Dementia Paranoides)
   (paranoid mechanism)
5. Case of Wolf man (1918) (1914)
   From the History of an Infantile Neurosis.
   (psychosexuality)

Table III

Neurosis

1. Actual Neurosis
   Neurasthenia, Anxiety Neurosis
2. Psychoneurosis
   Hysteria, Obsessive-Compulsive Neurosis

(S. Freud)

2. *Typification of Neuroses by Factor-analysis*

On one hand, there are easily curable neurotic patients who respond to a minor tranquillizer with simple psychotherapy. On the other hand, some cases require a regular long term psychoanalysis. It is very difficult to apply theories based on a small number of cases to a large number of neurotic patients. Consequently, I have tried factor-analytic studies of the neurotic symptoms.

I have picked up one hundred items from symptom, attitude, and behaviour meaning neuroses in many older and newer textbooks and/or articles. And I have made up a rating scale for neuroses.

In the first step of our factor-analytic studies on neurotic symptoms in fifty cases using our rating scale, four clusters were found as seen in Table 4. These were

(1) anxious and hypochondriacal group,
(2) nervous and depressive group,
(3) phobic and obsessive-compulsive group and
(4) behaviour disorder and hysterical group.

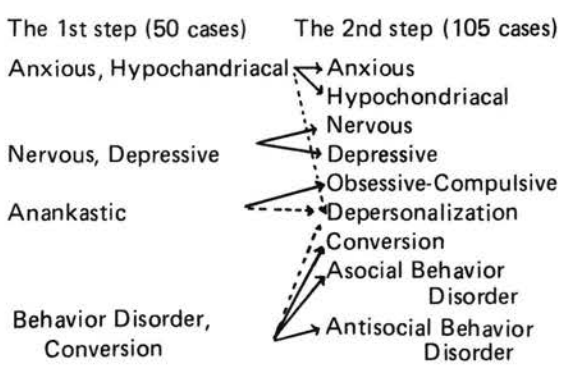
In the second step of our studies, in which the number was increased to one hundred and five cases, the clusters also increased to nine.

Each group of symptoms in the first step was separated as follows in the second step.

The anxious and hypochondriacal group became
(a) anxiety neurosis and (b) hypochondriasis.
The nervous and depressive group became
(a) nervousness (Morita-type) and
(b) neurotic depression
The anankastic type was changed to
(a) obsessive-compulsive neurosis and
(b) depersonalization.
The behaviour disorder and hysterical group became
(a) conversion
(b) withdrawal type of behaviour disorder and
(c) assaultable type of behaviour disorder

Table IV

Clusters of Neuroses were found Factor-Analysis



3. *Neuroses and Life cycles*

Some manifestations of neuroses are related to the life cycle. There is a common mentality in each generation, therefore, the nature and types of neuroses would be determined by this mentality. I have examined the characteristics of each generation, about 1,533 cases in all generations, as noted in Table 5. In this study, I found conversion and obsessive-compulsive neuroses, which S. Freud had studied as the model of neurosis, distributed among all generations. Then, these types of neuroses

Table V

Neurosis be seen in each Generations

Childhood Neurosis
nightmares, nightenuresis, animal-fear, tic, school-phobia.

Pre-Puberty Neurosis
insomnia, headache, social withdrawal and violent behavior

Puberty Neurosis
anxiety, tension, school-refusal

Adolescent Neurosis
self-insufficient feeling, anthopophobia, feeling of loss of his way

Adulthood Neurosis
anxiety, hypochondriasis, depression

Senile Neurosis
hypochondriasis, depression

Neurosis beyond Generations

Conversion
Obsessive-Compulsive Neurosis

should be called infantile neurosis in adulthood. By contrast, anxiety, hypochondriasis, and depression that we often find in adulthood are suitable for treatment with psychotropic medication and do not require a complicated psychotherapy. And, origins of these neuroses are rooted in the realistic life situation. Namely, these neuroses have causal conflicts related to production, care, and love as manifestation of emotional needs of adulthood Therefore, these types of neuroses are adulthood neurosis or actual neurosis in adulthood. S. Freud had presented the unconscious, resistance, transference, and anxiety as important concepts. His many theories are accepted by his successors, but they hesitated to follow his attitude towards the libido theory. In my opinion S. Freud thought that the transformation mode of psychic energy was determined in developmental stages. He eagerly emphasized infantile sexuality, particularly the oedipus desire and did not say so much about postoedipal developmental stages, namely psychoanalytic elucidations of anxiety, hypochondriasis and depression.

4. *Some Therapeutic Results of Neuroses.*

I have experimentally treated neuroses for three years. I used bromazepam medication with a thirty minutes interview in this experiment. Bromazepam is a newer high potential derivate of benzodiazepine. The results of the treatment are shown in Table 6. The efficacy of the treatment was most excellent in anxiety neuroses. In second place, neurotic depression and hypochondriasis showed improvement. These types of neuroses are actual neuroses in adulthood. By contrast, phobia, obsessive-compulsive neurosis, conversion hysteria and nervousness did not show satisfactory results. We could not reach into the deep parts of the mind of a patient in a thirty minutes interview so we used relation therapy. Therefore, infantile neuroses in adulthood is incurable by that treatment.

Table VI

Types of Neuroses and Effects of their Treatment
(bromazepam, 30 minutes Interview)

Cases \ Effects		+++	++	+	±	X
Anxiety Neurosis	10	10.0	70.0	10.0	0.0	10.0
Hypochondriasis	22	9.1	40.9	40.9	9.1	0.0
Anankastic Neurosis	21	0.0	19.0	52.3	28.6	0.0
Conversion	9	0.0	11.1	55.6	33.3	
Neurotic Depression	8	25.0	37.5	25.0	12.5	0.0
Nervousness	4	0.0	25.0	50.0	25.0	
Neurotic Behavior Disorder	9	11.1	22.2	33.3	33.3	0.0
Others	5	0.0	0.0	60.0	20.0	20.0
	88	6.8	30.7	40.9	19.3	1.1

5. *Types of Neuroses and their Treatment*

As I summarize my experiences in twenty years of the treatment of neuroses; the results are in Table 7.

Table VII

Types of Neuroses and their Treatment

1. Anxious and Hypochondriacal State
   benzodiazepine
   amitriptyline
   supportive psychotherapy
   relation therapy

2. Nervous and Depressive State
   amitriptyline
   benzodiazepine
   persuasion with emotional acceptance

3. Phobic and Obsessive Compulsive State
   (1) immature personality } benzodiazepine amitriptyline
   (2) immodithymic personality } support and relation therapy
   (3) anal personality — haloperidol psychoanalysis behavior therapy

4. Neurotic Behavior Disorder and Conversion
   psychoanalysis
   family therapy

(A) *Anxious and Hypochondriacal State*

Those neuroses are most responsive towards psychotropic medication. Slight anxiety and tension, particularly somatic anxiety reacts well to benzodiazepine, severe anxiety is more suited to amitriptyline. Of course, psychotherapy is necessary as a principle, but, therapeutic actions within a ten minute interview was limited to persuasion and/or guidance of symptom levels. In such a situation, treatment with psychotropic medication is most efficacious. The patient with psychic anxiety is not helped by such simple psychotherapy. More complicated psychotherapy is required in which the patient should confront his attitude towards the symptom and his family in a session of at least thirty minutes.

(B) *Nervous and Depressive State*

The central problem of these neurotic states is psychic anxiety. Anxielytic drugs including an anti-depressive effect, e.g. bromazepam or diazepam in benzodiazepine derivates, or an anti-depres-

sant including anxielytic effect e.g. amitriptyline are effective. The psychotherapeutic approach to those neuroses centres in support of the dependent patient by emotional acceptance. After these patients get back their spontaneity, they must learn how to live.

(C) *Phobic and Obsessive-compulsive State*

These neurotic states usually are understood as practically incurable. But I have found that some cases of these neurotic states also show a positive reaction to psychotropic medication according to the personality of the patient. Patients with anankastic neurotically bound immature personalities or immodithymic personalities as shown by Dr. Shimoda frequently complain of obsessive drives to achieve confirmation and seek reassurance by strong people around them. For the purpose of treatment of such patients, we have to try to reduce his tension level by using benzodiazepine or amitriptyline, and use relation therapy with emotional support. Most incurable cases of anankastic neurosis are people who have an anal personality with rigid and inhibited emotions. Although those patients usually are incurable, some of them show partial improvement by taking haloperidol. Of course, such cases always require intensive psychotherapy, particularly psychoanalysis. When psychoanalysis is used prescribing drugs often disturbs the progress of treatment. In the psychoanalytic treatment of obsessive-compulsive neurosis, classical technique is not so adequate, and I do not recommend the use of only free association. Rather I recommend an active and flexible attitude in the psychiatrist. Psychotherapy in such cases makes much of "here and now" rather than the elucidation of the infantile experiences of the patient. At first, the patient and psychiatrist look for the origin of insecurity in the patient. Next, they try to make a working-alliance, and finally, the patient has to learn the limitations of the nature of a human being.

(D) *Neurotic Behaviour Disorder and Hysteria*

Psychotropic medication usually has no effect on those conditions. Sometimes we can see a dramatic suggestive effect or secondary effect. When psychotropic medication is used in those cases, the process of treatment is usually disturbed. The basic approach in treatment of such cases should include psychoanalysis or psychoanalytically oriented psychotherapy. In addition, the psychiatrist must maintain neutrality towards his patient. And, neurotic depressions in younger adulthood often require family therapy.

6. SUMMARY

It is not reasonable that neuroses are understood as homogeneous psychogenic disorders. In my opinion, neuroses are a mode of different psychosomatic reactions. If we can elucidate the type of neuroses from the above mentioned view point, the treatment of neuroses may be advanced.

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REASONS FOR ADMISSION TO THE SINGAPORE MENTAL HOSPITAL

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A preliminary survey of the first 100 new cases admitted to Woodbridge Hospital in the months of January and early February was made, and the reasons of admission were elicited. Woodbridge Hospital is the only mental hospital in Singapore and caters for all mental patients requiring in-patient treatment. An out-patient service is provided and new cases, which are not acute enough to require admission are seen by psychiatrists in 2 out-patient clinics.

The number of new patients admitted in 1972 are: 1111

Method

A standard interview was given to each new patient. If relatives accompanied him, then a history was obtained from them. The patient was given a detailed examination and the reasons which caused him to seek admission were noted. The symptoms causing social and interpersonal stress were obtained from the relatives or referring to doctor's reports.

Results

100 new cases were seen.

Of these 61% were diagnosed by the consultant psychiatrists to be of schizophrenic origin. The rest were grouped as non-schizophrenic patients.

Table 1

Sex Ratio: The males outnumbered the female roughly on a 2 : 1 basis.

		M	F
Schizophrenic	61	43	18
Non-schizophrenic	39	27	12

The Singapore male to female proportion is roughtly 1 : 1

The number of Schizophrenic patients reached a peak in the 20 – 29 age group. Not surprisingly, there were none in the 60 – 69 group. The number of patients in the non-schizophrenic group were roughly equal up to the age range of 40 – 49, when they tailed down.

Table 2
Age Distribution

Age	Psychotic	Non-Psychotic
10 – 19	14	8
20 – 29	23	9
30 – 39	12	8
40 – 49	6	7
50 – 59	1	4
60 – 69	0	2
Total	56 + 5 UK = 61	38 + 1 UK = 39

UK = Unknown

Total No. of patients = 100

Table III: Ethnic Group and Diagnosis

	Schiz.	Non-Schiz.	Total	Racial dist. of Singapore in Mid 1972
Chinese	48	24	72	76.1%
Malay	4	5	9	15.1%
Indian	7	8	15	6.9%
Other Asians	1	)	4	1.9%
Caucasians	1	2)		

There were a predominance of Chinese which reflected the racial distribution. However the number of Malays were less than exepcted, and the number of Indians admitted were more than the expected number.

Table IV: Educational Attainment and Diagnosis

	Schiz.		Non-Schiz		Total
	M	F	M	F	
Illiterate	15	3	4	4	26
Primary	15	10	15	4	44
Secondary	13	5	8	4	30

About 74% of patients had some form of education, while 26% were illiterate.

Reasons for admission

I Social and Interpersonal Stress

Table V: Type of Behaviour and Diagnosis

	Schiz.		Non-Schiz.		Total
	M	F	M	F	
Abnormal behaviour	22	5	11	7	45
Irrational	17	6	4	2	29
Violent/Agg.	14	4	9	4	31
Disturbed	13	8	6	2	29
Withdrawn	4	2			6
Wandering	7	2			9

The above symptoms rarely occurred alone, but were usually continued with other symptoms. They were classified into symptoms of social and interpersonal stress and subjective stress. The presenting symptoms occurring in each individual patient were recorded. From the above table, 60% of patients were violent and aggressive or disturbed, 45% of patients showed abnormal behaviour, 29% of patients were irrational, 6% were withdrawn and 9% were found wandering. The latter 2 symptoms were complained of only in the schizophrenic group.

II Subjective Distress

The number of symptoms of subjective distress were less than those in the above group. Patients with strong suicidal ideas were usually admitted, unless they or the relatives refused admission. Delusions and hallucinations were associated with symptoms of the first group.

Table VI: Type of Symptoms and Diagnosis

	Schiz		Non-Schiz.		Total
	M	F	M	F	
Insomnia	10	1	1	1	13
Depressed	4	4	6	3	17
Suicidal	3	3	5	3	14
Delusions	9	8	3	3	23
Hallucinations	7	4	1		12

Diagnosis of non-schizophrenic group

6 – Behaviour disorder in dull or mentally subnormal
6 – Alcoholism
4 – Paranoid state
4 – Confusional state
4 – Depressive illness
3 – Personality disorder
2 – Attempted suicide
2 – Mania
1 – Hysterical fugue state
1 – Situational reaction
1 – Delirium tremen
1 – Epileptic psychosis
1 – Drug psychosis
2 – remand cases charged with (1) rape (2) theft were found to be normal.

DISCUSSION

The results of the study showed that 61% of the patients admitted were schizophrenic. The non-schizophrenic group consisted of a wide spectrum of psychiatric illness. The predominance could be because of the nature of the schizophrenic illness.

There was a significantly higher number of male patients admitted. This could be due to the greater intolerance of mental illness in males who comprised the major working group.

The racial distribution showed that more Indians and less Malays were admitted than expected. Possibly Malays sought traditional healers more frequently than Indians, or else their tolerance to social and interpersonal stress or subjective stress caused by mental illness was higher.

The symptom which was most frequently complained of was abnormal behaviour, and this was seen in 45% of patients. This varied from patient to patient, but talking, laughing and crying to himself was frequently reported. Stripping and walking around naked was also reported. One patient was admitted because he locked himself in a room and appeared abnormal to his relatives.

Violent and aggressive behaviour understandably, was an important reason why relatives, friends or police sought admission for the patients. 31 patients exhibited this – 18 schizophrenics and 13 non-schiz. 29 patients showed disturbed behaviour – they were noisy, shouting, restless or excited. Another 29 were irrational.

These 4 major reasons for admission, namely abnormal, violent, aggressive or disturbed behaviour and being irrational are recognized by the lay public as being associated with mental abnormality, and caused so much distress that the in-patient treatment was requested. They were also the major criteria by which admitting doctors assessed whether a patient required admission or not.

In the group of symptoms causing subjective distress and necessitating admission, insomnia, being suicidal and depressed ranked high. Patients with suicidal intentions had often to be persuaded

to be admitted as the stigma against mental hospitalization still presents high. Delusions and hallucinations were usually associated with symptoms of the first group, and there was no patient who was admitted for these two symptoms alone.

SUMMARY

A series of the first 100 new cases admitted to Woodbridge Hospital were studied and the reasons for admission elicited. The majority were admitted because of abnormal behaviour, being aggressive and violent or disturbed or talking irrationally. Subjective symptoms which required admission were those of insomnia, depression, suicidal feelings, delusions and hallucinations.

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CARDIOVASCULAR HAZARDS FROM INTERACTIONS BETWEEN IMIPRAMINE AND CATECHOLAMINES

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SUMMARY

Though hypertensive crisis and sometimes death resulting from interactions between monoamine oxidase inhibitor (MAOI) antidepressants and catecholamines are well known, similar cardiovascular hazards are seldom reported with tricyclic antidepressants. Therefore interaction experiments were carried out in human volunteers between imipramine, a tricyclic antidepressant, and sympathomimetic amines in this study. It was found that imipramine potentiated the pressor effect of phenylephrine by two- to three-fold, that of noradrenaline by four- to eight-fold and that of adrenaline by two- to four-fold. There was no significant change in the response to isoprenaline. Dysrhythmias were recorded during adrenaline infusion after pretreatment with imipramine. It is recommended that patients taking imipramine or other tricyclic antidepressants must avoid using local dental anaesthetic containing noradrenaline, phenylephrine as nasal decongestant and subcutaneous adrenaline for the treatment of bronchial asthma as the resultant interactions may precipitate hypertensive crisis and serious arrhythmias.

The pressor effect of some sympathomimetic amines has been shown by Elis et al (1967) to be potentiated in subjects receiving monoamine oxidase inhibitor (MAOI) antidepressant. Hypertensive crisis and sometimes sudden death resulting from the above interactions are quite well known. However, similar cardiovascular hazards with tricyclic antidepressants are rarely reported in pharmaco-therapeutic textbooks and medical literature. Therefore the use of tricyclic antidepressants in the treatment of depression predominates in the clinical practice as they are regarded to be less dangerous and toxic than MAOI antidepressants. The ability of tricyclic antidepressants to potentiate the cardiovascular effect of noradrenaline was first suspected by Sigg in 1959 and was later confirmed in animal experiments by Kaumann et al in 1965. Recently Svedmyr (1968) showed that in human volunteers a tricyclic antidepressant, protriptyline, potentiated the pressor effect of noradrenaline and adrenaline. As sudden deaths have been reported recently to have occured in patients taking tricyclic antidepressants (Coull et al, 1970; Moir et al, 1972), the safety of using tricyclic antidepressants is now questioned by many physicians. The mechanism underlying this sudden death is still not certain but it can either be due to direct cardiotoxic action of tricyclic agents on the heart or due to interactions with concomitantly administered drugs (Moir, 1972). In

view of the serious cardiovascular hazards which may arise as a result of interactions, it appears to be of great value to carry out interaction experiments between imipramine, a commonly prescribed tricyclic antidepressant and catecholamines, in human volunteers.

Method

Four healthy human volunteers (age range 30 to 48) received intravenous infusions of phenylephrine, noradrenaline, adrenaline and isoprenaline under control condition and after taking imipramine 25 mg three times a day for five days. At each experiment, the four sympathomimetic amines were infused in random order without the subjects being aware of the order. Before infusion started, each subject rested supine until blood pressure and heart rate had reached a steady state. Throughout the experiment, the blood pressure was measured by the London School of Hygiene sphygmomanometer (Rose et al, 1964) which is designed to eliminate observer bias. The rate and rhythm of the heart were continuously monitored by Mingograph recorder. Infusions were given for a period of five minutes at each concentration (steady state usually occurring after three minutes), and the concentrations being increased in logarithmic fashion. Phenylephrine infusions were started at 50 ug/min, and at five minutes' interval, the rate of infusion was increased to 100 ug/min, 200 ug/min and 400 ug/min, etc. Noradrenaline and adrenaline infusions were started at 2 ug/min, and at five minutes' intervals, the rate of infusions was increased to 4, 8, 16, 32 ug/min, etc. Isoprenaline infusion was started at 1 ug/min and then increased to 2, 4, 8, 16 ug/min etc. at five minutes' intervals. It was decided that infusions should be terminated when systolic pressure exceeded 170 mmHg or when the heart rate increased by 40 beats per minute or when the subject requested.

Table I. Summary of results. Figures in parentheses are standard errors.

	Phenylephrine			Noradrenaline			Adrenaline			Isoprenaline		
	Before	After	P	Before	After	P	Before	After	P	Before	After	P
Average dose:	200 ug/min			9 ug/min			18 ug/min			5 ug/min		
Imipramine 25 mg t.d.s. for five days (n = 4) B.P.* Systolic	143(9.9)	173(0.6)	<0.05	131(6.4)	174(1.4)	<0.05	123(10.2)	153(16.1)	<0.025	109(8.7)	104(7.4)	N.S.
Diastolic	89(1.4)	108(4.8)	<0.05	84(5.6)	99(1.3)	0.05	60(5.4)	72(4.4)	<0.05	49(5.1)	50(3.7)	N.S.
Mean	107(4.3)	130(3.3)	<0.02	100(4.4)	124(0.8)	<0.01	81(6.9)	99(7.8)	<0.01	69(6.2)	68(4.7)	N.S.
Heart rate*	45(3.2)	50(4.0)	<0.01	63(5.2)	53(2.0)	N.S.	86(6.9)	95(12.2)	N.S.	121(5.2)	127(1.9)	N.S.

*The quoted levels of B.P. and heart rate are those produced by the maximum tolerated doses of sympathomimetic amines after antidepressant compared with those levels produced by similar doses under control conditions.

Results

The final (steady state) blood pressures and heart rates during infusions of each amine after the subjects had been pretreated with antidepressant were compared with the blood pressures and heart rates produced by equal concentrations of amines under control conditions. These results are summarised in table I. The significance of imipramine-induced modification of the response of blood pressure and heart rates to infusions of amines was determined by means of paired t tests. The p values quoted are derived from two-tailed tests.

Imipramine 25 mg three times a day for five days was associated with dry mouth, tachycardia in all subjects. There was a two-fold to three-fold potentiation of the pressor effect of phenylephrine ($P < 0.05$), a four-fold to eight-fold potentiation of noradrenaline ($P < 0.05$), and a two-fold to four-fold potentiation of adrenaline ($P < 0.025$). (See figs. 1, 2, and 3). Some potentiation of adrenaline-induced tachycardia occurred in subject 2, but not in the other three subjects. However, striking changes in rhythm occurred — three subjects developed noticeable sinus arrythmia, and the other subject (subject 1) developed numerous atrial ectopics, ventricular ectopics and runs of nodal rhythm. Isoprenaline-induced tachycardia was modestly potentiated (nearly two-fold) in one subject but was unaltered in the other three. There was no significant change in the response of blood pressure to isoprenaline.

DISCUSSION

The results obtained in our study agree fairly

well with those of Svedmyr (1968) who found that protriptyline potentiated the pressor action of noradrenaline approximately nine-fold and that of adrenaline three-fold when these catecholamines were intravenously infused in man. However a two- to three-fold potentiation of the pressor effect of phenylephrine observed in our study is not in agreement with the observations made by Costa et al (1966) who showed that the tricyclic antidepressant reduced the pressor effect of indirectly acting amine. This difference can be partly explained by the fact that phenylephrine is a sympathomimetic amine with both direct and indirect action.

The mechanism of this interaction is not clearly known. It had been shown by Iversen (1967) that tricyclic antidepressants inhibited the uptake of noradrenaline into adrenergic nerve endings. As this amine uptake mechanism is one of the most important pathways of inactivation of free noradrenaline at the receptor sites, its blocade will result in an increase in local concentration of noradrenaline at the adrenergic receptors and hence the increased pressor effect.

The hazards of administering catecholamine containing drugs to patients on tricyclic antidepressants treatment are very real indeed. But so far hardly any warning appear to have been made against the concomitant administration of catecholamine though similar warnings are repeatedly made in the case of MAOI antidepressants. As a matter of fact, in some pharmacology textbooks, noradrenaline drip is recommended for the treatment of hypotension caused by overdosage of tricyclic antidepressants in man. This is obviously hazardous as it may well turn hypotension into a hypertensive crisis.

Boakes et al (1972) reported a series of adverse reactions to local anaesthetics containing noradrenaline at a concentration of 1:25,000 (40 ug/ml) during the dental treatment of patients on tricyclic antidepressants. A steep rise in blood pressure can occur and is hazardous to life. Therefore this type of local anaesthetics should not be used. Though the potentiation of the pressor effect of adrenaline at lower concentration is not as marked as that of noradrenaline, it has the additional hazard of inducing arrhythmia in subjects pretreated with imipramine. Therefore the use of subcutaneous adrenaline 1:1000 at a high concentration (1000ug/ml) in the treatment of bronchial asthma may lead to hypertensive crisis and serious arrhythmia. As many asthmatics are often depressed, it is therefore quite common in clinical practice to put the asthmatics on tricyclic antidepressants as well. It is not surprising that these cardiovascular hazards arising out of the above interactions may account for some of the sudden unexpected death among the asthmatics. On the other hand, it appears that coincident administration of tricyclic antidepressants will not increase the hazards of isoprenaline inhalation in bronchial asthmatics as our present study fails to show any potentiation of cardiovascular response to isoprenaline infusions in subjects pretreated with imipramine.

As phenylephrine was potentiated two- to three-fold in its pressor effect, its indiscriminate use may lead to serious consequences. Unfortunately phenylephrine is very commonly used as nasal decongestant and finds its way into many patent preparations like Coricidin D, Dristan etc. There are not less than twenty proprietory remedies described in Drug Index in Malaysia and Singapore (1973) which have phenylephrine as part of the constituents. Therefore the patients on tricyclic antidepressants should be warned. The use of other indirect acting amines like ephedrine and phenylpropranolamine which are present in many cough and cold cures should also be cautioned in these patients until human experiments are done to substantiate the finding of Costa et al (1966) that tricyclic antidepressants actually reduce the pressor effects of indirectly acting sympathomimetic amines.

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LEGENDS TO THE FIGURES

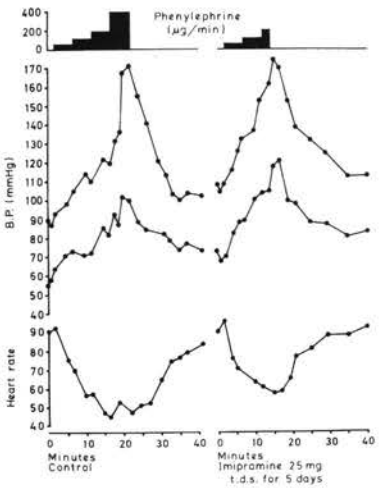

Fig. 1: Subject 2. Cardiovascular response to intravenous infusion of phenylphrine before and after imipramine.

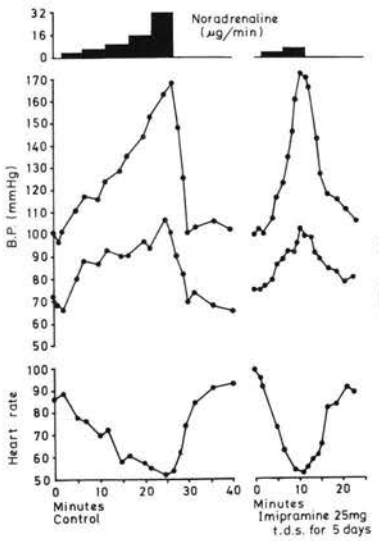

Fig. 2: Subject 2. Cardiovascular response to intravenous infusions of noradrenaline before and after imipramine.

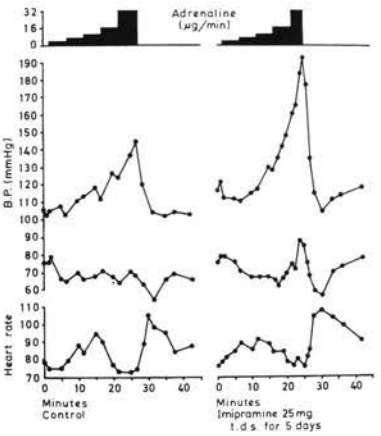

Fig. 3: Subject 4. Cariodvascular response to intravenous infusion of adrenaline before and after imipramine.

PSYCHOTROPIC MEDICATION FOR ANXIETY

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Anxiety is an ubiquitous existential symptom. Different era and culture not only have different sources of anxiety but also different manifestations and management. Anxiety also occurs as a symptom in almost any psychiatric syndrome or organic disease. A clinician may encounter different degrees of anxiety. Free-floating anxiety does not seem to relate to any stress-factor. Anxiety may be manifested via numerous somatic symptoms. Restlessness of increased tone of the musculature may proceed intense anxiety state known as panic.

Psychotropic Drugs Influencing Anxiety

In every category of psychotropic drugs, there are those which show, to a greater or lesser extent, an anti-anxiety effect. One should however differentiate drugs having a predominant effect on anxiety, i.e. minor tranquillizers, from those in which this effect is secondary, as exemplified by some antihistamines, hypnotics, major tranquillizers (neuroleptics) and antidepressant drugs. In the subsequent discussion, we shall see that for anxiety associated with various clinical features some of these psychotropic medications are indicated for the associated anxiety.

Minor tranquillizers, through their demand by patients and doctors had a lucrative market.

But marked tendency to produce addiction and seizure if withdrawn suddenly and lack of efficacy had resulted in the disappearance of a number of them from the markets. (Tan, 1970). The group that has the greatest success and is still being improved on is the Benzodiazepine (Hurlimann, 1972). Included under this group are Chlordiazepoxide (Librium) and Diazepam (Valium). The side effects of the benzodiazepine include nausea, drowsiness and paradoxical excitement.

Rationale for Treatment of Anxiety

Dally (1967) distinguished between a primary anxiety state from anxiety which is secondary to, and may mask depression, schizophrenia, organic disease or an early state of dementia.

To quote Cazzullo (1969): "The particular character of anxious phenomena, whether occurring in isolation or in conjunction with other symptoms, presents a range of problems which are appropriate to other treatments as well as pharmacotherapy. The *first* problem is the discrimination between degrees of anxiety, the *second* the relationship of anxiety with other clinical pictures and a *further point* is the distinction between the various phenomenological features of anxiety, psychic as well as somatic. The second and third points are obviously closely connected."

Rothman (1963) always used supportive psychotherapy first. Kielholz (1969) wrote that psychopharmacotherapy without psychotherapy was pointless. Kusumanto (1972) in "The Problems of Anxiety in a Non-Western Society." advocated a combined chemo- and psychotherapeutic approach to anxiety. The two methods must be co-ordinated: the more the anxiety is generated by emotional factors, the greater will be the part played by psychotherapy. A 'medical model' (psychopharmacotherapy) of managing anxiety is thus combined with a 'behavioural educational model' (psychotherapy).

The following classification of anxiety and its associated symptoms aids in the selection of the appropriate psychotropic drugs:—

I. *Primary Anxiety State*

When anxiety is a normal reaction to some unpleasant circumstances i.e. mild reactive anxiety, or existential anxiety, no medication is needed. In anxiety neuroses paroxymal, acute anxiety may be felt or shown by an individual without apparent reason or out of all proposition to the supposed cause. The patient may be physically and mentally affected by his anxiety to such a degree that he cannot cope with routine activities. This engenders even more anxiety and a vicious circle is set up. Treatment should aim to break this vicious circle: to reduce anxiety to a level at which the patient can function efficiently and deal with his problems. Once this is done, treatment can usually be tailed off and stopped. For primary anxiety, chlordiazepoxide (Librium), 5—10 mg per dose, daily dose range 10—80 mg or Diazepam (Valium), 2—10 mg per dose, daily dose range 6—30 mg may be used. The aims of medication here are these:—

(1) it facilitates contact with and communication with the patients;
(2) it helps to break down resistance which could not otherwise be overcome;
(3) it utilizes the action of the drug in relieving patients from unbearable anguish.

The efficiency of a tranquillizer upon anxiety symptoms should be apparent within a few days. It is reasonable to double the dosage if symptoms are unrelieved after a week, and to change if there is no improvement after a further week. Some claim that diazepams, with its more prominent muscle relaxant activity, is superior to chlordiazepoxide when both are given in a dosage of 10 mg three times a day, but that diazepam has a greater tendency to cause drowsiness.

Sometimes it is only necessary to treat the insomnia resulting from anxiety. A benzodiazepine, Nitrazepam (Magadon) 10—20 mg is a useful hypnotic.

An important determinant in the success of any treatment will be the personality of the patient. McDonald (1967) explored the effects of personality type on drug response. For the chronically inadequate group of patients suffering from anxiety, there is as yet no proper physical treatment. Sargant (1969) warned that these might be helped by sedative drugs at the expense of causing their increasing addiction and deterioration under them. In predisposed individuals, e.g. alcoholic, habituation and addiction to Meprobamate and Chlordiazepoxide may occur, although less likely than barbiturates. Overdosage with meprobamate or diazepam derivatives is unlikely to be fatal.

II. *Anxiety with Depression*

The relationship between anxiety and depression is very complex, depending on the features and the individual meaning of the depressive experience, with depression often being a final step in the dynamics of anxiety. Simon (1966) found that all thirty-seven patients hospitalized at the Psychosomatic and Psychiatric Institute,

Chicago with a diagnosis of depressive reaction ranked feelings of tenseness, focused anxiety, and sadness and blueness among their top initial concerns. The anxiety factor mean scores were highest. Hollister et al (1967) studied one hundred and one newly admitted depressed male psychiatric patients who were treated with amitriptyline (Elavil, Laroxyl, Tryptanol), perphenazine (Trilafon) or a combination of the two drugs over a four week period, using blind controls. They confirmed all of the following hypothesis which were the results of observations from previous studies: amitriptyline would be most efficacious in patients classified as retarded depressions; perphenazine would be the drug of choice for patients with anxious depressions and the combinations would be effective in both types, as well as in hostile depressions but would not offer any special advantage over the indicated single drug.

The therapeutic effect of amitriptyline may be delayed up to two to three weeks. If the suicidal risk is high, ECT may have to be used first. The danger of attempted suicide with amitriptyline should be borne in mind. Lethal dose has varied from 1,250 mg to 1,500 mg. Williams and Sherter (1971) described two cases of unresponsive cardiac standstill secondary to toxicity of tricyclic antidepressants. These drugs are contra-indicated in patients receiving drugs that deplete cardiac catecholamines (e.g. guanethidine).

Sargant (1969) found that a group of mixed anxiety, depressive and anguish states with an adequate previous personality and with low basal forearm blood flow responded to an MAOI group of antidepressant drugs e.g. Phenelzine (Nardil).

III. *Secondary anxiety or anxiety bound to different ideas and thought representations such as phobias, obsessions, hypochondrical ideas and delusions.*

When anxiety symptoms are secondary to the main picutre of the illness present e.g. schizophrenia, minor tranquillizers are effective only for this symptom, but not on the others. This lack of anti-psychotic effect distinguishes it from the group of major tranquillizers e.g. phenothiazines and butyrophenones. Cazzullo (1969) sometimes combined chlorpromazine with high dosages, 100 to 250 mg a day, of chlordiazepoxide, given intramuscularly.

In obsessional neuroses, anxiety may still persist in spite of displacement. Diazepam may be used. When obsessional thinking is related to a cyclothymic background, thereby assuming the character of a depressive equivalent, the association of antidepressant drugs (amitriptyline)may be of value. In the case where compulsive phenomena become autonomous, losing their emotional charge and tendency to stereotype, it is necessary to potentiate the treatment with butyrophenones (Cazzullo, 1969).

In alcoholic withdrawal state and delirium tremens, adequate dosage of tranquillizing drugs to allay the patient's excitement and fear must be given. If the patient has not gone into the state of frank acute organic brain syndrome but shows evidences of development in that direction, phenothiazines or butyrophenones in large doses should be prescribed. The tremulous, very anxious patient might be given a 50 to 100 mg of intravenous chlordiazepoxide for some immediate relief as well as to facilitate the diagnostic interview. Medication will be required for the next 4 days and most reliable control can usually be obtained with the use of phenothiazines (Hankoff, 1969).

Other Factors Influencing Outcome of Medication

Other elements which are important in influencing the anti-anxiety treatment: (1) The functions and the personality of the therapist, (2) the specific quality of the doctor-patient relationship and (3) the environment in which the treatment is carried out. In this connection also (4) the problem of the placebo effect cannot be overlooked and therefore great caution is necessary in evaluating the anti-anxiety effect of any drug (Cazzullo, 1969).

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TRIAL OF LITHIUM CARBONATE IN THE PREMENSTRUAL TENSION SYNDROME

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INTRODUCTION

Good results with the use of Lithium salts in the premenstrual tension syndrome have been reported (Sletten and Gershon, 1966; Rossman 1969). These observations however await confirmation. The value of Lithium is suggested by its known capacity to affect water and electrolyte balance which are implicated in the pathophysiology of the syndrome, and its efficacy in psychiatric disorders characterised by periodicity. (Gjessing, 1967; Schou, 1968, Forssman and Walinder, 1969; Hanna *et al.*, 1972). We therefore undertook a controlled study on the efficacy of lithium in the syndrome.

Methods

The study compared lithium with placebo, was double-blind with multiple random cross-over, and involved 19 Chinese out-patients. It lasted up to 8 menstrual cycles for each patient. The first cycle involved open lithium for dosage adjustment; thereafter the allocation to either lithium or placebo for a cycle was randomized so that a patient did not necessarily have equal numbers of lithium and placebo periods. Lithium was dispensed in capsules of 250 mg (6.8 mEq) of the carbonate salt. Dosage was flexible, ranging from 750–1000 mg daily and aiming at maintaining serum concentration at 0.8 – 1.3 mEq/1. Lithium estimation by flame photometry was carried out at least once a month when patients were interviewed. Dosage was regulated by the interviewing psychiatrist on the basis of serum lithium values reported to her from the laboratory, true values for the lithium periods and fictitious values within the same range for the placebo periods.

Patients were selected on the basis of symptoms being temporarily related to the menstrual period – marked emotional tension (irritability, anxiety, depression) and various somatic features, as originally described by Frank (1931). They had also to promise not to become pregnant during the trial.

They were not permitted to take diuretics or hormones, excepting oral contraceptives; other psychiatric medication including antidepressants (8 patients) and tranquillizers (18 patients) was maintained at fixed levels throughout. Excluded from the study were patients with brain damage, active somatic disease, alcoholism, character disorders, as well as those in whom lithium therapy was for one reason or another contraindicated. The majority (17) of the subjects had, at onset of trial, moderate to severe symptoms of premenstrual tension which had either not responded to medication or whose slight response had stabilised for long periods. Their ages ranged from 20 to 44 years (mean 32.3)

Concomitant psychiatric conditions were diagnosed in accordance with the U.K. Glossary of

Mental Disorders, 1968, as follows: Affective psychoses – depressed type, 2 cases, manic type 1; Neuroses – anxiety 2, depressive 1, hysterical 1. 5 were remitted schizophrenics. 7 patients had no psychiatric conditions apart from the premenstrual tension. The study was begun in November 1971 and completed in August 1972.

Results

There were 5 dropouts, one due to pregnancy and 4 to exacerbations of symptoms or side-effects requiring review of management; their assessments before the dropout were retained. 105 cycles were completed; the assessments of 15 of these were excluded because they were associated with serum lithium levels below 0.6 mEq/1 and those of another 11 because lithium was present in serum whilst the patients were supposedly on placebo. Of the remaining 79 cycles subjected to final assessment, 33 were treated with lithium and 46 placebo. Patients were rated on a Global Clinical Scale (GCS), which scored illness from 0 = asymptomatic to 3 = severely ill; a Target Symptoms Scale (TSS), which rated 9 symptom parameters from 0 = absent to 3 = severe; and a Self-Rating Scale (SRS) which scored overall condition from 0 = asymptomatic to 3 = severe. Initial scores obtained just before the trial were compared with post-cycle scores at the end of each cycle, the differences between these were the score changes, which when positive signified improvement.

GCS. The mean initial score was 2.26. The mean score changes were: with lithium, 1.35, with placebo 1.24 ($t = 0.673$, $P > .05$).

TSS. The mean initial score was 7.58. The mean score changes were: with lithium, 5.59, with placebo 5.13 ($t = 0.871$, $P > .05$).

The scores of the items were, given in the order of mean initial score, and mean lithium score change *vs* mean placebo score change, as follows: irritability – 1.68, 1.91 *vs* 1.80; depression – 1.42, 1.12 *vs* 1.28; headache – 1.16, 0.85 *vs* 0.61; abdominal distension – 1.00, 0.73 *vs* 0.78; anxiety – 0.74, 0.67 *vs* 0.54. dysmenorrhoea – 0.58, 0.15 *vs* 0.11; breast pain – 0.21, 0.30 *vs* 0.26 swelling of ankles – 0.11, 0.09 *vs* 0.09; swelling of face, 0.0, 0.03 *vs* 0,0. Significant differences at the .05 level or greater were not obtained on any of the items of the TSS.

SRS. The mean initial score was 2.26. The mean score change with lithium was 1.44 and with placebo 1.22 ($t = 0.995$, $P > .05$).

Overall, patients made good improvement with lithium and with placebo; they did slightly better with lithium but the differences were not significant.

The main adverse reactions noted in a minority of cases, were tremor, weakness of limbs, nausea, vomitting and abdominal discomfort. One patient became acutely confused. The pregnant patient who dropped out of the trial had a full-term delivery of a normal male infant.

DISCUSSION

Our experiences with lithium treatment of the premenstrual tension syndrome would appear to differ from those of Sletten and Gershon. One possible reason is the way in which lithium was administered. Sletten and Gershon gave a fixed dosage of 27 milliequivalents per day for ten days before menstruation. We adjusted dosages (range 20–27 milliequivalents per day) according to the serum lithium concentration and gave treatment throughout the month. It does not seem likely that these small differences could lead to so dissimilar results. A second possible reason is that the patient groups, although fulfilling the same diagnostic criteria, in fact differed in composition. The premenstrual tension syndrome may encompass a variety of clinical entities.

The difference in results between the study of Sletten and Gershon and our study is, in fact, more apparent than real. In both studies, good improvement was obtained with lithium. However in our study we also used placebo, with which we also obtained good improvement. Everyone who has studied the premenstrual tension syndrome will testify how easily this condition is influenced, at least temporarily, by new treatments and other psychological factors. We therefore considered it essential to record not only how much patients improved on lithium but also how much they improved on placebo. Our results therefore indicate that the major part of the improvement noted during lithium treatment was due to the psychological effects of the treatment and that the small fraction by which the lithium scores were better than the placebo scores may have been due to random variation.

TREATMENT OF AMBULATORY NEUROTIC PATIENTS WITH RO 5–3350 IN JAKARTA

(A Preliminary Report)

By J. TJANDRA and R. KUSUMANTO SETYONEGORO

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I. A new minor tranquillizer developed by ROCHE LABORATORIES was recently introduced to the medical profession. The drug, a benzodiazepine derivative (experimental code number RO 5–3350) is indicated for the treatment of severe neurotic conditions (obsessions, compulsions, obsessive compulsives, phobias). Basically it has the same indications as Diazepam (Valium) with the exception of epilepsy.

One hundred and ninety-five ambulatory neurotic patients were treated between October 1970 – and June 1971. Actually seventy-five more patients were treated in these series, but considered as "drop-outs" since less than the five weekly required evaluations were available.

The drug was given to – "new" (male as well as female), patients of ages 16–69 and to "old" patients as well if they had not taken psychotropic medication for 3–4 weeks.

Pregnant women were excluded from this study. The trial is a "straight, uncomplicated or open study" and carried out at the Out-Patient Service, Department of Psychiatry, University of Indonesia, Jakarta, and the Out-Patient Service, Dharmawangsa Sanitarium, Kebayoran-Baru, Jakarta, a private psychiatric facility.

II. *Method and Material*

The trial is open trial. All ambulatory neurotics coming to the Out-Patient Service, University of Indonesia, Department of Psychiatry and Dharmawangsa Mental Health Clinic were treated with the drug.

They were seen once weekly and followed up for at least six weeks. Some of these patients remained under therapy up to 2 months or even longer.

Dosages were changed according to the development of symptomatology and aimed at producing optimal improvement of the patient's condition. No or only very superficial psychotherapy was carried out. Concomitant drug therapy was not done.

Of the 195 ("recordable") patients, 120 were males and 75 females. The prominent ages were 20–29 years followed by the 30–39 years age group.

Laboratory tests were done if indicated.

III. *Rating*

Symptoms reported by the patients were rated according to a four-point numerical scale grading: 0 standing for absent, 1 for minimal, 2 for moderate and 3 for marked. Target symptoms for measurement are: anxiety, irritability, phobias, compulsive ideas and impulses, compulsive acts, loss of drive and interest, tension, restlessness, depression, trouble of onset of sleep, trouble of continuity of sleep, palpitation, sweating, gastro intestinal disturbances, vasomotor lability and some other symptoms.

IV. *Dosages*

Two forms of RO 5–3350 tablets are available for this study: 10 mg and 12 mg tablets.

Initial dosages are usually 6–10 mg per day, divided in 2–3 dosages, and maintained for one week.

In the second and following weeks dosages are either maintained or increased (up to higher than 32 mg per day) depending on the development of symptomatology.

V. *Drug responses.*

These are recorded according to the following categories:

- very good, if most of the target symptoms disappeared, subjectively as well as objectively;
- good, if most target symptoms are reduced in intensity and personality functioning is satisfactory.
- moderate, if symptoms are somewhat decreased while patient feels relieved subjectively and personality functioning is considered more or less reasonable;
- no effect, if symptoms remain as they were before treatment;

worse, if symptoms are increased in intensity and personality functioning has deteriorated.

VI. *Treatment results*

In general, it can be said that treatment results can be seen during the second week after the institution of treatment, to gradually stabilize the third and fourth week (table VI).

Most prominent dosages were between 18–20 mg, followed by dosages of 24–30 mg per day (table II).

Responses are very good in 20% of the patients, 38% good and 32% moderate, so that 90% showed improvement while under treatment, while 10% did not improve (table III). Diagnostic categories are listed in table IV with most patients showing anxiety neurosis (71) psychophysiologic reactions (47) and obsessive-compulsive reactions (26) as the largest groups.

Other diagnosis are personality disorders (16), depressive reaction (18), unspecified neurosis (7) transient situational disorders (6), phobic reactions (3) and conversion reaction (1).

In the anxiety group more than 75% improved markedly. The improvements obtained in transient situational disorder (67%), psychophysiologic disorders (more than 60%) and obsessive compulsive reactions (40%) was somewhat less. Neurotic depressions, personality disorders, conversion reaction and phobic reactions do benefit from the drug although their numbers as well as improvement rates are less impressive.

In general, it can be said that the treatment results are most satisfactory especially if we keep in mind the variety of conditions in which the drug proved beneficial.

VII. *Side effects*

Side effects consisted of fatigue, drowsiness, dizziness, disturbance of motoric coordination, gastrointestinal disturbances, cephalalgia, insomnia (very seldom), loss of appetite, general weakness, and sometimes excitement. It is our impression that side effects generally are not severe and have the tendency to diminish or disappear spontaneously afterwards, with or without reducing the dosage.

Usually side effects tend to appear in the first or second week of treatment both with low, as well as high dosages.

In our clinical study 13% (26) of the 195 patients developed side effects, 10 of them experienced one sort of side effect, 5 of the patients 2; 7 of them 3; and 4 patients 4 kinds of side effects.

Usually side effects are transient. Tolerance towards the drug is good.

VIII. *Conclusion*

A simple and open drug study was done with RO 5–3350 on 195 ambulatory patients suffering from a variety of neurotic conditions. The effectiveness of the drug was assessed and established based on clinical experiences. It is our impression that RO 5–3350 although at present not yet available commercially on the Indonesian market, can be listed as a highly effective anti-neurotic drug. It is well tolerated by the majority of patients.

Based on experiences with the drug further studies with this compound are suggested especially in diagnostic categories which are, so far very resistent to drug-therapy, such as obsessive-compulsive neurosis and psychopathic conditions, since RO 5–3350 seems to give new hope in the treatment for these conditions.

Table I

AGE AND SEX OF PATIENTS

Age	Number of male patients	Number of female patients	Totals
10–19	16	7	23
20–29	55	28	83
30–39	24	21	45
40–49	15	12	27
50–59	9	4	13
60–69	1	3	4
Totals	120	75	195

Table: II

DOSAGE PER DAY

Amount	Percentage
5 – 6 mg	6%
9 – 10 mg	20%
12 – 15 mg	19%
18 – 20 mg	38%
24 – 30 mg	29%
32 mg and higher	21%

Table: III

IMPROVEMENT RATES

Result of treatment	Number of Patients	Percentage	
Very good	39	20%	
Good	74	38%	90%
Moderate	63	32%	
No effect	19	10%	
Totals	195	100%	

Table: IV

DIAGNOSTIC CATEGORIES, NUMBER OF PATIENTS AND IMPROVEMENT RATES

Diagnosis	Number of Patients			Rating of Effectiveness			
	Men	Women	Totals	Very good	Good	Moderate	No Effect
Anxiety neurosis	50	21	71	20	34	14	3
Psychophysiologic - reaction	28	19	47	10	20	15	2
Obsessive Compulsive - reaction	15	11	26	5	8	8	5
Reaction/neurotic- depression	8	10	18	–	5	10	3
Phobic reaction	2	1	3	–	–	1	2
Conversion reaction	–	1	1	–	–	1	–
Transient situational disorder	3	3	6	3	1	1	1
Personality disorder	10	6	16	1	2	11	2
Unspecified neurosis	5	2	7	–	4	2	1
Totals	120	75	195	39	74	63	19

Table: V

RATING IN PERCENTAGES OF EFFECTIVENESS

Diagnosis	Very good	Good	Moderate	No effect
Psychophysiologic reaction	21%	42.5%	32 %	4.5%
Anxiety neurosis	28%	48 %	19.5%	4.5%
Obsessive-Compulsive reaction	19%	31 %	31 %	19. %
Reactive/Neurotic depression	–	28 %	55.5%	16.5%
Conversion reaction	–	–	100 %	–
Phobic reaction	–	—	33 %	67 %
Transient situational disorder	50%	17 %	17 %	17 %
Personality disorder	6%	12.5%	69 %	12.5%
Unspecified neurosis	–	57 %	28.5%	14.5%
Totals	20%	38 %	32 %	10. %

Table: VI

IMPROVEMENTS

First week	5%
Second week	55%
Third week	47%
Fourth week	8%

INTRODUCING VALIUM IN NARCOANALYSIS

(A preliminary report of 10 cases)

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Narcoanalysis is a well-known method of interviewing a person by putting him under the influence of a drug which acts by disinhibiting higher cerebral functions. Its introduction probably arose out of the observation that certain chemicals like alcohol could make a normally reserved person more talkative and willing to divulge secret information or exert a disinhibiting influence on the person's behaviour.

Psychophysiologically this could be explained by the tranquillizing effect to the drug on the person's higher cerebral activities, allowing shameful or embarrassing materials to be released from the subconscious (normally suppressed or repressed).

Alcohol as an agent, though effective, is difficult to administer and measure. A variety of substances have been tried as a substitute for this purpose amongst which are amylobarbitone, methylamphetamine, ether, nitrous oxide, carbon dioxide and even LSD.

Barbiturates had been used by Sargant & Slater (1940) in the treatment of war neurosis with success. It was found to bring relaxation and

abreaction to traumatic experiences and to assist in the recovery of amnesia. For the latter intravenous methylamphetamine was found to be more effective in producing talkativeness.

Barbiturate is undesirable because of its toxicity and depressing effect on the respiratory centre. Methylamphetamine may result in addiction and LSD is a very harmful drug. The drugs of the benzodiazepine group appear to have actions very similar to amylobarbitone without all its disadvantages in that they are non-toxic, less sedating and anxiolytic Of these drugs diazepam is the only member known to the author that can be given intravenously. Diazepam (Valium) has another advantage in that it also produces muscle relaxation.

Method

Unlike the use of other drugs, the patient does not require much pre-operative preparations except that the patient should be fasted for 4 hours. Even this is not an absolute necessity. The procedure can be performed in the ward with the patient sleeping on his bed or in the doctors' consultation room or any other quiet enclosed place.

The patient was told that he would be given an injection to relax his mind. Blood pressure was taken after every 5 mg. of Valium was introduced. Intravenous Valium was given at the rate of 5 mg per minute up to 15 mg after which the rate is reduced according to the patient's response. The maximum dose was 30 mg over a period of about 15 minutes. The patient usually started to talk after 10 mg was injected. The results are summarised in the table below.

Summary of Cases

No.	Age	Sex	Race	Indication	Diagnosis	Result
1	18	M	Chinese	Murder (mute) rape	Psychopath	Good
2	31	M	Chinese	Mute	Psychopath Personality	Good
3	41	F	Chinese	Mute	Depression	Good
4	24	M	Chinese	Mute	Schizo.	Fair
5	25	M	Chinese	Amnesia Murder	Inadequate Personality	Fair
6	40	M	Chinese	Amnesia Murder	Reactive Depression	Fair
7	63	M	Chinese	Mute	Depression	Poor Sleep
8	18	M	Malay	Mute	Malingering	Poor
9	21	M	Chinese	Mute	Psychopath	Sleep
10	23	M	Chinese	Mute	Inadequate Personality	Trance

The "success" rate of 3 good results was low compared with amylobarbitone which in the author's experience had a 50% good result. This comparison is not properly controlled, and the numbers were too small to be significant.

Indications and Results

Of the 10 cases, 8 patients underwent interview under intravenous Valium because they were mute or near mute to normal interview. For 2 cases who were alleged to have committed murder, the purpose was to resolve their amnesia for the murder. 3 patients showed very good response. This included one who was near mute but was alleged to have committed murder and rape. For these 3 cases the patients started to respond by talking after 10 mg Valium was injected. They continued to talk even after 30 mg of Valium had been injected. There was a tendency for them to continue to talk even though they were left alone. However their talk was not very informative.

DISCUSSION

The use of Valium as the agent in Narcoanalysis had not been tried out extensively, partly because this method of treatment was no more popular in recent years. Farb (1963) reported the use of intravenous Valium in 34 patients who were

resistant and unresponsive to psychotherapy and had good results. He used from 10 to 30 mg Valium and added 20 mg methylamphetamine to induce talkativeness. All the patients were alert throughout the interview.

The purpose of using intravenous Valium in this study is to induce a more productive interview or to recall Amnesia. If funtional amnesia is the result of a repressive force because of threat of anxiety and Valium reduces anxiety, then the patients should be better able to recall their repressed memories. This was not the case in the three patients with amnesia. Valium did not appear to be able to assist patients to recall amnesia if they do not wish to do so. (3 cases accused of murder, denied during narcoanalysis), On the other hand for a number of patients (5 patients), their mental state improved after the experience of interview under Valium injection. e.g. one patient who remained mute during the interview confessed that he was malingering. A similar result was also noticed in another case (not in the series) who was interviewed under sodium amylobarbitone.

Side effects

These were characterised by their absence. Only 2 patients felt drowsy and somnolent. The blood pressure remained unchanged or dropped only by 10 mm. Hg. systolic and diastolic. In one case, the systolic rose by about 20 mm. Hg.

CONCLUSION

As a method of treatment, Narcoanalysis does not seem to have much of a place in Psychiatry. This could partly be due to the dangers inherent in the treatment – which in some cases is equivalent to administering an anaesthetic. Intravenous Valium appears to have overcome this obstacle in that it can be given in the office or in the medical ward without any pre-operative preparation.

The author feels that there is room for a more extensive trial of this procedure, as it is not more difficult than giving an intravenous injection and is almost without danger. Valium should replace amylobarbitone for general use.

ACKNOWLEDGEMENT

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A TWO-YEAR FOLLOW-UP STUDY OF 85 SCHIZOPHRENICS

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In the investigation of prognoses of mental disorders, most previous reports have focused on follow-up studies of schizophrenia. However, they have used so many different methods and criteria that their resuits have hardly been comparable with each other. In order to collect a comparable sample, diagnostic tools applied should be clearly defined. To evaluate individual features in their relationship to a course of a certain illness, a treatment method or some social factors should be controlled. The International Pilot Study of Schizophrenia (IPSS) has been carried out in nine field research centres, located: Aarhus, Agra, Cali, Ibadan, London, Moscow, Prague, Taipei, and Washington, to meet the former conditions. This project has been under the sponsorship of the World Health Organization, which will publish the first report in 1973.

I am going to present a part of this research, a two-year follow-up study, relating mainly to neuroleptic medication which is the main theme, and also our concern in this Seminar; although this study has not been well controlled in terms of treatment methods and social environment.

Methods

As one of nine participating centres in the IPSS, we examined 127 psychotics and 10 neurotics between April 1968 and June 1969. We used the standarized methods with Present State Examination (PSE) originally developed by Dr. J. K. Wing and modified by IPSS collaborating investigators; also, Psychiatric History (PH), Social Description (SD), Physical and Neurological Examination (PNE), and Diagnostic Assessment (DA) schedules.

These cases should have resided in the catchment area for more than 6 months before the inclusion in this study. They should all be between ages 15 and 44, have suffered from mental illness without any organic manifestation for less than 3 years, and not have been admitted to a mental hospital for more than 2 years totally during the past 5 years. These 137 patients were followed up at the time of 2 years plus or minus 1 month after the initial examination, with the follow-up PH and SD schedules in addition to other forms used at the time of inclusion.

Results

1) *Diagnostic Classification*

The psychiatric diagnoses of each case were re-evaluated at the time of follow-up. There were 87 cases diagnosed as schizophrenic at the beginning, but two years later two of them were transferred to the category of reactive psychoses. On the other hand, three cases diagnosed as reactive psychoses and one case of depressive neurosis at the initial examination turned out to be schizophrenic. Therefore, at the time of the second-year follow-up, there were 89 schizophrenics all of whom we were fortunately able to locate and examine. Among five major diagnostic categories, the diagnosis of those suffering a paranoid state seemed to be most unchanged and the diagnoses of reactive psychoses were most changeable, 6 out of 21 cases (28.6%). There were altogether 10 of 137 cases (7.3%) that had changed their major diagnostic category at the time of follow-up.

Among 85 schizophrenics that had maintained the same diagnoses, some cases had changed their subtype classification. 72 schizophrenics did not shift their subtypes, but 13 of 85 (15.3%) were categorized in different subtypes. The subtype of acute schizophrenic episode seemed to be the most variable 3 out of 4; hebephrenics being the next closest with 5 out of 30. Five other subtypes had one each out of their categories.

2) *Patient Status at the Time of Follow-Up*

So far as the results of the second-year follow-up are concerned, there were 89 cases of schizophrenia, 10 affective psychoses, 11 paranoid state, 18 reactive psychoses and 9 depressive neuroses. In this report, clinical outcome at follow-up will be taken into consideration in relation to neuroleptic medication. The clinical outcome at follow-up is divided into the following five levels: i) not mentally abnormal, ii) mildly or moderately neurotic, iii) mildly psychotic or severely neurotic, iv) moderately psychotic, and v) markedly psychotic. The first three groups are regarded as improved and the last two groups as not improved. Treatment status is determined mainly by regularity of medication. If a patient had taken medication regularly during the two-month period prior to the time of follow-up, he would be considered on medication.

Of 89 schizophrenics, 4 cases were dead or missing: two died of suicide; one in a traffic accident, and another was missing on the front line. This paper will concentrate on the analysis of data obtained from the other 85 cases, mainly by comparing information gathered at the initial and follow up examinations.

Among 47 patients without medication, 17 cases (36.17%) still showed moderate or marked psychotic impairment. Among 38 patients with medication, 15 cases (39.47%) revealed the moderate or marked degree of psychotic impairment. Therefore, altogether 32 of 85 (37.65%) of the schizophrenics were regarded as not improved, in contrast with 7 of 48 (14.68%) of other psychiatric cases. The former is about two and a half times as many as the latter.

3) *Social Data at the Initial Examination*

The number of male patients was almost the same as females (43:42). However, while most of male patients were single, female patients were evenly distributed in the single and married classes. The sex and marital status did not relate significantly with treatment results. Neither age, education, nor social class of patients affected treatment results, though younger or single patients had received higher education than older or married ones.

4) *PSE Ratings at the Initial Examination*

In order to find out if there was any relationship between initial symptomatic manifestation and treatment results, 61 out of 367 PSE ratings at the initial examination were compared with four groups of treatment results. In regard to

"derealization", 27 of 32 cases who showed mild impairment eventually improved significantly. The only other symptom which indicates statistically significant improvement was obsessive-compulsive traits.

5) *Subtypes at the Time of Follow-Up*

Other subtypes than hebephrenic and paranoid showed the most favorable treatment results, the hebephrenic type was most unfavorable, and the paranoid was in the middle. These differences reveal statistical significance.

6) *Cost of Treatment*

During the two-year follow-up period, these schizophrenics received various kinds of treatment in different settings and for different lengths of time with different sequences followed. In order to evaluate this complicated treatment course, the weighting scale for cost of treatment is arranged. Psychiatric treatments are weighted according to: treatment status, drug therapy, electric convulsive therapy, psychotherapy, and frequency of outpatient visits. By adding weights of each treatment multiplied by treatment days, cost of treatment can be calculated. The group which improved without medication needed the least cost of treatment. The groups of the improved and not-improved, both with medication, had the most expensive treatment cost, while the group of the not-improved without medication had the middle cost of treatment. These differences are statistically significant. An interesting relationship between married status and cost of treatment indicated that single patients needed more cost of treatment than married cases which showed statistically significant difference.

7) *Correlation Coefficients*

Initial examination data such as 34 symptom units, 27 symptom groups and 9 clinical and social factors are correlated with each other and also with 5 items of follow-up data such as degree of impairment, number of relapses, number of readmissions, and cost of treatment. The correlation coefficients beyond ±0.25 are significant. Four out of these 5 correlations relate with cost of treatment. Age, suspiciousness and poor rapport correlate negatively, and previous treatment positively, with cost of treatment. Ideas of reference seem to correlate negatively with the number of readmissions.

DISCUSSION

1) *Change of Diagnoses*

The detailed examination such as a PSE interview and collection of information on PH and SD were given to each patient in the follow-up study as well as in the initial investigation. The final diagnoses established from all information are definitely more reliable than the initial diagnoses. Therefore, this report was based on the final diagnoses instead of using initial diagnoses which was the usual procedure of other previous studies. By utilizing the final diagnoses, predictors of prognosis can be derived meaningfully from careful analysis of the data obtained.

2) *Predictors of Prognosis*

The patients who displayed "derealization" or "obsessive-compulsive traits" showed better improvement than the ones having no such symptoms. Chapman (1966) enumerated some early symptoms of schizophrenia and emphasized the disturbance of visual perception which can be measured by ratings of derealization in our sample. Although Chapman found disturbances of visual perception to be associated with poor prognosis, Varsamis and Adamson (1971) reported these with good prognosis. Both derealization and obsessive-compulsive traits may be considered as early manifestations of schizophrenia, so that patients with these symptoms seem to be more responsive to psychiatric treatment than those with more advanced symptoms. Ideas of reference show negative correlation with readmission, and on the other hand, suspiciousness and poor rapport correlate negatively with cost of treatment. However, we need to accumulate more cases to formulate any explanation for these findings. Younger patients needed more intensive treatment which is reflected in higher costs of treatment and can be easily understood by our clinical experiences. The patients who had received psychiatric treatment previously may be rather intractable, so that they needed larger cost of treatment.

3) *Improvement Rate*

The percentage of the subcategory 1, 2, 3, 4, and 5 according to the level of impairment mentioned above was 12.4, 25.8, 21.3, 23.6, and 12.4 respectively, while 4.5% died. These numbers are similar to the recent study of Niskanen and Achte (1972) who used a five-way breakdown somewhat different from ours in assessing the patient's psychic condition. At the two-year follow-up study of 100 schizophrenic and paranoid

patients drawn from their sample of the year 1965, they found 14, 21, 27, 27 and 8 cases in each of the five groups from normality to severe abnormality, while 3 cases were dead. However, they did not mention the direct effects of therapeutic intervention prior to the follow-up time on prognosis of mental disorders.

Twenty-five of 85 schizophrenic (29.4%) relapsed and 28 (32.9%) were readmitted to mental hospitals during our two-year follow-up period. No comparison can be made with other studies which were carried out with different research methods in different treatment settings. It should be emphasized that research methodology had better be integrated for international comparison.

4) *Treatment Course*

As mentioned above, the drug-treated group and the non-treated group in our study showed almost the same improvement rate, 63.83% and 60.53% respectively. We have to discuss why the drug-treated group did not show better results than the non-treated group.

Firstly, we may suspect that patients with medication were not actually taking drugs. Parks et al. (1962) and Willcox et al. (1965) reported the well-known possibility of patients not taking their drugs. Hogarty and Goldberg (1973) also described that relapses in the placebo group were twice that of the drug group, but one half of all relapsers (drug and placebo) cease medication prior to relapse. Therefore, we should consider how to motivate patients to take drugs regularly and how to adjust adequate doses for patients in order to promote drug effects. This is the most important problem in the community care of mental disorders and we can succeed only by the team work of mental health personnel.

Secondly, we may speculate that we are dealing with different types of schizophrenia. The detailed analysis of the treatment course discloses the following findings:

i) The improved patients without medication needed the shortest treatment period and showed the best prognosis among the four groups. They received drug treatment for the average length of 4.9 months and discontinued their medication when they felt their symptoms were steadily improving. Full remission took place about 4 months later and had remained thereafter. We have to study these cases in more detail in order to detect any possibility that these are cases of "reactive schizophrenia."

ii) The improved patients with medication had taken drugs for the longest period among the four groups. These patients experienced exacerbation of their mental symptoms soon after they discontinued medication and realized that they would be better off as long as they continued their drug therapy. These cases should continue medication on a maintenance dose under psychiatric supervision.

iii) Most of the non-improved patients without medication would not accept psychiatric treatment because of lack of their insight and the family could not force them to be admitted to a mental hospital. Some patients of this group could not be given adequate psychiatric treatment because of their family's financial difficulty. Therefore, these patients will be given the privilege of receiving more intensive psychiatric treatment only after the establishment of a Mental Health Act and Social Security or Welfare System.

iv) Most of the non-improved patients with medication showed the worst prognosis among the four groups. The readmission rate was also highest; 6 of the 15 cases under in-patient care at the time of follow-up. These patients may be labelled as "process schizophrenia." A more intensive rehabilitation programme should be organized for these cases instead of merely giving drug treatment.

From these findings, the following three subgroups of schizophrenia may be derived in relation to neuroleptic medication: a) the improved cases with short-term treatment; b) the improved cases with long-term medication, and c) the non-improved cases even with continuous drug therapy. Further elaboration of these subgroups will contribute to the prediction of clinical outcome with neuroleptic medication.

Hoenig (1967) pointed out that nothing definite was known about the important question of how long neuroleptic drugs should be continued. Based on the above-mentioned results of our study, we may suggest that neuroleptic medication should be continued for about 5 months, and then if mental condition remits steadily, clinical check-up should be maintained for 4 or 5 more months to make sure if psychiatric improvement is well accomplished. In case that a definite improvement cannot be achieved at one-year follow-up, more intensive treatment and rehabilitation should be planned.

Although the present report is handicapped by uncontrolled treatment variables, our findings will

offer some orientation for a more systematic approach in studying prognoses of schizophrenia. It is reasonable to follow the demand of Renton et al. (1963) that a special follow-up clinic for discharged schizophrenic patients should be created to provide an adequate service and to facilitate proper research.

SUMMARY

In the International Pilot Study of Schizophrenia, 127 psychotics and 10 neurotics were included at the Taipei Field Research Center. Although 87 schizophrenics were registered at the initial examination, 89 cases were diagnosed as schizophrenic at the time of the second-year follow-up. Except for 4 cases, dead or missing before the follow-up, 85 schizophrenics were evaluated in terms of their initial social and clinical data and the treatment course during the two-year follow-up period.

The following findings emerged from this study:

1) Among 85 schizophrenics alive, 11 cases showed no abnormal mental symptoms, 23 cases were neurotic, 19 cases mildly psychotic, 21 moderately psychotic, and 11 markedly psychotic at the time of the second-year follow-up.
2) The schizophrenic patients who displayed derealization or obsessive-compulsive traits at the initial examination showed better improvement than the ones having no such symptoms.
3) The cost of treatment during the follow-up period related significantly to treatment status and clinical outcome at the time of the follow-up.
4) Three subgroups of schizophrenia are derived in relation to neuroleptic medication: a) the improved cases with short-term treatment; b) the improved cases with long-term medication, and c) the non-improved cases even with continuous drug therapy. Further elaboration of these subgroups will contribute to the prediction of clinical outcome of schizophrenia with neuroleptic medication.

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TRIAL OF LEPONEX (CLOZAPINE) IN SCHIZOPHRENIA

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INTRODUCTION

Leponex (generic name clozapine), a piperazine derivative of dibenzodiazepine, has been reported to have an antipsychotic effect (de Maio, 1968; Gross and Langner, 1969) but without the cataleptic activity or inhibition of apomorphine-induced

stereotyped behaviour in rats characteristic of neuroloptics (Stille and Hippius, 1971). So far as we are aware, no controlled study of its efficacy has been reported. We, therefore, undertook such a study on schizophrenic patients.

METHOD

The study involved 33 adult in-patients of both sexes, diagnosed schizophrenia with acute symptomatology. It was double-blind and compared Leponex with Placebo. Treatment duration was 11 weeks made up of the following successive periods: 1. dosage adaptation – 1 week; 2. Leponex treatment – 4 weeks; 3. Placebo treatment – 2 weeks; 4. Leponex treatment – 4 weeks. At the start of the trial, the patient was put on Leponex (tablets of 100 mg each, 2 – 4 times daily); during the period of dosage adaptation on optimum dose was arrived at, and thereafter he continued on the same number of tablets of Leponex or Placebo. Clinical assessments during the trial (there were 8) were made by the examining doctor with the help of the nursing staff, all of whom were kept unaware of the change from one therapy to another. Other psychiatric medication and ECT were withheld from two weeks before the trial. Laboratory investigations included complete blood picture and liver function tests in all cases. Data obtained were subjected to computer analysis.

FINDINGS

Of 33 patients selected, 2 dropped out of the trial because they became unmanageable, and one was omitted because his muteness made assessment with the BPRS difficult. The average dosage of Leponex was 442 (± 85.5) mg daily (range 200 – 600 mg).

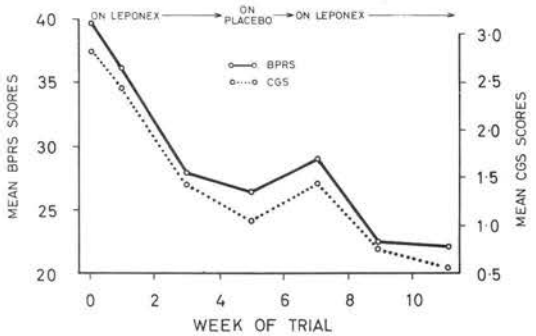
Patient Characteristics

All were Chinese – 22 males and 8 females. Age distribution by decades was: 2nd = 3, 3rd = 8, 4th = 11; 5th = 5; 6th = 3. (Mean 34.4 ± 11.4 years). There were 21 paranoid schizophrenics and 9 hebephrenics: 22 were relapses after symptom-free (or almost) intervals; 6 were first breakdowns and 2 had a chronic-productive course. The illness was rated as severe in 17 and moderate in 13. Mean duration of illness was 4.0 years (±3.3), of previous episodes 3.6 (±3.3) months, of present illness 3 (±4.5) months and of present hospitalisation 11.4 (±7.8) days. Mean number of previous episodes was 1.6 (± 1.3)

Scores

Patients were rated on a Clinical Global Scale (CGS) which scored illness from 0 = asymptomatic to 3 = severely ill, and the Brief Psychiatric Rating Scale (BPRS), which rated 28 symptom parameters, from 1= not present to 7 = extremely severe. It will be seen (Figure) that in terms of both the BPRS and the CGS patients steadily

Figure



and consistently improved on Leponex but deteriorated on Placebo. A similar pattern of response was found in most of the items of the BPRS: somatic concern, anxiety, tension, emotional withdrawal, conceptual disorganization, mannerisms and posturing, depressive mood, hostility, suspiciousness, motor retardation, un-cooperativeness, blunted affect and excitement. As regards the remaining items, there was improvement during both Leponex and Placebo periods in respect of grandiosity, hallucinatory behaviour, and unusual thought content, while there was little response to either Leponex or Placebo in respect of guilt feelings and disorientation. The items that showed the greatest improvement at the end of the trial were hallucinatory behaviour, suspiciousness and unusual thought content.

Clinical impression during and after the trial was that sedative action was more rapid and effective, and control of patients who showed continued aggressive and impulsive behaviour more effective than with the use of chlorpromazine or trifluoperazine.

Side-effects

These were noted only if the patient spoke of them or the doctor or nursing staff observed them, and were as follows: CNS – drowsiness (63%), headache (20%); autonomic – hypersalivation (87%); dry mouth (40%); disturbed visual accommodation (40%); sweating (13%); extrapyramidal – tremor (83%); rigidity (3%); circula-

tory – hypotension with collapse (13%); gastro-intestinal – constipation (53%), nausea or vomiting (23%). Most side-effects were mild and transitory but drowsiness tended to be prolonged, probably because of the high dosage used. A serious side-effect however was hypotension with collapse (13%) which occurred at onset of therapy but could be prevented by starting with low dosage and gradual increase. Some reduction of blood pressure – mainly systolic – and tachycardia (hitherto unreported) occurred in the majority of cases and persisted unabated throughout the trial (statistics supplied on request). Tremor was mild but only partially responsive to antiparkinsonic drugs given after the trial. There were no changes in blood picture and liver function.

CONCLUSION

Leponex appeared effective for control of the florid features of schizophrenia, particularly paranoid manifestations. Clinical impression during and after the trial was that onset of sedative action was more rapid, and control of aggressive patients often more effective than with say chlorpromazine, but Leponex caused more drowsiness. Extrapyramidal signs, apart from mild tremor, were virtually absent; hypotension however required caution at start of treatment. Tentatively at this stage the drug may be recommended for use in aggressive and impulsive patients who have not responded to the usual phenothiazines. The drug however needs to be further evaluated as regards its cardiovascular side-effects, and its efficacy in the long-term and in comparison with the established phenothiazines. The average daily dosage of 422 mg. in this trial was probably on the high side.

SUMMARY

33 Chinese in-patients in Hong Kong, diagnosed schizophrenia with acute symptomatology were involved in a double-blind cross-over trial comparing Leponex (clozapine) with Placebo. Leponex was found to be effective particularly in the control of paranoid manifestations and excited and aggressive behaviour, with rapid onset of action. The drug should however be used with some caution at this stage because of its hypotensive effects, which led to collapse in 13% of cases in the initial stages of treatment. The side-effect could be avoided by starting on low dosage.

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WITHDRAWAL OF MEDICATION AS A CAUSE OF RELAPSED SCHIZOPHRENIA: SOCIO-CULTURAL PERSPECTIVES

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INTRODUCTION

One of the most significant breakthroughs in the management of schizophrenia was the discovery and the introduction of a phenothiazine drug, namely, chlorpromazine, in 1952. However, despite the introduction of numerous other psychoactive agents in the management of schizophrenia, over the last twenty years, treatment has been essentially on an empirical and symptomatic level. Frequently, patients relapsed when the drug was removed, and re-admission to hospital was necessary. It appears then, that the most effective method of counteracting frequent relapses of schizophrenia, is continuous maintenance on phenothiazines at sufficient therapeutic doses.

Few experienced psychiatrists would deny the

pragmatic value of maintenance therapy with phenothiazines, although it has been observed (Rothestein, 1960) that the progress in the treatment of psychiatric patients may be attributed to a complex interplay of drugs and psycho-social factors. Studies (Pritchard, 1967) have indicated that pharmacotherapy definitely results in improved short-term prognosis of hospitilisation and improved general condition of the patient on discharge. In addition, maintenance use of drugs after discharge may possibly lessen re-admission rates. (Good et al., 1958) demonstrated that withdrawal of chlorpromazine for a period of three months or more, results in the reappearance of symptoms in schizophrenic patients; on the other hand, resumption of the same medication after a three-month abstinence produces the same effect as continuous maintenance treatment with drugs.

In a study conducted by Prien (1969), the withdrawal of medications from schizophrenic patients and its replacement by a placebo for a period of twenty-four weeks, resulted in a forty per cent relapse rate; furthermore, patients previously receiving high doses of medication were more liable to relapse than others.

It can then be said with at least ninety per cent certainty (Slater & Roth, 1969) that if a schizophrenic patient on maintenance therapy relapses, the reason for relapse is almost certainly due to default at medication. It is, therefore, worthwhile to enquire into the sociological and cultural causes for default in drug therapy. This insight would have tremendous prophylactic value, from the point of view of prevention of relapse of the illness. It would also be useful to find out the inter-ethnic, social class and educational differences in the causes of drug default. Of particular interest too, would be the average duration between stopping medication and onset of symptoms, and the length of time relatives wait before seeking treatment, once relapse has occurred.

Although theoretically, long-term drug therapy of schizophrenia is ideal, there are many socio-cultural and psychological factors that do not facilitate long-term maintenance therapy. Frequently, schizophrenic patients do not have the insight or volition to continue medication, which may be unpleasant to take, due to side effects; furthermore the intrinsic family pathology may not serve as a supportive milieu for regular medication and follow-up.

It is a well-known fact that the majority of schizophrenic breakdowns occur in the lower socio-economic groups (Slater & Roth, 1969). These socio-cultural factors further reduce the chances of long term medication. It has been demonstrated that schizophrenic patients at Woodbridge Hospital, Singapore, relapsed approximately once a year (Yap, 1968). Frequent re-admission to mental hospitals would definitely be more expensive than if patients were kept on an out-patient basis with regular medication.

Thus the importance of identifying the reasons for default at medication of schizophrenic patients, is not only for academic curiosity but for the practical management of a psychiatric in-patient centre.

Aims of Study

The aims of the study were to discover:—

1) The percentage of schizophrenic patients who relapsed because of default in medication.
2) The socio-cultural and psychological reasons for default at psychotropic medication.
3) The socio-cultural characteristics of such patients and their relatives.
4) The causes of relapse of schizophrenia besides default at psychotropic medication.

Method of Study

The case material consisted of all cases diagnosed as Relapsed Schizophrenia who were admitted to the psychiatric wards of the University Hospital, Kuala Lumpur, over a period of five months. The cases were selected at random, according to consecutive admissions.

Cases included:—

1) Re-admissions of old cases treated previously at University Hospital and
2) New first admissions with relapse of schizophrenia.

A total of forty-three cases were studied, averaging 2—3 cases per week. All patients and their relatives who accompanied them, were interviewed on a structured questionnaire by the authors. Relatives were especially questioned on the various reasons for relapse of the illness and the default of medication.

Results of Study

a) *General Demography* — A total of forty-three in-patients who relapsed with schizophrenic illness, was surveyed. Fifteen (35%) were males and twenty-eight (65%) were females. This is consistent with the 1:2 ratio of male/female rates of admission into the psychiatric centre, University

Hospital (Teoh, 1968). Only five (12%) Malays were seen while twenty-three (62%) Chinese and nine (20%) Indians were included in the study. Seventy-seven per cent of all cases seen originated from the lower socio-economic group, of which twenty-three (51%) were unemployed.

b) *Causes of Relapse* – Twenty-five cases (58%) had relapse of schizophrenia due to default in drug therapy, while eighteen (42%) had a relapse while still on medication.

c) *Causes of Default at Medication*–– The following were the reasons given by the patients and their relatives for stopping medication on their own:–

(See Slide I)

i) Eighteen (72%) patients felt well (symptom free) and relatives believed they were completely cured.

ii) Two (8%) patients refused to co-operate with medication.

iii) Five (20%) patients claimed that the doctor in charge had stopped the medication.

It was interesting to note that fifteen of the eighteen patients had been advised by their physicians in charge that drug default would cause a relapse of their illness; despite this knowledge, they stopped medication on their own initiative, believing that they were completely cured.

Generally, the aetiology of schizophrenia is still an unknown entity to the minds of many practising psychiatrists, not only do they not understand the causes for relapse, but often they are unsure of the duration of long term medication. When the patient is symptom free, these vague concepts of aetiology and duration of medication are sensed by them and their relatives, thus frequently resulting in their taking the initiative to stopping medication on their own. Within the context of native and indigenous therapy in Malaysia, the concept of long-term therapy does not exist. This observation was made by Kinzie et al., (1971) when he commented that traditional healers do not engage in long term relationships. This cultural influence of relying only on short-term treatment could possibly account for the reluctance in accepting long-term medication as a therapeutic necessity

d) *Reasons for Relapse Despite Continued Medication* – Of a total eighteen patients who relapsed while still on medication, the reasons for relapse were:–

(See Slide II)

i) Irregular medication 3 (17%)

ii) Sudden psychogenic stress 5 (28%)

iii) Pathological family structure..... 6 (33%)

iv) Socially deprived family circumstances..... 4 (22%)

The results are consistent with Rahe's study (1969) that the onset of illness is significantly related to on-going life adjustment and different life crises. This proves that psychotropic medication is only one of many factors in preventing relapse of illness, thus one should not be over-eager to explain patient improvement only in terms of chemotherapy.

e) *Follow-up Treatment and Duration of Medication* – Of the forty-three cases studied, thirty-four (78%) were previously followed up at the University Hospital out-patient's clinic.

(See Slide III)

The majority of patients, twenty-three (51%) took medication regularly for a period of up to one year.

(See Slide IV)

f) *Period of Drug Default Leading to Relapse* – The critical period for discontinuation of medication prior to relapse fell between 4–5 months. Ten out of twenty-five cases were re-admitted after this period of drug discontinuation. These studies (Judah et al., 1961 & Good et. al, 1959) where withdrawal of chlorpromazine for periods of 3–5 months resulted in a reappearance of symptoms.

g) *Duration Between Onset of Symptoms and Consultation* – It was interesting that twenty-six (60%) patients sought consultation within one week of relapse of symptoms. Furthermore thirty-four (78%) of all cases were previously treated at the University Hospital out-patient clinic. Only five (12%) ever sought the advice of native healers, and only 3 (7%) resorted again to traditional methods of treatment prior to present consultation. Practically all those seeking traditional methods of treatment belonged to the Malay ethnic group. These results contrast significantly with an earlier study (Teoh et al., 1971) done in the same unit, where 31% of patients seen admitted to having consulted native healers prior to psychiatric consultation. It would appear that, subsequent contact with modern psychiatric treatment diminished the patient's confidence in traditional methods of treatment.

Reasons for Default of Medication	No.	%
Patients felt well prior to relapse) Relatives believed patients were cured)	18	72
Patients refused to co-operate with medication	2	8
Doctor i/c stopped patients' medication	5	20
Total No. of Patients	25	100

Table 1: Reasons for Default/Stoppage of Medication

Other Causes for Relapse	No.	%
Irregular medication	3	17
Sudden psychogenic stress	5	28
Pathological family structure	6	33
Socially deprived family circumstances	4	22
Total no. of Patients	18	100

Table II: Reasons for Relapse Despite Continued Medication

Type of Follow-up	No.	%
University Hospital Psy. Clinic	34	78
Government Psy. Clinics	2	5
General Practitioner	3	8
Total default at follow up	4	9
Total No. of patients	43	100

Table III: Type of Follow-up Treatment prior to Relapse

Duration on Last Medication	No.	%
1 year	23	53
2 years	11	26
3 – 4 years	4	9
5 years and above	5	12
Total No. of Patients	43	100

Table IV: Duration on Last Medication Prior to Relapse

CONCLUSION

A total of forty-three patients with relapsed schizophrenia were surveyed at a University Hospital Psychiatric centre. Fifty-eight per cent of cases relapsed because of default of medication, while 42% relapsed despite continuous medication. The main reason for default at medication was due to the fact that patients felt well and their relatives believed that they were completely cured. This was despite the fact that 35% of the relatives had been advised that default would cause a relapse.

Other reasons for relapse were discussed.

The critical period for discontinuation of medication prior to relapse occurring, was shown to be between 4 – 5 months. It was interesting that twenty-six sought early psychiatric treatment – within one week of onset of symptoms.

The results indicated too, that subsequent contact with modern psychiatric treatment dimi-

nished the patient's confidence in traditional methods of treatment.

ACKNOWLEDGEMENT

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VESTIBULAR REACTIVITY IN SCHIZOPHRENIA AND ITS CORRELATION WITH THE EFFECTS OF NEUROLEPTICS

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By an accidental finding when the author practiced caloric test and found some of the chronic schizophrenic patients whose reactivity was completely absent while the non chronic schizophrenic patients were normally reactive. Reviewing the literature and finding that the results of caloric stimulation on schizophrenia were so fragmentary and in some respects contradictory, it seemed advisable to obtain first hand information on the possible changes of caloric reactivity in the schizophrenic group. It was decided to conduct the present study which was designed to test whether or not

1) Chronic and non-chronic schizophrenia might differ in caloric test.
2) Any relation with usage of neuroleptics.

Along with these explorations, the present study was also designed to investigate if the difference of caloric responses had any effect on the pharmacotherapy.

METHODOLOGY

Subjects: Fifty-four hospitalized schizophrenic patients served as subjects in which 20 patients were tested at Boston State Hospital (8 were from chronic ward while all the other 12 were from acute intake ward) and 34 patients at Taipei City Psychiatric Center in this investigation. Patients with defective ear drums and with a history of middle ear infection or similar ailments were

excluded. Otherwise, no selection was made. Technique: The nystagmic reaction to caloric stimulation was tested in the Fitzgerald and Hallpike method. The patient was placed in a bed with his head raised 30 degrees. The temperatures used were 30°C and 44°C. Each of these was allowed to flow into the external acoustic meatus from a reservoir for 40 seconds, during which period no less than 250 ml of water would flow. The effects were measured in terms of the time interval between the application of the stimulus and the end of the resulting nystagmus. (2) (3) (9). Each non response to caloric test patient should be repeated with the time interval of at least 2 days. On the other hand, the positive response patients should receive another test 13 weeks after the initial test or at the time when presence of neuroleptics induced extrapyramidal symptoms.

Clinical and Psychiatric Evaluation

These were measured only on the 34 patients at the T.C.P.C. and were designed on a blind basis.

1) The clinical impression of chronicity was made by the resident in charge.
2) Diagnostic Scale for Chronicity (D.S.C.) was rating 6 weeks after the initial caloric test from patient's record. (4) (5) (6) (7) (Table I)
3) Brief Psychiatric Rating Scale (B.P.R.S.) was completed at the beginning and at the end of 12 weeks or at the time of discharge from hospital by the same psychiatrist. All of the 34 patients in T.C.P.C. were in the same milieu and were on different kinds of neuroleptics; the dosage adjustment and drug selection were assigned depending on the clinical needs by the psychiatrist in charge.

RESULT

Twenty patients were tested at the B.S.H. Out of 12 patients from the acute intake ward, 11 patients showed positive while only 1 showed negative response to caloric stimulation. The remaining 8 patients from chronic ward showed negative or markedly reduced response. The differences were significant at $P < 0.005$ level (Table 1). Thirty-four patients were tested at the TCPC; out of 15 patients who were labelled as non-chronic schizophrenia by clinical impression of chronicity, 13 showed positive and only 2 showed negative response to caloric stimulation, while only 2 out of 19 chronic schizophrenia showed positive response to the test. The differences were again highly significant at $P < 0.005$ level (Table II). Analysis of D.S.C. also showed significant differences between caloric test positive and negative group at $P < 0.002$ level (Table III). These results of two different ways of measurement of chronicity indicate that the negative caloric response is related to the chronicity of schizophrenic illness.

The further B.P.R.S. evaluation revealed significant differences of mean change between positive and negative group at $P < 0.005$ level (Table IV). Three out of 13 positive response to caloric test patient developed definite drug induced extrapyramidal sign but repeated caloric tests were still reactive at that movement, except on patient whose caloric test became temporarily negative at the movement of occulogyric crises.

Table I

Caloric test for 54 schizophrenic patients

	Positive	Negative	Total
B.S.H.*			20
Acute Intake ward	11	1	12
Chronic Ward	0	8	8
T.C.P.H.**			34
Non chronic	13	2	15
Chronic	2	17	19
* $x^2 = 17.9$	N = 1		$P < 0.005$
** $x^2 = 17.9$	N = 1		$P < 0.005$

Table II

Diagnostic Scale for Schizophrenic Chronic Vs Non Chronic

Factor	Scale 0	1	2	3	4
1) Onset	more than 2 yrs.	6 mths–2 yrs.	1–6 month	< 1 month	Suddenly
2) Precipitating factor	None	mild	moderate	marked	Strongly
3) Married (also age factor)	None age 40	None 30–40	None 20–30	Some Problem < 20	yes Any age

4)	Schizophrenic Premorbid History	definite	moderate	mild	Very mild	Not Present
5)	Duration of illness	> 10 years	4 yr–10 yr.	2–4 yr	6 mths–2 yr	6 mths
6)	Presence of Previous episode	> 6 times or continue for 5 yrs.	4–6 continue for 2–5 yrs.	2–4	1–2	Not Present
7)	Length of present Hospitalization	>2 yrs.	6 mths–2 yr	2–6 mths	1–2 mths	< 1 month
8)	Age of onset	< 16	16–20	20–30	30–40	> 40
9)	Effective on treatment	None	mild	moderate	marked	dramatic
10)	Clinical impression of chronicity	Severe	moderately severe	moderate	mild	Not present

Table III

Result of Diagnostic Scale

Caloric	N	Score
Positive	15	25 ± 4.9
Negative	19	15 ± 5.6

* Maximum Score: 40

** $P < 0.002$

Table IV

Mean Change of Total B.P.R.S.

	CALORIC TEST	
	Positive	Negative
Case number	15	19
Initial Score	64.2	58.8
12 weeks after medication	29.87	46.85
mean change	46.85	11.95
% of improvement	74.33	29.29

$P < 0.005$

DISCUSSION

Before proceeding to discuss the results, certain errors of caloric test technique must be pointed out. In some cases in which the reactivity was very low only a few extremely weak movements of the eye could be observed, and it is questionable whether these could be counted as true nystagmic beats. Therefore, in instances in which the total reaction consisted 6 or less feeble or incomplete beats, the counts were negative. The main source of error in this study was in the measurement of time, it was therefore not possible to stop the watch at exactly the last nystagmic beat. However, in spite of these errors of technique, we only counted positive or negative. The data were reliable enough to demonstrate the important gross features of the reaction, either positive or negative response.

The striking evidence of negative response to caloric stimulation in chronic schizophrenia, seemed to indicate the relationship between the vestibular function and the chronicity of schizophrenic illness. In the literature, there were occasional reports on abnormality of vestibular function in schizophrenia 30 years ago. As early as 1921, Pekelsky reported 2 cases of catatonic schizophrenia in which there was a transitory absence of the nystagmus in response to vestibular stimulation. In 1940 Amgyal reported several papers on caloric test and concluded that in total group of schizophrenic patients vestibular reactivity was generally reduced with particular low responsibility. Claude, Joo olaimed that the reduction of vestibular response in schizophrenia is related to the duration of the illness rather than to the clinical type.

The results of the present study seemed to indicate the abnormality of vestibular reactivity in chronic schizophrenic group. The question arose, whether the result of negative response to Fitzerald and Hallpike caloric test indicated the labyrinth was dead, or by some reason not sensitive enough to produce nystagmus. We tested again for the 19 non-reactive patients with a stronger test, Barany mass caloric test (8) (9), by imigating cold water at 16.6°C, the irrigation was continued until nystagmus began. If no nystagmus ensued in about four minutes the labyrinth was considered dead. The result by this method, we found that all of the 19 patients showed reactive and the nystagmus started after 2 to 3 minutes of continued irrigation of water. It became more clear that in the chronic schizophrenic group the sensitivity of vestibular reactivity decreased.

The result of significant difference of B.P.R.S. changed in the same milieu between positive and negative groups indicating the significant correlation with the effects of neuroleptics. We could not find any change or vestibular Sensitivity during the time of neuroleptic-induced extrapyramidal sign. A follow-up study to find out any relation with the long-term usage of neuroleptics and the decrease of vestibular reactivity is indicated.

In discussing the mechanism and localization of the changes of vestibular reactivity, it is however impossible to determine which parts of the vestibular apparatus are responsible for this change in function in the present study. However it is a worthwhile and valuable method of Fitzgerald and Hallpike caloric test in predicting the prognosis and the effect of neuroleptics for schizophrenic patients.

SUMMARY

The vestibular reactivity to caloric stimulation in 54 schizophrenic patients has been studied at Boston State Hospital (B.S.H.) and Taipei City Psychiatric Center (T.C.P.C.).

In response to Fitzgerald & Hallpike caloric stimulation, the significant differences between the acute and the chronic schizophrenia were observed, and they were correlated with the therapeutic response of the neuroleptics.

Twenty patients were tested at the B.S.H. Out of 12 patients from the acute intake ward, 11 patients showed positive while only 1 showed negative response to caloric stimulation. The remaining 8 patients from the chronic ward showed negative or markedly reduced response. The differences were significant at $P < 0.005$ level.

Thirty-four patients were tested at the T.C.P.C.; out of 15 patients who were labelled as non-chronic schizophrenia, 13 showed positive and only 2 showed negative response to caloric stimulation, while only 2 out of 19 chronic schizophrenia showed positive response to the test. The differences were again highly significant at $P < 0.005$ level.

The above findings seemed to indicate the relationship between the vestibular function and the chronicity of schizophrenic illness. Further psychopharmacological studies by B.P.R.S. were performed. The differences were also highly significant at $P < 0.005$ level. The value of Fitzgerald and Hallpike caloric test at the measure of vestibular function in predicting the effect of neuroleptics is discussed.

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THIOTHIXINE (NAVANE): AN UNCONTROLLED CLINICAL TRIAL ON 28 CASES OF SCHIZOPHRENIA

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INTRODUCTION

Thiothixine is a derivative of thioxanthine. There are two basic structural differences between thioxanthines and phenothiazines: (i) the nitrogen (N) atom in the tricyclic nucleus is replaced by carbon (C) and (ii) the side chain is attached to the nucleus by a double bond that prohibits any rotation of the first carbon in the chain.

Animal studies have shown that thiothixine is a potent anti-emetic and that it interferes with conditioned avoidance learning in low doses. It exhibits only weak anticholinergic, antihistaminic, hypotensive, hypothermic and sedative properties. The results suggest that thiothixine may be useful in chronic psychotic excitation with active delusions and hallucinations (1).

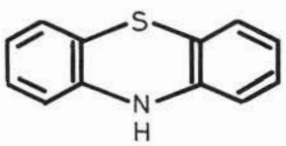
Numerous uncontrolled clinical trials (2–10) with acute and chronic schizophrenics indicate that thiothixine is an effective antipsychotic agent. The symptoms most frequently reported to have improved were suspiciousness, thought disorder (conceptual disorganisation), hallucinations, tension, unusual thought content, emotional withdrawal and excitement (agitation). Subjects were also noted to have shown improvement in social competence and personal neatness.

Controlled studies (11–14) however, have not indicated that thiothixine is superior to the more commonly known phenothiazine compounds such as trifluoperazine, chlorpromazine, perphenazine and thioridazine.

The aim of our study was mainly exploratory. We hoped to evaluate the short-term efficacy and toleration of thiothixine in the treatment of hospitalised schizophrenic patients.

Selection and Characteristics of Patients

Consecutive female admissions to Tampoi Mental Hospital with a diagnosis of schizophrenia, during the period of 18th September to 19th October, 1969, were considered for inclusion in the trial. The criteria used in diagnosis were the presence of at least two of the following symptoms:– thought disorder, auditory hallucinations, flattening or incongruity of affect, and feelings of passivity. Patients below the age of 12 and those with epilepsy, galucoma, anaemia, liver



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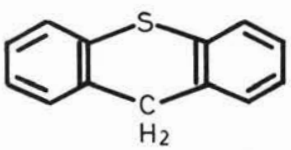

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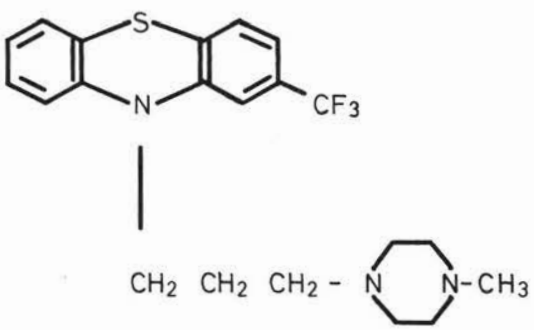

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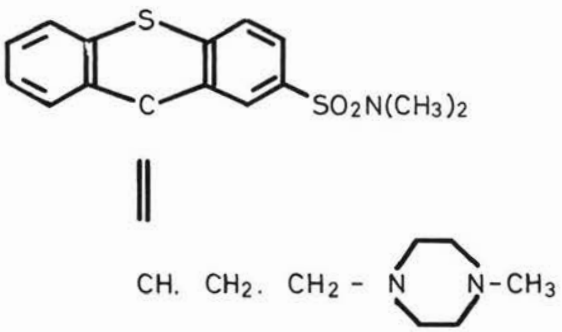

THIOTHIXINE

failure, leucopaenia and sensitivity to thiothixine were exlcuded.

Initially thirty patients were admitted to the trial, but two were subsequently excluded because they received electro-convulsive therapy. Of the remaining 28, there were 11 first admissions and 17 readmissions. (mean readmission figure: 2.4). Their mean age was 32 with a range of 14–47 years. 24 were engaged in domestic duties housewife or helping at home), and 19 (68%) were married.

METHOD

Previous specific medication, if any, was discontinued at least one week prior to starting on thiothixine. Assessment of the patients' symptoms, using a modified Gorham Brief Psychiatric Rating Scale, was done at the following intervals:–

a) immediately before commencing treatment with thiothixine and
b) after 7, 14, 30 and 60 days treatment with thiothixine.

At each of the above intervals, independent ratings of the patients' symptoms were made by all four assessors. The mean score (to the nearest whole number) for each symptom was computed and recorded.

During the trial, no other psychotropic drugs, with the exception of symptomatic remedies for the control of side effects (benzhexol), acute excitation (paraldehyde), and insomnia (sodium amytal) were administered.

Depending upon the severity of symptoms on admission, subjects were started on 10–20 mg/day orally of thiothixine. The dosage was increased if necessary, judging on the response, until the optimum dose for each patient was determined. The recommended maximal dose of 60 mg. daily was not exceeded. Except for those on 10 mg. daily, medication was administered in two divided doses per day. Table I shows the mean dose per patient at each assessment (rating) interval.

Before treatment and at the end of the trial, the following laboratory investigations were carried out on each patient:– full urine examination, haemoglobin, total white and differential blood count, blood urea and liver function tests.

RESULTS

(i) *Gorham Brief Psychiatric Rating Scale*

The sum of mean ratings on target symptoms at each assessment interval is shown in table II.

Table I

Time Interval(Days)	0	7	14	30	60
Mean Daily Dose/Patient (mg.)	13.6	25.4	35.0	33.9	27.1
Range (mg.)	10–20	10–40	20–60	20–60	10–60

Table II

Symptoms	Time (Days) 0	7	14	30	60	No. of Patients rated as having symptom	
						Pretrial	Post Trial
Somatic Concern	11	11	11	6 (p. 02)	5	10	4
Anxiety	5	6	5	0	1	4	1
Emotional Withdrawal	47	30	21(p. 001)	16(p. 001)	10	25	8
Conceptual Disorganisation	37	10(p. 01)	3(p. 001)	3	4	23	3
Guilt Feelings	0	0	0	0	0	0	0
Tension	40	11(p. 001)	4(p. 001)	4	4	24	4
Mannerisms & Posturing	20	4(p. 001)	0	0	0	12	0
Grandiosity	6	3	0	0	3	3	2
Depressive Mood	9	11	8	0(p. 001)	1	8	1

Hostility	27	4	4(p. 001)	6	0	17	0
Suspiciousness	32	7(p. 001)	5	3	3	19	3
Hallucinatory Behaviour	59	21(p. 001)	10(p. 001)	6	4	24	2
Motor Retardation	23	27	20	7(p. 001)	6	16	5
Uncooperativeness	25	7(p. 001)	4	1	0	16	0
Unusual Thought Content	20	3(p. 001)	0	0	0	13	0
Blunted Affect	52	44	42	33(p. 01)	26	26	28

The results were analysed using the uncorrelated test for all the data. The ratings at 0 day were taken to be the controlled group and subsequent ratings at 7th, 14th, 30th and 60th day were assumed to be independent.

At the end of 7 days treatment, a significant improvement ($P < 0.001$) was noted in the ratings of tension, suspiciousness, hallucinatory behaviour, uncooperativeness, unusual thought content and mannerisms and posturing. This improvement was maintained in each category throughout the trial. Symptoms of emotional withdrawal, conceptual disorganisation and hostility showed a significant and sustained improvement after 14 days treatment; and in the case of depressive mood and motor retardation, only after 3 days. The symptoms which did not appear to have been influenced in this trial were somatic concern, anxiety (subjective), grandiosity and blunted affect.

(ii) *Overall Therapeutic Effect*

At the end of the trial, the overall therapeutic effect was assessed for each patient on a five point scale: marked improvement, moderate improvement, slight improvement, no change, worse. The results are shown in Table III

Table III

Degree of Improvement	No. of Patients	%(N = 28)
Marked	10	36
Moderate	9	32
Slight	6	21
No change	3	11
Worse	0	0

A total of 19 cases (68%) were rated as having shown marked or moderate improvement at the end of the trial. Slight improvement was noted in 6 patients, and 3 remained unchanged. None was rated as having become worse.

(iii) *Side Effects*

Side effects were reported in 20 patients (71%). They were of moderate severity in 11 cases and mild in 9. The frequency of their occurrence is shown in Table IV.

Table IV

Side Effect	No. of cases reported
A. Extrapyramidal	
Rigidity	15
Tremor	5
Akathesia	2
Gait	2
Dystoxia	2
Oral Dyskinesia	1
B. Autonomic	
Salivation	1
Constipation	1
C. Central	
Sedation	1
Insomnia	1
Hyperactivity	1
Lactation	1

The most frequently occurring side effects were of the extrapyramidal type, with rigidity and tremor predominating. In all except two cases, they were controlled by the administration of benzhexol.

Autonomic and Central side effects were infrequent and did not unduly interfere with the treatment regime. Stilboestrol was effective in controlling the case with lactation.

(iv) *Laboratory Findings*

One patient, aged 20, with a history of two previous admissions, was found to have leucopaenia (total white count 3,5000; polymorphs 30%, cosinophils 4%, lymphocytes 64%, monocytes 2%) at the end of the treatment period. Her blood picture was normal on admission. She had no past history of allergy and during her previous admissions, she was treated with chlorpromazine without adverse effect. Chlorpromazine was reintro-

duced, and blood investigations including platelet count obtained a month later were within normal limits.

No abnormal laboratory investigations were found in the other 27 patients.

DISCUSSION

The results reported in this study have to be interpreted in the context of an uncontrolled clinical trial. The recording of the mean score (of all four assessors) for each target symptom may minimise errors in clinical observation and evaluation, but does not eliminate rater bias. Though the trial patients were not segregated in a special ward, the nursing staff were aware that they were receiving a new drug. In addition to the greater degree of attention and observation, the patients were subjected to more investigations than the routine admissions.

Nevertheless, the main findings appear to reflect the observations reported in earlier uncontrolled trials (2–10), which reported significant improvement in "schizophrenic" symptoms: hallucinatory behaviour, suspiciousness, thought disorder, mannerisms and posturing, negativism (uncooperativeness), tension and emotional withdrawal (indifference to environment). Unlike the report of Kurland et. al (6), blunted affect was not observed to improve in the present study. This could be explained by the erroneous interpretation of facial rigidity (a side effect) as blunting of affect

Depressive mood and motor retardation improved significantly after 30 days. This finding supports the contention of Goldstein (15) and overall (16), that thiothixine may be useful in the treatment of patients with depression. In this area, thiothixine has the added advantage of the ability to control tension and to activate anergic patients.

As reported in previous studies (2–16), extrapyramidal symptoms were the most frequently observed side effects. Their appearance was not correlated with clinical improvement. They were of mild to moderate severity and did not significantly interfere with treatment, autonomic side effects were rare. Restlessness (hyperactivity) and insomnia, reported in 80% of patients in one study (8) was seen only, in two cases (7%). Lactation, a side effect unreported in previous studies and occasionally encountered with the use of phenothiazines, was noted in one patient.

The discovery of leucopenia in one patient on thiothixine is worth noting. Laboratory studies carried out on a total of 412 patients in previous studies (2–16), have not revealed this abnormality, though photosensitivity has been reported in one patient by Goldstein (8). It is interesting that the leucopenia improved, despite the substitution of chlorpromazine.

In conclusion, the present sutdy on 28 patients appears to confirm that thiothixine is an effective antipsychotic agent, useful in the management of schizophrenia especially those cases not responding to phenothiazine. Its range of activity may be compared to that to trifluoperazine, with which it has a close structural resemblance. The antidepressive properties suggested in the results of this and other studies deserve further inquiry. Like the phenothiazines, unwanted reactions e.g. blood disorders may occur.

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GROUP PSYCHOTHERAPY IN COMBINATION WITH PSYCHOTROPIC MEDICATION

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INTRODUCTION

Group psychotherapy has been generally accepted as a method of treatment in psychiatry and is at present a well established field of psychotherapeutic procedure undertaken in many psychiatric centres all over the world. However as this treatment was derived from Western thought and ideas, Asian therapists who utilize group psychotherapy should carefully adapt the procedure to the cultural background of the patients.

Since psychotropic medications have been introduced in the field of psychiatry, the progress in therapy has clearly revealed that a number of patients have recovered and gone back to their community faster than ever before. Unfortunately, the rate of relapse has also been high. Thus Hoch (1958) suggested that the combination of group psychotherapy and psychotropic medication would prevent relapsing of the patient. Many papers have been published with regard to the benefit of group psychotherapy in combination with psychotropic medications; Bindelglas and Goline (1957) found that chlorpromazine and reserpine facilitated relatedness, awareness in the course of group psychotherapy with psychotic female patients. Winkleman (1959) also found trifluoperazine effective as an aid to short-term group therapy. Borowski and Tolwinski (1969) found combined treatment with chlorpromazine and group therapy more effective than chlorpromazine alone and particularly "in the quality of the improvement obtained and the speed of disappearance of such symptoms as delusional thinking and lack of insight."

Therapeutic Setting

This report deals with the experience of group psychotherapy in two countries; Malaysia and Thailand. In Thailand, group psychotherapy was introduced in Srithunya Hospital, Nondhaburi in 1963 (Suwanlert 1964), as a method of treatment for psychiatric patients, and also in Hospital Permai, Tampoi, Malaysia in 1972. Malaysia and Thailand are different both traditionally and

culturally. Malaysia appear to have heterogeneous culture and rich cultural heritage based on the separate traditions of the various races which make up the Malaysian society. The later, Thailand, is homogenous in culture and has a distinct culture, peculiar to herself, with traditions handed down through generations. It must be recognized that Buddhists compose 95% of the population and Buddhism is a very important force in the daily life of the people. However group psychotherapy is applicable to both countries.

A study on open mixed group psychotherapy in combination with psychotropic medication has been done in Thailand and Malaysia. Purpose of study: to study the optimum dosages of tranquillizing medications which can be valuable in assisting patients to achieve a more successful communication outcome. The technique used was the dynamically ,oriented approach, emphasizing the relationship of the therapist and patients; the patients with other patients; and the patient with groups. The method of group psychotherapy was evocative, and didactic lectures were given and reading material assigned to the group. Therapeutic sessions were 20 in both countries. Selection of patients was based on those who maintained no confusion, were in fair contact with reality, with the majority being schizophrenics and two were psychoneurotic patients and one alcoholic patient. The age range in the study was 18–45, 8 females and 2 males (Thailand), 8 females and 6 males (Malaysia). The size of the group was 7–10 patients. Educational background was at least that of completing secondary school; the highest level was university education. The economic status was primary middle class. Religion was not a limiting factor for inclusion in the therapy groups but all in Thailand were Buddhists. In Malaysia, the patients were Muslim, Hindus, Buddhist and Christians. Patients must be motivated and volunteer to participate.

The communication of group psychotherapy in both countries was different. For instance, in Malaysia, the three races, Malay, Chinese and Indian were in the group and to facilitate communication within the group, a compromise language, English, had to be used as the medium of communication and only English speaking patients were chosen. In Thailand, Thai a common language, is the language used in group psychotherapy. The manner of expression and content of verbalization was also somewhat different.

RESULT

Table I

Content of Verbalization

Topic of discussion	Thai Session		Malaysia Session	
Free floating discussion	40	8	35	7
Sexual problems	15	3	5	1
Religion	10	2	–	–
Parental authority	10	2	–	–
Individual problem	10	2	25	5
Didactic lecture and reading material	10	2	20	4
Folk belief or charms	5	1	15	3
	100	20	100	20

Prior to group psychotherapy, the patients had received medications in maintenance doses of psychotropic drugs and had already participated in occupational therapy, and seldom has the opportunity to speak with the staff. When they had their problems, some patients talked to others, however they afforded little help as must be expected. At the most, they remained happily in the ward under the influence of medications. On beginning group psychotherapy, their medications were still at maintenance dosages. Later on in only a few patients was the medication reduced or increased. We would like to bring your attention to average daily dosage of medication studied in the female admission wards and convalescent wards in the two countries during the period of group psychotherapy.

Table II

Female average daily medication

	Medication (mg)	Admission ward		Convalescent ward	
		Malaysia	Thailand	Malaysia	Thailand
1.	Chlorpromazine	335.7	202.51	248	158.34
2.	Thioridazine	372.5	166.67	182	150
3.	Trifluoperazine	18.4	16.80	20.8	19

In both countries, it was found there were more female patients than male patients who participated in the therapeutic sessions. One of the chief reasons for this is the disproportion of male and female patients in the groups. Another point is that women in the group were found to need constant readjustment of their medication dosage to arrive at optimum dosage. Male patients in Thailand were out-patients, while in Malaysia the male patients were in-patients at the hospital. Even though the dosage of male patients would be an interesting point of study, no comparison of male patients in Malaysia was attempted as conditions in the session were not similar. In our observation we notice that average dosage for female patients is higher than in Thailand. The reason for this is that psychiatrists in Thailand attempt to prescribe combined medication and injections on some occasions while this is not the case in Malaysia. Group activities as well are used in Thailand indicating lower drug dosage. Another important factor explaining discrepancies between drug dosage can be explaihed by economic factors of the medication. In Thailand, patients buy their own medication while in Malaysia, it is a free part of their treatment.

Table III

Daily dosage (mg) which result in good verbalization in therapeutic session

Medication	Malaysia (H.P.)		Thailand (S.H.)	
	Female	Male	Female	Male
Trifluoperazine	20	–	10	–
Chlorpromazine	200	200	150	–
Thioridazine	300	–	300	–
Perphenazine	–	24	12	–
Perphenazine + Amitriptyline	–	–	6 + 75	–
Chlordiazepoxide	–	30	–	30

According to this table in Malaysia, dosages of medication are higher than in Thailand except chlordiazepoxide and the use of a combination of antidepressive agents and neuroleptic drugs. Diazepam (Valium) injections are frequently administered for anxiety patients in Thailand.

H.P. = Hospital Permai, Tampoi, Johor., Malaysia.
S.H. = Srithunya Hospital, Nondhaburi, Thailand.

Some Observations on Combined Therapy

1. *Psychotropic Medication and the Relationship of the Therapist and Patients; the Relationship Between Patients and Patients.* In the beginning of the treatment, female patients and male patients had poor and weak relationship, and female patients remained inactive. Usually the patients asked direct questions of the therapist. Male patients are more active in bringing up problems in direct question form to the therapist. Patients who had received high dosage of medication for the most part remained inactive and did not cooperate in the sessions. In such cases after the sessions proceeded three or four times, we found that the relationships of the patients and the therapist decreased in intensity and increased among their fellow patients both of the same and of opposite sexes. Patients who had received high dosage of medication were reduced to a moderate dosage (according to individual basis). After this period, we found activity and participation increased in the group and higher intensity of relationships among themselves. In this period, patients began to discuss and verbalize their individual problems among themselves and attempted to help fellow session members. At the same time, efforts to define and describe the problems they discussed accurately. Patients who had high anxiety or disconnected thoughts were found to be poor relaters to others in the group. In session 15 through 20, the relationship among the patients represented improved achievement for the group and a satisfactory condition of treatment. At this period, if patients were absent from the session, they were asked at following sessions what was the problem and if the absent member was in any harm. In one case a patient L, said "I am able to express myself better now. I feel more relieved, and do not think of my worries. I have the opportunity to air my worries in the meetings. The group members discuss my problems and this has been a great relief to me". R. reported to the group, "I now know a number of people who are friendly to me. At the beginning of the session I was shy and seldom spoke, but now I am able to speak freely."

In some patients in Thailand, the dosage was low. In such cases, the therapist had to increase the dosage in the patients and subsequently the patients felt better and were able to actively participate in the group.

2) *Psychotropic Medication and Clinical Symptoms.* A study of patients' case profiles revealed that in some individuals, after phenothiazine was given, thought disorders and hallucinations were

reduced. However it is to be noticed that on many occasions, patients maintained their hallucinations while at the same time becoming more communicative and cooperative in the group. However, in these cases after a number of sessions, these patients were able to relate the experiences with their own hallucinations and attempted to adjust themselves to this reality of their own mental health.

On the other hand, patients who were found to believe in charms as a subsequent factor of their illness were found to maintain this position after a period of sessions, even though they did not disturb the other members of the group. In such cases, the therapist encouraged these individuals to express their relation to the effect of the charm on them in as much detail as possible. These expressions of charms were followed by a discussion by the group in general. On several occasions the therapist was able to explain the causes of mental illness and emphasize especially the personality of the person as related to early background in the individual's life, as an important factor in mental health problems the patients had experienced and knew about. Following lectures and discussions on these points, the position then began to attain a more objective picture of mental illness.

3) *Psychotropic Medicaton, Depression and Anxiety.* As patients began to communicate and become active participants in the therapeutic session, a concomitant factor was their increased anxiety or depression about their own future. In such instances, psychotropic medications were indicated. In Thailand,anti-depressants were orally prescribed as well as diazepam in injection form.

4) *Psychotropic Medications and Dreams:* Free floating discussions were effectively utilized to bring unconsciousness matter to consciousness. Dreams are a very important aspect of effective treatment and observation of patients in this period of their group therapy. However in the group, there was found to be very few discussions about the dreams individuals experienced. In our opinion perhaps (Sandison 1963) — tranquillizers were the inhibiting factors that prevented dreams from being experienced and therefore not expressed by the group. The common dreams were of returning home, dreams that the father, in an authoritative role, died. The last dream expressed in the group was a dream of experiencing a charm being administered to them.

DISCUSSION AND CONCLUSION

From our observation at Srithunya Hospital and Hospital Permai, we find many similarities. Chief among these is a shortage of psychiatrists in both hospitals. Therefore the method of treatment by individual psychotherapy would consume an impractical amount of time. Group psychotherapy is one attempt to answer this problem and has been found to be an effective tool in both the institutions. We have found that drugs have relaxed the patients while group psychotherapy allows the patients to understand themselves better than in any other approach to date, while increasing their awareness of their specific problems and allowing them a more effective compromise with the realities of their particular mental problem.

The amount of average daily dosage in Hospital Permai is higher than Srithunya Hospital, because as mentioned before Srithunya Hospital uses combined drug therapy rather than single tranquillizers. In Thailand there is a tendency to use antidepressant combined with atractic drugs.

Advantages to be gained from this study are:

1) Patients who received group-therapy experienced more meaning in their lives and this seems to be a more detailed programme of treatment.
2) Psychiatrists in group psychotherapy are able to find and work on deep-rooted problems among the patients while the chance of meeting such problems in individual therapy is limited owing to a low frequency of meeting with the patient and a restricted amount of the time for each individual patient.
3) Patients are able to realize more about their problems and are able to live and communicate with other people.
4) Observations on attaining optimum drug dosages if successfully attained allow a fair chance for good relationships with the therapy session and provide satisfactory progno sis.
5) The effort to maintain mixed group therapy affords an excellent opportunity where problems concerning the opposite sex are concerned.

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THE USE OF TRANQUILLIZERS IN THE TREATMENT OF HEROIN ADDICTION IN TEENAGERS

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Heroin addiction is at present a serious problem in Thailand and lately, more teenagers are being involved. In our country since the outlawing of opium smoking in 1959, former opium addicts were turning to heroin chiefly, because of the case of consumption. At present, it is estimated that there are about 300,000 heroin addicts in the Kingdom. The techniques used for taking the drug vary from smoking opium, "chasing the dragon" (inhaling the fumes obtained by beating the rather impure heroin), smoking from cigarettes in which some tobacco shreds have been removed and "white powder" (purer heroin) inserted instead, to injections (usually self-administered, both intramuscular and intravenous (the main line). Moreover the percentage of heroin in the drug here in Thailand is about 80–90 p.c. (for the "white powder") and 15–20 p.c. for the purplish granules, whereas in the USA the white powder stuff is only 2–5 p.c. heroin.

Motives for the Study:

There are many approaches to the treatment of heroin addiction, namely – the Cold Turkey treatment, the Methadone Maintenance or the substitution treatment by using derivatives of opium in gradually reduced doses.

Many hospitals have tried various forms of tranquillizers in the treatment of heroin addicts, the major and the minor tranquillizers producing varying results. At present, many hospitals have adapted the technique of Methadone Maintenance because the control and management of patients are easier, and the suffering of the patients during the withdrawal period is not so severe.

We found out that Methadone, also a kind of narcotics, when once used for a period of time, is difficult to do without and the patients have to remain in hospital for a longer duration. In Thailand, the number of heroin addicts is considerable – and we have only three weeks in which to withdraw the drug. Methadone therefore is not suitable for this technique of treatment.

Methadone Maintenance Treatment programme is not so successful in Thailand because of the fact that transportation and communication for the patient are still far form satisfactory. Accordingly the patients could not keep their regular appointments to visit the unit for their dose of methadone.

Tranquillizers are, at the moment, most successful in the treatment programme. At present, it is not yet known which tranquillizer will be most effective. It is not practical to await for research results from the USA or Europe, simply because of the fact that there is a big difference in the

percentage of heroin in the drug used. This results in the big difference in the severity of the withdrawal symptoms. Thai addicts certainly show more severe withdrawal symptoms, the dose of tranquillizers required here will differ from abroad.

METHOD

Since January 1972, the addiction unit of the Psychiatric section of Pra Mongkut Klao Army Hospital has used the following tranquillizers in the treatment of the withdrawal phase of Heroin Addictions:– Trifluoperazine HCL (Stelazine), Diazepam (Valium), Thioridazine (Mellaril) and Medazepam (Nobrium). All the patients are teenagers, varying in age from 16–19 years. All volunteer for treatment. After admission, all are subject to complete physical examination including chest X-Ray and a detail history of the addiction is obtained from the patients and relatives, including their emotional developmental history and problems in the family. It is generally known that the majority of the young addicts are not really determined to receive treatment, therefore an assessment of the motivation is necessary before admission. They are asked to visit the unit on every Monday for four consecutive Mondays. If their attendance in these four Mondays is regular and prompt, they are assumed to have good motivation and accepted for admission and treatment. Right after admission, they will stop their heroin consumption and put on one of the stated tranquillizers – in the Double-blind method – the physician will not know which tranquillizers a patient is taking. Because Thai addicts consumed drugs of high heroin percentage – the following maximum doses are used:–

1. Trifluoperazine HCL	40 mg/day
2. Diazepam	80 mg/day
3. Thioridazine	1000 mg/day
4. Medazepam	80–100 mg/day

The patient will receive a minimum dose of the drug on the first day of admission – and the dose will be increased on the following day when the withdrawal symptoms became more severe. If patients are not able to take some food, supportive intravenous saline drip will be given. In patients who are very disturbed, sodium amytal is used.

RATING

The effect of the drugs used will be studied by the therapist in charge morning and night, paying paritcular attention to:

1. The severity of the withdrawal symptoms
2. Idiosyncracy
3. Subjective feelings of the patient for the used
4. Drop out rate
5. Running away

160 patients were studied, all male, aged 16–19 years. The dose of heroin used on the average is 120 mg/day. Those who cannot tolerate this regime of treatment will drop out – to which we have no objection. It is interesting to note that there are only two p.c. drop-outs.

On account of the high percentage of heroin in the drug consumed, the withdrawal symptoms after 24 hours will be much more severe here than in England and the USA. All the patients treated became delirious after 24–36 hours. They were disorientated, restless and crawling around the room; they were able to answer questions but in a confused manner, not mentioning any craving, refusing food. After 48 hours, these symptoms improved; they sat up and began to eat some food, then came the greatest craving for the drug, it is during this particular moment that they either dropped out of treatment programme or escape from the ward.

1. *The severity of the withdrawal symptoms*

Symptoms	Trifluoperazine HCL	Diazepam	Thioridazine	Medazepam
Yawning				
restlessness	++	++	+	++
goose flesh	++	++	None	+
muscle cramps	++	++	+	++
Insomnia	++	++	+	++
Diarrhea	None	+	None	None
Delirious	++	++	None	+

2. *Idiosyncracy*

Symptoms	Trifluoperazine HCL	Diazepam	Thioridazine	Medazepam
muscular spasm	++	None	+	None
Salivation	++	None	+	None
Oculo-gyric crisis	++	None	None	None
Dizziness	None	++	None	+
Hypotension	None	+	+	None

Those patients who received high doses of 40 mg/day of Trifluoperazine will show signs of extrapyramidal tract involvement. 50 percent showed oculo-gyric crisis. The rest have muscular spasm and salivation. These symptoms are lesser in Trioridazine, but most patients will complain of stuffy nose, unsteady gait difficulty in swallowing. For Medazepam and Diazepam, the patients will complain of dizziness, blurred vision and vertigo on changing positions after the disappearance of withdrawal symptoms.

3. *Subjective Feelings*

Most of the studied patients have once been treated by Methadone Maintenance technique and by questioning. It was noted that they craved for nothing except heroin. From the rating estimated by attendants and nurses, it was found that, with Diazepam there was the least complaint, followed by Medazepam. In the Trioridazine group which was supposed to be most effective for causing such symptoms, many complained of uncomfortable symptoms like stuffy nose and salivation. In almost every patient, Stelazine produced signs of extrapyramidal poisoning in varying degrees.

4. *Drop-out Rate*

As these patients were voluntary, they were free to drop-out when they so desired – posisbly they could not tolerate the symptoms any longer. These patients were teenagers who had already problems at home, so it was surprising to find that only four drop-outs (two from 40 mg/day Trifluoperazine, one from 80 mg/day Diazepam and one from 100 mg/day Medazepam)

5. *Running away*

The patients who could not tolerate even drop-out state, naturally ran away, two from Diazepam and two from Medazepam on the second day of admission.

Summary of the results

1. Trioridazine is the most effective in controlling symptoms of heroin withdrawal, any undesirable side-effects being treated by appropriate doses of muscle relaxants. After one week of hospitalization, the dose was reduced to maintenance level that most patient could tolerate well.
2. Diazepam and Medazepam are the next most effective drug. The symptoms of withdrawal was most severe, 48–72 hours after the last dose of heroin. The side-effects were mild but uncomfortable for the patients, namely dizziness during change of position and unsteady gait.
3. Trifluoperazine is accompanied by considerable side effects and the withdrawal symptoms remained severe in spite of large doses of the drug.
4. The psychiatric section of the Pra Mongkut Klao Army Hospital have tried both Methadone Substitution programme and tranquillizers, and found that there was a higher relapse rate in the Methadone group.

CONCLUSION

During 1972 and the beginning of 1973, we have studied the effectiveness of four tranquillizers in the treatment of heroin addictions. The 160 teenager addicts were stopped from using heroin immediately after admission, and each in turn was given a tranquillizer according to their serial number in doses that could control severe symptoms. The duration of admission for almost every patient was 21 days. They were otherwise fairly healthy and accepted on a voluntary basis. The patients were observed morning and night and their symptoms tabulated. Detection of heroin in their urine was done periodically without their knowledge in order to assure that heroin was not taken during admission. After one year of study we found that Trioridazine was effective in controlling withdrawal symptoms, but side-effects were always present.

Next on the list of effectiveness came Diazepam and Medazepam which are equally useful, but the symptoms were more severe than in Trioridazine

group. Trifluoperazine was accompanied by severe reaction and withdrawal symptoms were greater than the previous three.

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AVERSION THERAPY IN A CASE OF FETISHISM

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Behaviour therapy is based on the premise that abnormal behaviour has been acquired by learning as a conditioned response and as such can be eliminated according to the laws of learning theory.

One of the best known methods of behaviour therapy is aversion therapy in which the aim is to eliminate the unwanted behaviour by associating it with an aversive stimulus. It was used early in the treatment of alcoholism and the aversive stimuli were drugs such as apomorphine and emetine which induced nausea and vomiting. In 1956, Raymond reported the successful treatment of a handbag and perambulator fetishist by apomorphine conditioning. Following this account there was a renewed interest in aversion therapy and several reports of success were made in the treatment of other sexual deviations, such as homosexuality, and transvestism. One important development in aversion techniques was the substitution of drugs with electrical stimuli.

Chemical aversion therapy had several disadvantages. The patient had to be admitted to a hospital to be treated. The drugs had dangerous side-effects which could be fatal and the whole procedure was unpleasant. In addition there was great difficulty in timing the interval between the conditioned stimulus (abnormal behaviour) and the unconditioned response (nausea and vomiting).

To date, most therapists, prefer electrical methods over chemical aversion methods. The electrical stimulus is relatively safe and easy to administer. It affords better control in timing and can be given at a desired intensity and at the precise moment of time. All the available evidence indicates that aversion therapy is effective in the treatment of sexual disorders.

My first experience in the use of electrical aversion therapy began 2 years ago. I have treated 3 cases of alcoholism and 2 homosexuals. The results were encouraging. Of the 3 alcoholics, 2 improved and stopped drinking. One homosexual whose main complaint was recurrent fantasies of homosexual desires on a young boy was helped to rid himself of these fantasies. The other overt homosexual was not helped by the treatment.

There has been very little work done on behaviour therapy in Singapore or in Malaysia. The following study therefore merits a report as being the first case of fetishism treated by aversion therapy in this region.

The patient was a young Malayalee, aged 19 doing National Service. The father had caught him dressed up in his sister's brassieres on a number of occasions at night under his blanket and had punished him without much effect. Soon after enrolment into National Service his fetish acts became more frequent, and he was finally referred by his general practitioner for an opinion.

He was the eldest of six children (two boys and four girls) of an Indian Roman Catholic family. His father was very strict and authoritarian and used to punish him very severely for minor infringements during his early childhood. His father exerted great pressure on him to do well in his studies. However his academic work was poor for which he was punished. He failed the School Certificate examinations twice before passing on his third attempt. He was fearful of his

father, lacked confidence and had marked feelings of inferiority. After school hours, he resorted to smoking ganja with his friends in order "to relieve his frustrations". He smoked ganja daily for the past three years.

His sexual awareness began at the age of 13 with masturbation which he picked up from his classmates. He stopped this habit after the teacher warned him that it could disturb his concentration on his studies.

Soon after, he met a 16 year-old English girl who was sexually more mature. She initiated him into playing sexual games with her. Being much younger and inexperienced, he was terrified at first and yet fascinated. The sexual play involved petting and fondling and there was no sexual intercourse. "She would take off her clothes and mine. I was innocent, I did not know anything. I was trembling the first time." The sexual play occurred 1 – 2 times in a week and continued for about two years with the girl generally playing the more active and aggressive role and the patient, a passive one. The girl eventually left the neighbourhood. About 2 to 3 months after she left, he felt a vacuum and complained of uncontrollable urge to steal brassieres and panties and to put them on. "I would then imagine myself to be this English girl responding to sexual stimulation." He would also conjure up a picture of a girl in sexual ecstasy. Both these fantasies produced sexual excitement in him.

TREATMENT

Treatment was carried out in a darkened room with the patient lying on a couch and the electrodes of the shock box taped to the back of his hand. Before each treatment, he was asked to select an intensity of electrical shock which he experienced as unpleasant but not too painful. Treatment was conducted biweekly, with each session lasting approximately 45 minutes. There were two stages of treatment. In the first stage, the patient dressed in his normal clothes was instructed to conjure up in fantasy the stealing of brassieres, the putting on of the garments and the girl in sexual ecstasy. In the second stage, the patient was asked to put on a brassiere and to imagine that he was the girl responding to sexual excitation.

At a point when the patient reached maximum sexual excitement, he was asked to signal by tapping his hand, immediately following which 1 – 2 shocks were delivered.

On the average from 6 to 10 shocks were applied in each treatment session. Altogether, he completed 10 treatments in 5 weeks. It was incidental that 5 treatment sessions were conducted with the patient normally attired and the subsequent 5 treatment sessions with him wearing a brassiere. The switch from normal clothing to the use of brassieres was determined by the increase in latency in producing the fantasy. At the end of the 5th treatment he had great difficulty in producing the fantasy or image. The use of a brassiere during the 6th treatment session facilitated the appearance of the fantasy. At the end of the 10th treatment, he was again unable to produce any fantasy and treatment was stopped.

PROGRESS

During the first two weeks of treatment, he admitted having indulged in the fetish act once. After the 4th treatment, he continued to have urges to steal brassieres but these were controllable. These urges were precipitated by advertisements of brassieres in magazines.

During the rest of his treatment, he became less preoccupied with the thoughts of brassieres and the urges were less strong.

Throughout the treatment, the patient did not complain or show any signs of irritability or hostility to the therapist.

2 months after the last treatment, he succumbed to a strong temptation to steal a brassiere, took it from the sister's cupboard then suddenly discarded it and went to sleep.

Follow up 6 months after, he had stopped completely the fetish acts. He was more relaxed, less depressed and was not bothered by fetish desires.

DISCUSSION

Some methods of behaviour therapy require elaborate and sophisticated set-up which are beyond the reach of the clinician in private practice. However, aversion therapy method based on a punishment model is relatively easy to construct and does not involve complicated procedure. It is therefore a method of choice for the treatment of patients in a clinical setting.

While most aversion treatments were given daily, I have deviated from this practice by adopting a biweekly procedure which did not seem to have any adverse influence on the results of the treatment. *

In this case, the results after a 6 month follow-up is considered to be successful. Whether further "booster treatments" will be required remains to be seen.

One interesting feature is the absence of irritability and aggression on the part of the patient. Most studies report the presence of irritability, anxiety or aggression during the course of treatment. Some degree of hostility would not be unexpected of the patient considering that he was rebellious against the strict punitive atmosphere in his early childhood. Could this be related to the infrequency of the shocks used or the spaced intervals between the trials? It has been shown that the more often the shock is presented, the greater the frequency of aggressive responses: (Ulrich, Hutchinson and Asrin in Aversion Therapy and Behaviour Disorders: an analysis, Pg. 92).

So far, no study has been done to determine the optimum number of trials or the optimum number of shocks required in aversion therapy to successfully suppress the abnormal behaviour to be eliminated.

A study on such lives will be of great help to the clinician who aims to employ aversion therapy.

SUMMARY

This paper describes the successful use of aversion therapy in a case of fetishism.

A young Malayalee national serviceman, aged 19 years old presented with a 3 year history of fetishism. From the age of 13 to 15 years, he was exposed to the excitement of sexual play by a more mature 16 year old Caucasian girl. Soon after the girl left, he began to wear brassieres and panties and indulged in fantasies simulating their sexual play.

He was treated as an outpatient with aversion therapy twice weekly. The shocks were delivered with the patient in fantasy when he imagined carrying out the fetish act and also in practice when he put on the brassieres.

He recovered after 10 treatments and was free of fetish acts six months later.

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CLONAZEPAM IN THE TREATMENT OF PETIT MAL

By BENJAMIN CHANDRA

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Petit mal is a disease long known for its resistance to medical treatment. In 1945 trimethadione was introduced by Davis and Lennox as a drug against petit mal. Soon its hematologic and renal complications restricted its use. In 1947, the same authors (3) used dimethylethyl oxazolidine-diona in the treatment of patients with minor attacks, but this proved itself no better than its predecessor.

The invention of the benzodiazepines heralded a new era in the treatment of petit mal. At first Mogadon was used; it decreased the attacks of absences considerably, but its side effects like somnolence or tiredness were troublesome.

Since 1969, Clonazepam was used with more success. Also the results of a preliminary clinical trial by the author were good (2). On the basis of these results, a double blind study was set up, to compare the results of Clinazepam with Diazepam.

Materials and methods

All patients with petit mal who consulted the author directly or indirectly (were referred by other physicians) during the period from 1 January 1971 until 1 July 1972 were asked to cooperate in this study. Originally this group comprised 44 patients, but two parents refused and 3 patients did not continue the medication long enough to allow proper evaluation.

The remaining 39 patients ranged in age from 3 to 12 years with a mean of 7 years. There were

22 girls and 17 boys.

The diagnosis was based on: (1)

1. a short transient attack coupled with a loss of consciousness and characterized by staring and absence.
2. a distinct EEG pattern of three per second spike and wave.

The EEG's were made on an eight channel EEG and 17 electrodes were used for children.

To rule out the possibility that symptoms of brief duration might subside spontaneously and be falsely attributed to the medication only, patients who had the disease for more than six months were selected.

All the 39 patients were initially seen by the author. Their progress was followed by means of personal interview or by questionnaire at monthly intervals. Of the 39 patients, all had been treated with phenobarbital previously in dosages ranging between 30 and 60 mg.tid. Four patients had some reduction of the frequency of the seizures, but most of them had no benefit from the treatment with phenobarbital. Ten days before the controlled study began, all previous medication was withdrawn. None of the patients included in our study had associated illness such as meningitis or cerebral palsy, either initially or later.

Clonazepam and Diazepam were prepared in identical capsule forms and coded in such a way, that neither the investigator nor the patient knows, which was clonazepam and which Diazepam.

The dosages were 3 to 6 mg. Clonazepam daily 0.1 mg/kg. – 0.2 mg/kg. (one capsule contains 1 mg. Clonazepam or 6 to 12 mg. Diazepam; one capsule contains 2 mg. Diazepam). The duration of treatment was one year. The following initial laboratory determinations were made for each patient before administration of the test drug – complete blood count and differential count, platelet count, urinalysis and liver function tests such as serum glutamic exaloacetic transaminase content, serum alkaline phosphatase content and sulfhbromophthalein retention. Determinations of the values were reported after administration of the drug at monthly or bimonthly intervals, depending on the age of the patient.

Responses were graded as excellent when all the absences vanished, good when there was a reduction between 99% and 55% of the attacks, fair when there was a reduction between 54 and 25% of the attacks and poor when there was a reduction of 24% or less.

Results:

Breaking the code showed that 19 patients had received Clonazepam and 20 patients had received Diazepam. The results may be seen in table I.

Two of the patients, who had received clonazepam had a recurrence of the attacks, whereas in the group, who had received Diazepam, only one patient showed a sustained improvement.

Side effects

As may be seen in table II, side effects occurred in both the clonazepam treated group and in the Diazepam group. In both groups, side-effects were mild.

As can be seen in table II, there were some side effects. Two patients complained of dizziness, when bending, turning or lifting their heads. One patient complained of nausea during Clonazepam treatment. These complaints disappeared when the dosage of Clonazepam was lowered from 0.2 mg/kg. to 0.1 mg/kg. bodyweight. It was never

Table I Results of double blind study using Clonazepam and Diazepam in 39 patients with petit mal.

Drug	Excellent	Good	Fair	Poor	Total number
Clonazepam	14	3	2		19
Diazepam	0	1	8	11	20

Table II Frequency and Intensity of side effects

Side effects	Clonazepam group	Diazepam group
Dizziness	2 patients	0
Drowsiness	0	4
Nausea	1	1

Table III Influence of test drug on EEG

Drug	3/sec spike and wave	fast activity
Clonazepam	disappeared (in 17 pat)	increased (in all pat)
Diazepam	still seen (in all pat)	increased (in all pat)

Table IV Statistical data of both groups

symptom	clonazepam group (19)	Diazepam group (20 patients)
frequency absences	Excel/good 17	excellent/good 1
disapp. 3/sec S.W.	17	0

necessary to interrupt the treatment because of these side effects. In the Diazepam group, the chief complaint was drowsiness, which vanished too when the dose was adjusted.

Influence on the EEG

In all patients, an EEG was made before and during administration of the test drug. The results may be seen in table III.

In both groups, the EEG was altered; there was an increase of fast activity. In the Clonazepam group, however, the three per second spike and wave activity disappeared in 17 patients while in the Diazepam group they were still seen in all patients. In two patients from the Clonazepam group, who showed only a fair improvement, the 3/sec spike and wave complexes were still seen.

Statistical Analysis

To emphasize the difference between the Clonazepam and Diazepam treated group, a table was made, which showed the chief differences between both groups (table IV)

t-Tests for paired observations then showed, that for both symptoms the p values were < 0.001, making it highly significant.

DISCUSSION

The results of table *1, corroborate the improvement reported in earlier uncontrolled studies (2, 6, 8) of Clonazepam treatment in petit mal. Although it was formerly reported, that Diazepam had a favourable influence on petit mal, the results of this study showed, that this is not true.

As can be seen from table II there were only mild side-effects, which never necessitated the interruption of the treatment. Two boys stated however clearly, that they felt dizzy, when bending or turning their heads. The ENT specialist who was consulted, stated however, that he did not find any abnormalities in the vestibular apparatus, and the complaints disappeared when the dosage was lowered from 0.2 mg/kg to 0.1 mg/kg.

The influence on the EEG, which was reported earlier (2, 6, 8) in uncontrolled studies, was remarkable. It seems to correlate, with the clinical improvement of the absences.

Statistical analysis for the clinical symptoms and EEG signs, gave highly significant levels for both symptoms.

Pharmacology and Mechanism of Action of Clonazepam

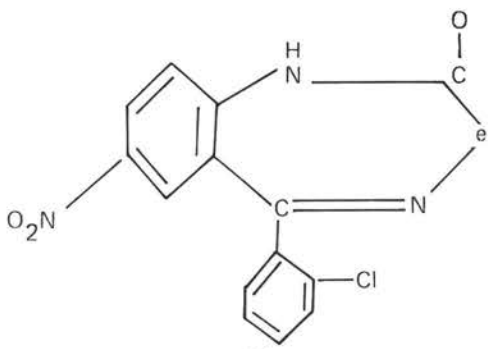
Clonazepam is a benzodiazepine derivative, which possesses stronger anticonvulsant activity than Diazepam. Its formula is shown in table V.

In the antimetrazol test, Clonazepam showed a potent anticonvulsant action. Preparations, which in animal studies show a potent protective effect against metrazol convulsions generally turn out to be clinically effective drugs in the treatment of petit mal. Since 1963, Fromm (4) has used the spinal trigeminal nucleus of cats as an experimental model but until now, the effect of Clonazepam on this model is not known.

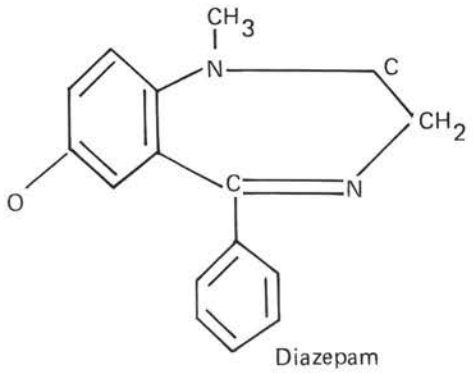
The tranquillizing properties of Clonazepam are five times weaker than that of Diazepam and it also has a very weak muscle relaxant activity (7). All these properties make Clonazepam an ideal drug against petit mal, especially because of its mild side effects.

According to Gastaut, (5), petit mal attacks represent paroxysmal activity in cortical inhibitory pathways and it seems therefore that Clonazepam has the capacity to depress cortical inhibitory pathways. The precise mechanism of action of Clonazepam in the control of epilepsy is not yet known.

Table V Structural Difference between Clonazepam and Diazepam



Clonazepam



Diazepam

SUMMARY

The anticonvulsant properties of Clonazepam were investigated in a double blind clinical trial on 39 patients. 19 patients received Clonazepam and 20 patients received Diazepam, during one year.

Statistical analysis of the results, gave highly significant levels for the symptoms of absences and EEG. On the basis of these results, we believe that Clonazepam is an excellent drug for the treatment of epilepsy, especially because of the lack of serious side-effects.

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Clonazepam – Rivotril, Roche. The supply of Rivotril needed in this study was donated by the Roche Research Foundation.

ATTITUDES OF FILIPINO PSYCHIATRIC PATIENTS TOWARDS PRESCRIBED MEDICINAL DRUGS

By L. V. LAPUZ

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The study pertains to attitudes and interpretations by Filipino patients regarding drugs prescribed for them by doctors. Thirty doctors, practising in Manila, were asked through letters, questionnaires and follow-up interviews to record their observations of patient-attitudes towards

drugs they prescribe. Half of these doctors were internists; the rest was a sprinkling of surgeons, obstetricians, and psychiatrists. Their collective responses indicated definite attitudinal patterns of patients towards the prescribed medications.

Some broad cultural factors may help to understand the background for these attitudes. Firstly, the Filipino has great respect for his body and is even likely to invest it with excessive narcissism. Child rearing practices, particularly parent-child communication, emphasize the importance of the body and of physical health. He grows up with a built-in unique dread for body dysfunction or disease. This also appears related to the preponderance of somatization as an equivalent of psychological distress and as an effective bid for help and sympathy.

Secondly, there is a magical quality attributed to drugs, simply because its source, nature and action are ill-understood and therefore mysterious. Rural folk continue to prefer familiar herbs and advice of local healers (herbolarios). Drugs viewed as "foreign" agents seem to always evoke a little doubt, an element of fear, about what they can do.

Thirdly, the Filipino patient still tends to look at his doctor as an omnipotent figure. The phrase describing him as "next to God" continues to be heard from patients. The doctor-patient relationship becomes quite real to the patient and the concern and strength of the doctor are regarded as a major source of emotional support for the patient and his family and a crucial factor in the salvation of his body from illness and death. Thus, the relationship with the doctor becomes highly personalized in terms of interaction and expectations.

Although the level of education and sophistication of a patient may be high, it is not unusual to find the above factors operating to an unrealistic degree.

In view of the above, some of the attitudes towards prescribed medicinal drugs are easily undertsood; others appear puzzling and inconsistent with the above-mentioned concern for body health, the child-like dependence on the doctor and the tendency to magical expectations.

Easily understood are attitudes which give the drug sole credit for the patients' improvement or recovery. The patient sees the doctor and the drug he prescribes as an all powerful team. The more drastic and dramatic the mode of administration the more heroic the role given to the doctor and drug.

The drug in such cases almost attains a personality of its own. The patient adopts it like a friend, an ally, a protector. Doctors complain that the patient at some future date will self-medicate with the same drug, without consulting a physician. He may also pass it on to a relative or friend as something worth trying, without seeing a doctor.

One patient referred to dosages of the drug as "rounds of ammunition". Another patient, a female accountant, suffering from migraine headaches, referred to her tranquillizer as a "rider", which she would take whenever a difficult situation needed to be smoothed out. One business man-patient asked if it was all right to continue taking vitamins along with a tranquillizer. Vitamins, being viewed as potent agents, might collide in his body with the tranquillizers and literally overpower and nullify the effect of the latter.

On the other hand, practically all the doctors complained of difficulty in getting the patients to follow instructions strictly. The element of doubt or distrust about what the drug may do tends to persist and the doctor likewise is not completely trusted. Patients tend to modify dosages on their own.

When asked why they do this, their reasons vary. Some reason out that if it is such a good drug, they should get well with only one or a few doses. The patient may discontinue the drug if no improvement comes quickly, even if it has been carefully explained to him to wait for a few more days. If given a number of drugs, the patient may take only one or few. One patient remarked that a good drug should do "everything". If a doctor happens to emphasize one drug somewhat more than the others, the patient takes this as the clue as to which is the all powerful one.

Choosing only one drug among several prescribed by the doctor also simplifies the disease in the patient's mind. Too many pills means that the illness must be a complicated one. Similarly, if the schedule and mode of administration of drug dosages are complicated, the patient may give up taking them altogether. (Example: Workers in Family Planning in one village find that the rural womenfolk cannot comprehend how a small pill can stop an awesome process like conception. They are also bothered by the regimen that the pill be taken every day).

Some of the doctors referred to this free-wheeling manipulation of their instructions as simply the patient's trait of being stubborn or whimsical in which case he has to be followed up

closely. Apparently, doctors take this as part and parcel of the problem and quickly shift the responsibility of correct and adequate dosage to the patient and the family.

Replies of patients when asked by their doctors why they changed the dose or schedule of dosage do indicate the presence of the element of fear or distrust; the patient tries to gain control of the situation by some token manipulation of the drug.

When it comes to psychotropic medication, the fear or distrust can be understandably exaggerated by an overanxious or depressed or psychotic patient. The non-psychotic patient is only too eager to be helped and with little difficulty, obeys instructions. The depressed patient of course views the pill with the same pessimistic outlook that he does everything else. "Will I get addicted?" "If I take this, I may never wake up", "This might really make me snap" are frequent remarks by such patients before they agree to try the drug.

The doctors also mentioned the opposite extreme in attitude, namely, a readiness to accept and over-value drugs. In such instances, only a prescription gives validity to the medical consultation. A doctor who does not give a prescription during the patient's visit for one reason or another (e.g., more work-up needed) is reminded by the patient to please prescribe "something".

A published study by one Filipino doctor about patient-attitudes states that Filipino patients associate a drug with a certain specific symptom, rather than with an illness. Thus patients think that the drug can be given to anyone with the same symptom. Partly, this is responsible for self-medication and for recommendation of a drug to friends or relatives, without medical consultation. The same author makes the claim with supporting statistics that the pharmaceutical industry in the Phillipines ranks with steel and oil in size and importance. By the same token, doctors mention a frequent observation: that many of the houses they visit have "pocket" drug-stores for a medicine cabinet, with a different drug for every symptom.

In conclusion, one may hypothesize that the contradictory patterns in attitudes towards drugs reflect changes in the orientation of the society towards the practice of medicine. Whenever a society undergoes changes, traditional beliefs compete with new ideas. Individual members react and adapt to change, each in his own way. The doctor, because he wants his tools to be effective and because he has to make a living, then tries to adopt a style of prescribing drugs which he feels will work with a majority of patients.

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A CLINICAL TRIAL OF COMBINED THERAPY WITH CHLORPROTHIXENE AND NORTRIPTYLINE IN PSYCHOTIC PATIENTS WITH DEPRESSIVE SYMPTOMS

By VICHARN VICHAIYA and KRICH CHEUNSIRI

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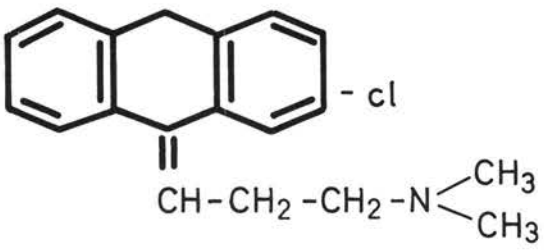
The use of a combination of known effective drugs has become widespread during the past decade. Fairly numerous reports [1, 2, 3, 4, 5, 6, 7, 8, 9] have appeared in the past ten years on the use of a combination of antidepressive agents and neuroleptic drugs in the treatment of schizophrenia. The author reported favorable results in treating psychotic patients with depressive symptoms with combined Pericyazine Trimipramine.[10]

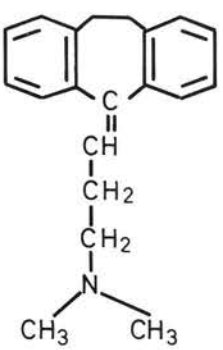
Chlorprothixene, the oldest known member of thioxanthene group of tricyclic neuroleptic has been developed by Research Laboratories of Lunbeck in 1958. It differs from phenothiazine

derivatives in that the nitrogen atom in the phenothiazine ring is replaced by a carbon atom to which the side chain is attached by the double bond.

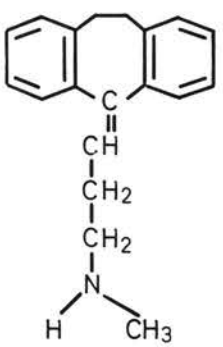


Preliminary animal and human studies seem to suggest that its pharmacodynamic and therapeutic properties are similar to those of Chlorpromazine and should be given in doses of the same order of magnitude as chlorpromazine [11] Chlorprothixene appears to exert approximately the same antipsychotic effect as Chlorpromazine.[12] It was observed that chlorprothixene exert a weak antidelusional and antihallucinatory effect, so that the drug should be combined with another neuroleptic which has more potent neuroleptic action.[13] In schizophrenia, 33 to 80.3 per cent of patients had good to excellent results,[11, 14, 15] Particularly good response was obtained in paranoid varieties[15] and in schizophrenic patients who manifested depression and or anxiety.[16] A favourable result was seen also in depressive neuroses.[15] It is more indicated as the drug of choice in agitated depression. It is beneficial to the result in treating disturbed geriatric patients [18] and alcoholic psychosis.[19]

Side-effects were: orthostatic vertigo and collapse, tachycardia, allergic dermatitis,[20] slurred speech,[11] dryness of mouth, akathisia, convulsion.[14] It seems to show no serious toxic effects, particularly the extrapyramidal symptoms were rarely encountered.[21]



AMITRIPTYLINE



NORTRIPTYLINE

I.F. Benett introduced nortriptyline in the clinic in 1962. From the clinical point of view nortriptyline is the demethyl derivative of amitriptyline (desmethylamitriptyline).

Early reports suggested that nortriptyline, aside from being an antidepressant could also be used as a minor tranquillizer.[22, 23, 24] Later reports did not support such effect. On the other hand, many others found that nortriptyline has slight anxiety and restlessness producing effect and possibly exerts a selective effect upon depression inhibition syndrome with quick onset of action [25, 26, 27]

Mendels,[28] in a comparative trial of nortriptyline and amitriptyline found that patients with nortriptyline responded significantly more rapidly than patients treated with amitriptyline, but there was no difference in response to the two drugs after six weeks of treatment.

This drug has been found to be effective in the treatment of childhood enuresis[29] and useful in the symptomatic treatment of autisti children. [30] Because of its activating effect, it should not be used or contra-indicated in agitated depression.[31, 32]

Side-effects were: dryness of mouth, increased psychomotor activity, insomnia, panic episode, increase in irritability particularly in the paranoid schizophrenic patients, dizziness, blurring of vision, sweating nausea, weakness and constipation has been reported.

The purpose of this study is to determine synergistic effect of the two agents by adding tranquillizing and antipsychotic effect of Chlorprothixene to the activating and mood elevating of nortriptyline.

METHODOLOGY

A pilot study was conducted by using Chlorprothixene and nortriptyline to determine therapeutic effect in newly admitted or readmitted psychotic patients with depressive symptoms. The study was carried out in the Female Section of the In-Patient Department of Somdet Chaopraya Hospital. The patients belonged to the following diagnostic Categories:

– Involutional Melancholia	5
– Manic Depressive Psychosis, depressive phase	3
– Senile dementia with depressive symptoms	1
– Schizophrenia paranoid type with depressive symptoms	4

– Schizo – affective, depressed 7

The patients were randomly selected, assessed and Scored on the Verdun Target Symptoms Rating Scale (Table I) and Verdun Depression Rating Scale (Table II) by the author prior to treatment and every fortnightly during the six-week period. Apart from physical and mental examinations, routine laboratory examination was performed at the beginning and again at the end of the treatment period of six weeks. Blood pressure was recorded every day during the first two weeks.

The patients ranged in age from 23 to 66 yeras (average 39.9 years). They were started on the combination of chlorprothixene 200 to 800 mg. and nortriptyline 50 to 200 mg. daily in two or four divided doses. The dosage was gradually increased until clinical improvement was noted.

Table I 12 items of the Verdun Target Symptoms Rating Scale.
(0 = none, 1 = slight, 2 = medium 3 = severe)

1. Excitement
2. Suspiciousness
3. Hostility
4. Anxiety
5. Depression
6. Impairment in object Relation
7. Hallucination
8. Disturbance of Thinking
9. Delusion
10. Memory Disturbance
11. Impairment of Consciousness
12. Impairment of Expected Social Response

Table II 12 items of the Verdun Depression Rating Scale
(0 = none, 1 = slight, 2 = medium, 3 = severe)

1. Mood
2. Facial Expression
3. General Appearance
4. Psychomotor Retardation (Observed)
5. Impairment of Work and Social Interests
6. Agitation
7. Depressive Ideation
8. Suicidal Tendencies
9. Insomnia
10. Somatic Compaints
11. Loss of Appetite
12. Loss of Weight

Table III Duration of admission

Duration of admission	1st week	2nd week	4th week	6th week	more than 6th week
	3*		10	2	5

* Against medical advice.

The following criteria were used to rate improvement:–

Excellent – if there was complete remission of symptoms or a minimal residue of symptoms, and the patient was being considered for release from hospital.

Good – if the patient was almost asympatomatic with improvement in the majority of symptoms.

Fair – if the patient became adjusted to the hospital environment, but psychotic and depressive symptoms were still present.

Poor – when there was no demonstrable improvement.

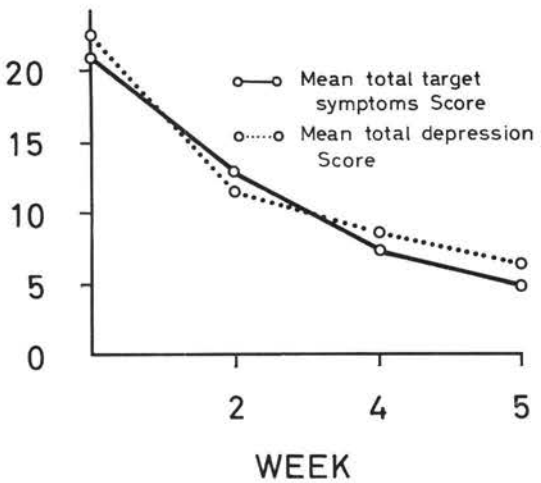
RESULTS

During the six-week period of study, 3 patients left the hospital against medical advice. Only two cases needed E.C.T. to control depression.

Results of improvement are shown in table IV. The mean total target symptoms Score and depression Scores are shown in Figure 1.

Table IV Results of improvement

Diagnosis	No. of Cases	Results of improvement				
		Excellent	Good	Fair	Poor	Against Medical advice
Involutional Melancholia	5	2	1	–	–	2
Manic Depressive Psychosis, depressive phase	3	–	3	–	–	–
Senile dementia with depressive symptoms	1	1	–	–	–	–
Schizophrenia paranoid type with depressive symptoms	4	2	–	2	–	–
Schizo-effective, depressed	7	–	2	2	2	1
Total	20	5	6	4	2	3



SIDE-EFFECTS

During the study, two cases attempted suicide. Almost all of the patients showed mild degree asymptomatic hypotension. Only one case complained of fainting and a few complained of dry mouth. There was no detectable extrapyramidal symptoms or other serious side-effects.

DISCUSSION

The author has the impression that the combination of such two agents provides some synergistic effect and yields favourable results in pure affective disorders. So this drug combination should be tried in double-blind method in both manic-depressive psychosis, depressive phase and in Involutional Melancholia.

SUMMARY

Uncontrolled pilot study was done in 20 cases of newly admitted or readmitted psychotic patients with depressive symptoms. The results of this clinical trial showed that the combination of such drugs was beneficial to pure affective disorders for controlling both psychotic and depressive symptoms. There was no observable serious side-effects. The results are sufficiently encouraging to warrant controlled clinical trial in depressive psychotic patients.

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A DOUBLE BLIND CROSSOVER TRIAL ON LEXOTAN AND PLACEBO IN THE TREATMENT OF PATIENTS WITH PSYCHOPHYSIOLOGICAL DISORDERS

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Many psychopharmacological agents are now available for the treatment of psychiatric patients from the somatotherapeutic point of view as part of the comprehensive approach. The tranquillizers, also called "minor tranquillizers", are widely used in the handling of the 30% – 50% psychoneurotic and psychosomatic patients in the daily medical practice (1) as an important complement to other therapeutic means.

Lexotan or Bromazepam (Ro 05–3350 of Hoffmann-La Roche laboratories), a benzodiazepine derivative, has entered the arena and careful studies are being conducted now as in phase III of clinical research aspects of psychotropics (4) to establish the effectiveness of this new-comer. The "true drug effect" can only be determined by comparing it with a placebo, as was done in this study.

Material and Method

All patients with predominant psychophysiological complaints, without organic disorders, and who are willing and able to participate, are included in this controlled double blind crossover clinical trial. Pregnant women were excluded. So were patients of 50 years and over for eventually organic changes in the brain.

The drugs, all in the form of 3 mg.tablets, with a placebo as reference, were administered to the patients on an ambulatory basis at random according to the table of randomization of Moses and Oakfor (3). In the first week two times, one tablet a day was given, and further three times, one tablet a day until the end of the six-week trial. If the patient was taking other psychotropic drugs already, they were stopped for 2 – 3 days to allow a "wash-out" period (2). A crossover was done after four weeks.

Assessment of specific symptoms (7 categories of 15 psychic and 39 somatic symptoms) was done according to a 4-point rating scale (0 = absent, 1 = slight, 2 = moderate, and 3 = marked) before trial and further at a biweekly interval until the end of the sixth week. Routine laboratory tests for blood (white and red blood cells, haemoglobin, sugar-fasting, urea) and urine.(protein, sugar, bilirubin, urobilin, sedimentation) were also done before trial and during the last week.

At the end of the fourth week (before crossover) and of the sixth week (after crossover) a general assessment was made by the investigator and patient according to a 5-point rating scale (very good, good, moderately good, producing no change and causing deterioration) as was also done for the general tolerance (rated: good, moderate or unsatisfactory). Occurring side effects were stated as transient or lasting. Adjunctive therapy was given only when it was really necessary.

RESULTS

50 patients were evaluated and after the key was known, it appeared that 24 patients (5 men and 19 women between 17 and 48 years with a mean age of 32.0) started with Lexotan and 26 (12 men and 14 women between 17 and 39 years with a mean age of 27.5) with placebo.

46 patients had previous therapy already, 39 with various psychotropic drugs, most of them combined with other drugs as analgesics and spasmolytics, a few also had massage. Of these patients, only 11 had moderately good results with the previous therapy, the others reported no improvement.

The duration of the disorders in the Lexotan group is between 1 month and 10 years with an average of 129 weeks. In the placebo group it is between 3 weeks and 8 years with an average of 68 weeks.

Of the 26 placebo patients, there were 5 drop-outs: 3 before and 2 after crossover. After home visits and inquiries, it was found out that of those 3 one went back to his village without further message, 2 stayed away because they felt no improvement. Of the other 2 who did not return after crossover for final evaluation, one felt better already and went out of town for business. The other one, a female student, attempted suicide 3 days after crossover from placebo to Leoxtan with 22 tablets (= 66 mg) Lexotan because of

growing depression which was masked by her many somatic complaints. She was seen 2 days after her suicide attempt and was admitted to the hospital in the Department of Internal Medicine. She stated that she was not unconscious but had only a tired feeling and a heavy head during the first day.

Of the 24 Lexotan patients, one dropped out before crossover, a young man with a queer personality, who was not to be found at his given address. One did not come back after crossover because he went to help his father in the village who had difficulties with his business. The patient, a senior high school student with ideals for intellectual performance, had to stop his study, which was one of his major conflicts, but in spite of this until crossover he was not deteriorating and took the decision.

Adjunctive therapy was given to one patient with Lexotan before crossover (Mogadon when necessary) and to 4 after crossover to placebo. This was also done to 5 placebo patients before crossover and to none after crossover to Lexotan.

Table I and II show that the physician's rating for Lexotan patients before crossover is 43.5% very good and good to 26.1% for placebo patients. ($P > 0.05$). The patients' rating for Lexotan is 47.8% very good and good to 34.8% for placebo ($P > 0.10$).

The physician's rating after crossover from Lexotan to placebo is 27.2% very good and good and from placebo to Lexotan 57.1% ($0.01 < P < 0.05$). The patients' rating for very good and good after crossover from Lexotan to placebo is 27.2% and from placebo to Lexotan 47.6% ($0.01 < P < 0.05$).

The mean morbidity score of the group starting with Lexotan is 30.0 before trial, 12.9 before crossover (percentage fall in mean = 57.0) and 20.4 after crossover (there was a deterioration and the percentage rise in mean = 57.7) as can be

Table I

	4 weeks Lexotan (before crossover)		2 weeks placebo (after crossover)	
	Physician	Patient	Physician	Patient
Very good	6 (26.1%)	5 (21.7%)	3 (13.6%)	3 (13.6%)
Good	4 (17.4%)	6 (26.1%)	3 (13.6%)	3 (13.6%)
Moderately good	7 (30.4%)	7 (30.4%)	2 (9.1%)	2 (9.1%)
Producing no change	5 (21.7%)	4 (17.4%)	2 (9.1%)	1 (4.6%)
Deterioration	1 (4.4%)	1(4.4%)	12 (54.6%)	13 (59.1%)

Physician's and patients' general assessment of treatment of group starting with Lexotan and crossover to placebo.

Table II

	4 weeks placebo (before crossover)		2 weeks Lexotan (after crossover)	
	Physician	Patient	Physician	Patient
Very good	1 (4.4%)	1 (4.4%)	5 (23.8%)	5 (23.8%)
Good	5 (21.7%)	7 (30.4%)	7 (33.3%)	5 (23.8%)
Moderately good	6 (26.1%)	7 (30.4%)	4 (19.1%)	6 (28.6%)
Producing no change	10 (43.4%)	7 (30.4%)	2 (9.5%)	3 (14.3%)
Deterioration	1 (4.4%)	1 (4.4%)	3 (14.3%)	2 (9.5%)

Physician's and patients' general assessment of treatment of group starting with placebo and crossover to Lexotan.

Table III

4 weeks (before crossover)		2 weeks (after crossover)	
Lexotan	– 57.0	Placebo	+ 57.7
Placebo	– 40.5	Lexotan	– 42.7

Decrease or rise in mean morbidity score expressed as the percentage fall (–) or rise (+) in mean of the Lexotan and placebo groups before and after crossover.

Table IV

	4 weeks (before crossover)			2 weeks (after crossover)	
	Psychic Symptoms	Somatic Symptoms		Psychic Symptoms	Somatic Symptoms
Lexotan	–46.7	–61.8	Placebo	– 1.8	+ 97.4
Placebo	–45.3	–37.8	Lexotan	–28.1	–50.8

Decrease or rise in mean of the psychic and somatic morbidity scores expressed as the percentage fall (–) or rise (+) in mean of the Lexotan and placebo groups before and after crossover.

seen in table III. Of the group starting with placebo, the mean morbidity score is 30.9 before trial and 18.4 before crossover (percentage fall in mean = 40.5) and 10.5 after crossover (there was further improvement and the percentage fall in mean = 42.7).

If the symptoms are broken down in psychic and somatic ones, the results can be seen in table IV: the somatic symptoms showing the best results for Lexotan with a percentage fall in mean of 61.8 before crossover to placebo and 50.8 after crossover from placebo against 46.7 and 28.1 for psychic symptoms. After crossover to placebo, the mean score of somatic symptoms deteriorated with 97.4%, that of the psychic symptoms improved further with 1.8%.

Of the Lexotan group the mean blood pressure in mm. Hg. in lying position before trial, before crossover and at the end of the trial is: systolic = 125, 114 and 121, and diastolic = 80, 73 and 76; in standing position it is: systolic = 132, 117 and 122, and diastolic = 83, 77 and 80. Of the placebo group it is: systolic = 119, 116 and 115 lying, and 129, 123 and 122 standing; diastolic = 75, 74,and 71 lying, and 82, 79 and 77 standing.

Of the Lexotan group the average pulse rate per minute is: 86 before trial, 82 before crossover and 79 after crossover; for the placebo group it is: 87, 82 and 80.

Concomittant effects registered in Lexotan patients were slight drowsiness, in 3, of whom 2 were transient and 1 lasting. Slight tiredness was reported by one and a transient dry mouth by another. Two placebo patients complained also of drowsiness during the first two weeks No side effects were found in the laboratory tests done.

DISCUSSION

Although the number of patients is very limited, we can see that Lexotan scores significantly higher than placebo for very good and good (Lexotan effect 43.3% against placebo effect 26.1%), although the average duration of the disorders in the Lexotan group is much longer than that in the placebo group (129 weeks against 68 weeks). The low placebo effect may be explained by the rather high number of "old" patients (in the Lexotan group 8 new patients and 16 old patients with a total visit of 144 times; in the placebo group 10 new and 16 old patients with a total visit of 93 times) and also that minimal superficial expressive psychotherapy was done.

Before crossover, the percentage fall in mean morbidity score of the Lexotan group is also much higher than that of the placebo group. After crossover from placebo to Lexotan, further improvement was found, while after crossover from Lexotan to placebo there was a significant deterioration.

There was a decrease in the mean blood pressure (but still within normal limits for our patients) of the Lexotan group before crossover and a slight increase after crossover to placebo. Of the placebo

group there was a slight decrease before crossover and until the end of the trial. The mean pulse rate in both groups decreased slightly before and until after crossover. This decrease and increase may be explained as the patients became less or more tense in the course of the trial.

The dose used in this trial is very low: 9 mg Lexotan a day. Tjandra and Kusumanto Setyonegoro (5) in an open trial on Lexotan gave 18 mg – 20 mg a day to most of their patients, followed by a group with 24 mg. – 30 mg. a day and their result was 50.8% very good and good.

SUMMARY

A double blind crossover trial on Lexotan or Bromazepam (Ro 05–3350 of Hoffmann-La Roche Laboratories) versus placebo was done in the treatment of patients with predominant psychophysiological symptoms on an ambulatory basis.

The average duration of the disorders happened to be considerably longer in the Lexotan group (129 weeks) than in the group starting with placebo (68 weeks).

Lexotan did much better than placebo with a decrease in the average morbidity score expressed as the percentage fall in mean of 57.0 for Lexotan before crossover to placebo and a rise (deterioration) of 58.1 after crossover to placebo, against a fall of 40.5 for placebo before crossover and a further fall (improvement) of 42.9 after crossover to Lexotan.

Lexotan scores better for the somatic than for the psychic symptoms as the percentage fall in mean morbidity scores show 61.8 against 46.7 before crossover (4-week treatment) and 50.8 against 28.1 after crossover (2-week treatment).

Minimal undesirable concomittant effects were found.

Lexotan or Bromazepam, a new benzodiazepine derivative, may be of valuable help in the treatment of patients with psychophysiological disorders.

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THE MANAGEMENT OF GILLES DE LA TOURETTE'S SYNDROME BY CHEMOTHERAPY

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INTRODUCTION

The syndrome of multiple tics accompanied by explosive utterances was originally described by Itard in 1825 and was later differentiated into a syndrome by Gilles de la Tourette (1885) when he described eight cases. The following features are considered essential for the diagnosis of Gilles de la Tourette's syndrome, namely:

1. Childhood onset (below the age of 16)
2. Multiple motor tics
3. Unprovoked loud utterances, which may progress to the forced shouting of obscenities (coprolalia).

According to Fernando (1967), the illness usually commenced with multiple motor tics sometimes accompanied by utterances (vocal tics).

The more common tics were the motor tics usually affecting the head, face and neck, while the less common were the abnormal movements of the limbs and trunk muscles. The disease progressed rapidly after onset with an increase in the variety of motor tics such as head retraction, rolling, blinking, grimacing, twisting of the neck, shrugging of the shoulders and flexion or extension of the arms or legs. Other tics, like smiling, teeth grinding and tongue protrusion were sometimes reported, but more complex movements like the slapping of the face or genitalia were rarer.

Less than 200 cases (Shapiro, 1971) have been reported in world literature. Morphew and Sim (1969) described six cases for study, while Fenichel (1945) observed the sexualization of speech and interpreted it as a form of compulsive neurosis. When the distinction between corprolalia and vocal tics were difficult, where sounds made were often partially resembling obscenities, it might be more appropriate to diagnose the case as a Gilles de la Tourette's disease (Corbett et al., 1969).

The prognosis has been described (Chapel, et al., 1964) as 'sinister' and uniformly poor, with a relentless clinical course and Faux (1966) described the tragedy of life-long institutionalization where treatment previously had been mainly socio-psychiatric methods. However spontaneous improvements in late teens and twenties have been reported by Bockner (1959) and Heuscher (1953) and remissions were said to have lasted several years.

The illness has a marked social impact. Patients seen often sought help for social, personality and behavioural difficulties. When treatment failed, their behaviour often worsened and psychopathic behaviour resulted.

AETIOLOGY

a) *Psychogenic Theory*

The aetiology of the syndrome is unknown. Belief in a psychological aetiology was based on the medical vogue to a diagnostic 'waste-paper basket' labelled 'psychogenic'. There is little agreement about psychological factors common to patients, except for frequent reports of compulsivity and inhibited aggression. Several authors (Ascher, 1948; Eisenberg et al., 1959; Dunlop, 1960 and MacDonald, 1963) suggested that the underlying psychodynamic cause may be a suppressed hostility to parents or to other significant persons. Downing et al., (1964) described a female patient with elements of obsessive-compulsive, hysteric and schizophrenic-like psychopathology in the family. Likewise, Fernando's report (1967) showed that 57% of all cases had marked obsessional tendencies, and the majority (Morphew et al., 1969) had some precipitating psychological stress such as a tonsillectomy or a circumcision.

Otto Fenichel (1945) commented on the stuttering, saying that the strong anal-sadistic component of speaking and utterances of obscenities was an aggressive act directed at the listener. He postulated that there was a 'magical' temptation to utilize obscene or profane words to attack the listener violently or sexually.

b) *Organic Theory*

An organic aetiology has been suggested by several authors (Corbin, 1968; Wagner, 1970; and Shapiro & Shapiro, 1971) although there is no evidence of a consistent association between the onset of tics and any physical illness. Some similarity can be observed between the syndrome and symptoms of clearly established illnesses like Sydenham's Chorea, Huntington's Chorea, Encephalitis Lethargica, Manganese poisoning and Acanthocytosis. All that is known is that the basal ganglia may be the probable site of disturbance. The only positive autopsy case (Claus and Balthason, 1954) showed an immature cell sturcture of the striatum. Generally positive neurological findings are rare in all reported cases, although abnormal EEG findings were reported in a quarter of all cases analysed.

c) *Neuro-physiological Theory*

Several lines of evidence (Snyder et al., 1970) suggested that symptoms of the disease may be related to brain dopamine in the corpus striatum. Recently the dramatic therapeutic responses have been obtained with the butryophenone, Haloperidol. Phenothiazines and butryophenones markedly accelerate the turn over of dopamine in the corpus striatum. This mechanism of accelerated turn over is thought to be due to the blockade of dopamine receptors in the striatum, causing enhancement of a postulated feedback of the pre-synaptic dopamine neurones, which respond by increasing dopamine synthesis. Thus, both the symptoms of idiopathic and drug-induced Parkinsonism can be attributed to relative deficiency of dopamine at receptor sites in the striatum. The fact that Haloperidol is unique in its great potency for blocking dopamine receptors and that it is effective in Gilles de la Tourette's Syndrome may account for a pathophysiology of the condition. It is proposed that in the corpus striatum of such patients, there is a hyperactivity of dopaminergic

systems. Whether this is produced by enhanced release of dopamine, impaired inactivation of dopamine, or hypersensitivity of receptors is a matter for speculation. The proposed hypothesis would account for the resemblance of symptoms of Gilles de la Tourette's Syndrome to the side effects of l-Dopa therapy. This would also explain the specific therapeutic efficacy of Haloperidol.

Although the syndrome cannot definitely be attributed to an organic aetiology until more neuro-physiologic or anatomic pathology is evident, the clinical manifestation suggest that the condition is a bizzaire organic neuro-physiologic impairment of the central nervous system.

Treatment with Haloperidol

A large number of psychotropic agents have been administered to such patients with discouraging results. In 1961, Seignot reported using R1625 (Haloperidol) in a case of Tourette's diseases with dramatic symptomatic improvement. Its effectiveness was further proven by Challas and Brauer in 1963, by Chapel et al., in 1964 and by Shapiro in 1968. However, whenever Haloperidol was discontinued, relapses occurred.

The Present Study

a) *Aim*

The aim of the study was to observe and measure the degree of symptomatic improvement of 4 cases of Gilles de la Tourette's Syndrome treated with Haloperidol.

b) *Methodology*

Four cases of Gilles de la Tourette's Syndrome (see Table I) were treated by the author with Haloperidol. As a controlled measurement of symptomatic improvement, all four patients were video-taped for 10–15 minutes prior to treatment. The patients were then treated with varying doses of Haloperidol at gradually increasing doses until symptomatic improvement was observed. The doses of Haloperidol ranged from 6 mg to 33 mg per day (see Table II). The increasing dosage was stopped when side effects of the drug interfered with the patient's functioning. The side effects of Haloperidol were drowsiness, parkinsonism, poor concentration and blurring of vision. Parkinsonism was controlled with Benzhexol, dosage ranging from 12 mg. to 36 mg. per day. Approximately one month later, they were subsequently video-taped and the degree of improvement was measured.

c) *Case Histories*

Case I

A 19 year old Chinese male, a fishmonger, developed the illness at 8 years old when he felt an urge to clear his throat frequently. This progressively worsened as he started producing grunting noises. By 14 years old, he felt a compulsive urge to frequently hit his abdomen with his hands. Two years later, he started grimacing and shouting out obscene names of his friends repetitively. He left school at this juncture because of his anti-social symptoms. By the time he reached 17 years old, he was compulsively shouting obscenities, indecently gesticulating with his hands and repeatedly stamping his feet. He eventually gravitated his corprolalia to women essentially and this behaviour was reinforced when he was assaulted by their husbands.

Table I: Characteristics of patients with Gilles de la Tourette's Syndrome

	Case I	Case II	Case III	Case IV
Ethnic Group	Chinese	Chinese	Chinese	Chinese
Sex	Male	Male	Male	Female
Age	19 years	25 years	22 years	16 years

Table II: Maximum doses of Haloperidol and Benzhexol/day duration of medication in treatment of Gilles de la Tourette's Syndrome.

	Case I	Case II	CaseIII	Case IV
Maximum dose of Haloperidol/day	31.5 mg	33.0 mg	6.0 mg	9.0 mg.
Maximum dose of Benzhexol/day	36 mg	24 mg	12 mg	12 mg
Duration of test period	27 days	33 days	30 days	28 days

He gave a history of having frequently observed his parents performing coitus, when he was 7 years old. He developed hostile feelings towards his father and would attempt to sleep in between his parents to prevent coitus and deliberately made throat sounds to distract his parents. His symptoms appeared to have been precipitated by witnessing the primal scene.

By the time he was admitted to hospital, he was depressed, ashamed of his symptoms and harboured strong sado-masochistic tendencies.

Case II

A 25 year old Chinese male, a motor car mechanic, developed insidious symptoms of coughing at 16 years old. His concentration deteriorated and he developed insomnia. Very soon he started cursing in an explosive manner and compulsively cursed obscenities directed mainly at his mother. He felt more relaxed after corprolalia. Later he began gesticulating obscenely within his hands. The symptoms became progressively worse, with echolalia, corprolalia and indecent gesticulations several hundred times per hour. He would hit his testes until they hurt and stamp his feet repeatedly. Eventually, he learnt to distort his obscene corprolalia by swallowing the 'four letter word' and by sucking his thumb. This resulted in pressure headaches which he suffered for many years.

He blamed excessive masturbation for his illness and was unable to stop the habit which he indulged in 3–4 times per day. The symptoms had a devastating social effect on his life. He isolated himself socially, avoided female company and female clients avoided him. He felt very ashamed of his symptoms, which he was unable to control and became very depressed and desperate during the time of admission to hospital.

Case III

A 22 year old male Chinese, a College student, gave a history that at the age of 17 years old he witnessed his parents performing coitus. This traumatic experience made him hate his parents and he became depressed each time he spoke to them and painstakingly avoided staying at home. He became so obsessed by the sexual act that he ruminated over the incident even until the time of consultation. Since then his relationship with his parents has been cold and distancing. This incident coincided with a female neighbour, whom he was infatuated with, and who had left the neighbourhood.

Soon after that incident, he started coughing and making queer noises in this throat. This was followed by the wrinkling of his nose, the repeated winking of his eyes and active nodding of his head. At times, while walking, he would stamp his feet. These symptoms developed gradually and fluctuated in intensity. Occasionally he would compulsively blow his nose and make semi-purposeful movements.

His symptoms interfered with his studies, caused him untold embarrassment and he socially isolated himself. His concentration deteriorated and he became nervous and depressed by this uncontrollable disorder.

Case IV

A 16 year old student, a female Chinese, was brought by her father who noted that she had insidiously developed fidgetiness at 13 years old. Initially she developed a blocked nose and started a sneezing habit, with a twitching of the nose. This subsequently spread to mouth twitching and grinding of her teeth. One and a half years later, she developed jerky limb movements and was unable to control hitting herself.

Her symptoms increased and she became withdrawn. Her self-hitting became more severe and spread to hitting her mother and grandmother. Frequently she would make grunting noises and swear curse words under her breath and then feel most embarrassed and repentant. During the time of admission she had obsessive-compulsive rituals, corprolalia, echolalia, stamping of feet and had learnt compensatory movements to dampen her gesticulations.

Her father described her as a reticient girl who fared poorly at school. He had taken her to approximately 100 doctors, native healers and mediums in a search for a cure to this strange malady.

d) *The Video-tape Technique of Recording*

The video-tape recording system provided a continuous observation and a permanent recording of the frequency and quality of tics in each case. It is unfortunate that the measurement of man's behaviour cannot be done adequately in man's natural environment because of insurmountable technical difficulties, and because variant conditions cannot be controlled out in the natural environment. Hence to achieve stable environment conditions, thereby excluding variableness, an experimental studio situation was utilized. This unfortunately, while it controls environmental variables, destroys the naturally occurring contexts of behaviour of the patient.

Table III: Inter-rater reliability: Scoring agreement between two observers.

	Before Treatment	After Treatment
Case I	70.8%	96.4%
Case II	81.8%	94.8%
Case III	94.3%	100%
Case IV	91.1%	97.2%

Each video-tape recording was thus done in a similar controlled studio condition. Patients were given exact instructions to behave naturally in a sitting position. The number of helpers remained constantly the same.

e) *Operational Definitions*

The recording of the nature and frequency of the tics and body movements were divided into 8 body components representing different parts of the body. They were:

1. Head
2. Grimace
3. Upper Limb (R)
4. Upper Limb (L)
5. Lower Limb (R)
6. Lower Limb (L)
7. Trunk
8. Vocalization

Each body component was graded (by standard criteria) for its movements or tics i.e.

Code 0 No Movement
1 Minor movements
2 Moderate movements
4 Major or mass movements

f) *Scoring and Inter-Rater Reliability*

The scoring of body movements was recorded by two independent observers every fifteenth second (with the aid of a metronome) before and after treatment with Haloperidol. Raw data was collected from the first minute to the 3½ minute (i.e. total observation period of 2½ minutes of 12 observations each) and from the 6th minute to the 8½ minute (i.e. 2½ minutes observation) before and after treatment with Haloperidol.

Since the major problem of scoring was the reliability of different observers' scores, the reliability of two independent observers scoring the raw data simultaneously was calculated by simple percentage agreement-disagreement of raters scores (see Table III).

The range of percentage agreement was:—

(i) Before treatment: 70.8% to 94.3%
(ii) After treatment : 94.8% to 100%

Percent agreement was a vigorous method of testing inter-rater reliability because even small deviances of one point were more apparent than in a correlation technique where small deviances simply contributed to small correlation coefficient.

The first task was training in scoring and the determination of maximum possible level of agreement was set by a learning curve at which the flatenning of the curve indicated maximum scorers' agreement. Hopefully, the minimum acceptable percent agreement was 80 – 90%.

Low inter-rater agreement occurred in Case I because this was the first scoring session and a satisfactory level of agreement was reached as scorers became more used to the scoring system.

High inter-rater agreement was reached after treatment due to the marked reduction of the frequency and nature of tics.

g) *Results of the Study*

i) Correlated 't' test of significance for sequential observations of tics before treatment: The x^2 is a test commonly used to evaluate significance with a nominal or ordinal scale. However, independence of each score is a basic assumption of the x^2 test of significance. The data obtained does not meet the criteria because within each 15 seconds of observation, the scores are highly related and dependent. This excludes the possibility of using a x^2 to test statistical significance.

Instead a correlated t test of signficance was used so as to determine whether significant changes occurred before the administration of Haloperidol during the first 2½ minutes of observation and the subsequent second 2½ minutes certain items from the data of the two observations were analysed. The reason for selecting only certain items was because the changes appeared significant, while the items not selected for testing showed minimal change. (See Table IV).

The correlated t test in each of the 4 cases was significant ($p < 0.05$ level) in certain body components of movement.

It is interesting that the patients showed increased or decreased frequency of tics during the second 2½ minutes before treatment, in the different body components of their tics.

Yates (1955) experimentally demonstrated that mass negative practice resulted in a significant decline in the frequency of tics. This method of

Table IV: Correlated 't' test for significance in different body components of movement in Cases I – IV.

Patient	Scores of 1st 2½ mins.	Scores of 2nd 2½ mins.	't' test
Case I			
Head Mov.	20	9	t = 2.24, p < 0.05, df = 11 (significant)
Upper Limbs (L)	19	13	t = 1.67, p > 0.05, df = 11 (not sig.)
L Limb (L)	21	10	t = 1.84, p > 0.05. df = 11 (not. sig.)
Case II			
Head Mov.	20	15	t = 0.59, p > 0,05, df - 11 (not sig.)
L. Limb (R)	2	12	t = 3.46, p < 0.01, df = 11 (significant)
Case III			
U. Limb (R)	16	8	t = 1.29, p > 0.05, df = 11 (not sig.)
U. Limb (L)	7	18	t = 2.49, p > 0.05, df df = 11 (Significant)
Case IV			
L. Limb (L)	2	11	t = 1.92, p > 0.05, df = 11 (not sig.)

Table V: Mean scores of different body components of movement in Cases of Gilles de la Tourette's Syndrome before and after treatment with Haloperidol.

	Head Mov.		Grimacing		Upp. Limbs		L. Limbs		Trunk	
	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.	Bf. Tr.	Af. Tr.
Case I	29	5	32	3	52	8	56	10	33	4
Case II	35	5	26	12	43	7	28	13	9	1
Case III	9	0	13	1	49	0	47	0	26	0
Case IV	24	16	14	4	29	25	61	22	10	2
Mean scores	24.0	6.5	21.3	5.0	43.3	10.0	48.0	11.3	19.5	1.8

Overall mean score before treatment = 156.1
Overall mean score after treatment = 34.6

treatment essentially utilizes the reactive inhibition and drive reduction theory of Hull (Yates, 1970). This theory states that reactive inhibition would be generated as mass negative practice continues and the dissipation of reactive inhibition would be reinforcing, thereby effecting a reduction in tics. Although the patients were not told to deliberately evoke their tics, nonetheless the theory suggested that there will be drive reduction thus resulting in a significant diminution of tics during the second 2½ minutes of observation.

The results of the correlated t test may give an indication as to why mass negative practice does work in certain cases of Gilles de la Tourette's Syndrome, and in only certain body components of the tics. In another patient (not quoted in this paper) the author found that mass negative practice seemed to reduce the quality

Table VI: Percentage Improvement in various body components of tics in Cases of Gilles de la Tourettes' Syndrome following Treatment with Haloperidol.

	Head Move (%)	Grimacing (%)	Upp. Limbs Mov. (%)	Low Limbs Mov. (%)	Trunk Mov. (%)	Oberall Improv. (%)
Case I	82.8	96.7	84.6	82.1	87.9	86.8%
Case II	88.9	53.9	83.7	53.6	88.7	73.8%
Case III	100.0	92.3	100.0	100.0	100.0	98.5%
Case IV	33.3	71.4	13.8	64.0	80.0	52.5%

of tics but did not seem to affect the frequency of tics.

ii) Degree of Percentage Improvement following Haloperidol Therapy The total mean scores of all 4 cases for each body component of movement before and after treatment with Haloperidol was noted. (See Table V).

	Tot. Mean Scores Before Treatment	Tot. Mean Scores after After Treatment
Head movements	24.0	6.5
Grimacing	21.3	5.0
Upper limbs movements	43.3	10.0
Lower limbs movements	48.0	11.3
Trunk movements	19.5	1.8

Overall mean scores before treatment = 156.1
Overall mean scores after treatment = 34.6

There was a marked reduction in scores for each body component of movement after treatment. The overall percentage improvement of tics after treatment with Haloperidol ranged from 52.5% (in Case IV) to 98.5% (in Case III). There was a remarkable improvement in terms of reduction of tics in all components of the body following treatment with Haloperidol (See Table VI).

CONCLUSION

Four cases of Gilles de la Tourette's Syndrome were treated with varying doses of Haloperidol for an average period of 4 weeks. The technique of video-tape recording to measure the degree of improvement following chemotherapy was discussed. Paired independent observers coded the raw data from video-taped recordings before and after the administration of Haloperidol. The inter-rater reliability for scoring agreement ranged from 70.8% to 100%.

The correlated t test of significance for sequential observation of frequency and quality of tics, before treatment, indicated varying significant improvements of symptoms in certain body components. Results of this observation gave an indication to supporting the reactive inhibition theory of mass negative practice, but showed that only tics in certain body components were reduced by mass negative practice.

The overall percentage improvement of the 4 cases of Gilles de la Tourette's Syndrome following Haloperidol therapy was dramatic in terms of reducing the quality and the frequency of tics.

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A CLINICAL TRIAL OF R6218 IN THE TREATMENT OF OBSESSIVE-COMPULSIVE NEUROSIS

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In this paper a clinical trial of the new neuroleptic Janssen R6218 (fluspirilene) in the treatment of obsessional states, involving 8 male, Malaysian, patients is reported. The patients ranged in age from 14 to 32 years with a mean of 23 years and the duration of their illness ranged from 1 to 11 years with a mean of 6 years. They had previously been treated with benzodiazepines, tricyclic antidepressants and in some cases with Haloperidol and other drugs with amelioration in anxiety and depression without the basic symptoms of the illness being affected directly as a result of drug therapy and those who spoke English (and thus could converse with the therapist) had had an exposure to various forms of psychotherapy, chief among their being paradoxical intention with defocussing technique, but for one reason or another had failed to derive any benefit from it.

In this trial, which was mainly exploratory in nature, a new chemical compound was being tested, for the first time perhaps, to determine if it could basically alter the dominating symptoms of these patients, viz. their obsessive thoughts and compulsive actions. As such, the conditions of trial were (except in the case of one patient –T.S.D.)

totally uncontrolled. There was no drug-free period as one individual subject was taken off his former medication and placed on the new drug and concurrent use of other drugs could not be withheld in all cases because of such factors as his response to the trial drug, its side-effects and the prevailing effect of the patient. Both the doses and the interval between any two doses of the drug varied, there being no guide lines in this respect – the manufacturers only indicate that it should be used with caution in endogenous depression, Parkinsonism and possibly epilepsy – and the total period of trial varied from two weeks in one to the maximum of sixteen in another.

Only one patient on low dose therapy did not show any response to the new drug (his case has been left out from discusson), while seven benefitted from it. Among those whose condition improved, one subject had failed to respond to the drug when given in low doses but as experience with the use of the drug built-up he was, after a lapse of eight weeks, once again included in the trial on a high dosage level and rated weekly on four different rating scales for assessment, of progress. Progress made by other subjects was recorded weekly, based on the interview findings: individual subjects and their relatives were asked to make a crude assessment of change in the intensity of prevailing symptoms in terms of variation in the number of times a ritual was carried out, and the time spent on it and finally as a proportion of the base line 100.

The cases are described briefly in the order in which they entered the trial as this point has an important bearing on both the determining of the effective dose of the drug and as to how the experience gained from one subject was utilized in the handling of the case that followed him.

Four patients showed marked improvement in their symptoms; one who was making satisfactory progress dropped out of the trial possibly because of the side-effects of the drug; one was taken off the drug immediately after he gave a false alarm of suicidal thoughts, although he clearly indicated that he was benefiting from the new drug; one on low dose found no change in his condition; and the most resistant of the cases, who was included twice in the trial, found about 30 to 40% improvement in his condition on the conclusion of the trial.

Side-effects encountered in all cases were the same as those seen in schizophrenia patients being treated with fluspirilene, chief among them being weakness, muscular restlessness and extrapyramidal side-effects which appear within 24 hours of the administration of the drug and disappear after 2 to 3 days. For these side-effects, anti-parkinsonian drugs and methylphenidote were given, where indicated, in small doses for 2 to 4 days after the periodic intramuscular administration of fluspirilene.

There was no waning effect of the drug noticed by the patients in the interval that elapsed between two doses nor did they find any positive change which could be attributed to the use of anti-parkinsonian drugs like dexetimide and benzhexol hydrocholoride or to methylphenidate which was given to counter the distressing symptoms of fatigue and weakness.

Fluspirilene or Imap is a new chemical compound belonging to the diphenylbutylpiperidine family of drugs, structurally different from haloperidol and belonging in the same class as pimozide and penfluridol. Its selective action on the striatal dorpamine – it is a potent antidopraminergic agent – is its most interesting property. It inhibits the stereotypic chewing movements in rats induced by the administration of amphetamine. This latter property is to a variable extent shared by other neuroleptics which are not so specific in their site of action, but is more marked in this series of drugs.

Other actions of fluspirilene noted in animal studies are:

1. In jumping-box the interval between the onset of buzzing and the flight reaction i.e. the latency is extended in animals treated with this drug and this failure for the flight reaction.
2. Similarly, in Sidman Shock-avoidance test in rats the number of responses to escape shock by pressing the lever drops after the administration of fluspirilene.

The drug has been tried extensively by the present investigator at the University of Malaya Hospital, KualaL Lumpur in the treatment of *schizophrenia, where it is given in 4–12 mg. doses i.m. and seems to be specifically effective, like pimozide, inthose forms which was dominated by autism, delusions and repetitive stereotypic traits in thinking and/or movement.

Based on those observations, it was felt that the drug may have a place in the treatment of obsessional states and allied conditions which have been a matter of great concern to therapists of all ages.

Talking of the prognosis and treatment of

obsessional states, John Pollitt observed in 1957: ".....the obsessional state has a much better prognosis than is usually thought and the view that it has an inevitable gloomy outcome can no longer be held." However, the same author writing twelve years later, when both psychotherapy and behaviour therapy had made sufficient progress admitted: "True obsessional states are among the few illnesses which can still torture patients almost for a lifetime." The disappointment with various forms of treatment is apparent and goads one to seek new methods of treatment for one of the most crippling forms of these known to mankind.

Material, Method and Outcome

The eight subjects included in this study had the primary diagnosis of obsessive-compulsive neurosis and their symptoms were not part of any other illness, schizophrenia, psychotic depression and organic states having been ruled out. The range of their age at the onset of illness was 12 to 26 years with a mean of 17. The symptoms they described were innumerable as, although all obsessive compulsive patients may look alike in being tortured in their obsessions and compulsions, each individual patient is tortured by symptoms which he considers as specific to him.

The dominating traits are here classified under the following headings:

1. Obsessive thoughts concerning health, death and allied themes.
2. Other ruinations.
3. Checking rituals (doubts) and repetitions.
4. Washing/purification/ablution.
5. Complicated rituals and obsessive.
6. Insistence on precision and orderliness.
7. Other compulsions.

For the sake of brevity, the patients' response to fluspirilene therapy is given at this stage.

Case No. 1, G.K.S., a Cantonese-speaking 27-year-old factory worker with 2 years' duration of illness and suffering from obsessive thoughts of death due to accident or tetanus, compulsive hand and leg washing and checking rituals, was given 4 mg. of fluspirilene by mistake by the investigator instead of two, as the starting dose. In the first week, he became extremely depressed, complained of insomnia and severe weakness but mentioned that in less than one week all his symptoms had dropped by at least 50% and although checking behaviour did not come to an end completely, his checking of locks had stopped altogether. He received a total of 13 mg. of fluspirilene over a period of 10 weeks given in 6 doses with an average of about 2.2 mg per dose. His excessive leg washing stopped after the second dose, while after the fourth dose he said all his symptoms had gone down by 85–90%. While continuing to dislike the new drug because of its unpleasant side-effects, he admitted that for the first time instead of being calmed down, his basic symptoms had yielded to treatment. Eight weeks after the commencement of therapy, he could control himself from doing things against his wish and could "forget" his compulsions. His wife admitted that there had been a definite improvement in his symptoms.

Results: His obsessive thoughts of death had improved by 80% in the fifth week of treatment and were absent after eight weeks onwards. Other ruminations were less by 90% in the fifth week of treatment. Checking rituals were absent in the fifth week and excessive handwashing stopped in the ninth week.

Case No. 2, J.N.M., a 25- year-old English-speaking Malay bachelor, had the onset at the age of 14. He had found little relief from conventional therapy and had been putting up "a tremendous fight" against his symptoms. His complicated obsessive thoughts decreased by 90% in the tenth week of treatment, checking rituals became less by 80% in ten weeks, washing and purification rituals diminished by 75% in the fifteenth week. He received a total of 18.5 mg. of the drug over a period of sixteen weeks in 11 doses.His were the most complicated rituals and obsessive thoughts. Checking behaviour showed a gradual fall after the first dose and the patient stopped counting the number of times a ritual had to be carried out after 3 days of its administration. After the eight dose he conceded reluctantly: "The main change in me is that I can now ignore compulsions without worry."

After the ninth dose he was smiling but in the following week he developed free-floating anxiety which coupled with akathisia was contributing to his miserable condition. It became apparent that having few leisure interests, no aim in life and without obsessions and compulsions were removed he had become painfully aware of the existential vacuum in him.

Case No. 3, L.K.T., a Hainanese-speaking puny boy of 14, had developed severe obsessions and rituals after a bus accident in which no one was hurt.

He received a total of 18.5 mg. fluspirilene in 11 doses spread over a period of 11 weeks, average dose being 1.7 mg.

Results: His obsessive thoughts of violence,

death and drowning had gone down by 90% in 10 weeks, checking behaviour by 65% in 11 weeks, washing and purification rituals by 87% in 9 weeks and the extremely complicated rituals and other compulsions were negligible (less than 10%) after 9 weeks.

Throughout the treatment,he disliked injections but admitted that his obsessive thoughts had started diminishing after the second dose.

Overall assessment of improvement by the patient after the sixth dose was 70% and by his mother 50%.

Case No. 4, H.Y.F., a 26-year-old English-speaking clerk of Chinese origin with onset of illness at the age of 16, received a total of 10 mg. of fluspirilene over four weeks, averaging 2 mg./dose.

His obsessive thoughts diminished by 30% in the fourth week, other ruminations by 40% in the third week and doubts by 75% in the fourth week. He preferred the trial-drug to any previous form of therapy but was dropped out of trial after the fifth dose as he gave a false alarm of suicidal thoughts.

Case No. 5, T.W.K., a Chinese 32-year-old English-speaking lawyer's clerk, received only 2 doses of 2 mg. each with an interval of 1 week in between. Within one week,his obsessive thoughts were lessened by 20%, checking by 56% and other complicated rituals by 50–100%. However, his response to the side-effects was out of all proportion for, although he did not seem to have any extrapyramidal signs, after the second dose he defaulted treatment.

Case No. 6, C.C.B., a Hokkien-speaking 21-year-old young man, received a total of 6 mg. of fluspirilene in 4 doses, each of 1.5 mg. over a period of 12 weeks.

Results: After the first dose, his checking rituals had gone down by 80% and obsessive thoughts by 70% after the third dose.

Case No. 7, T.S.D., a 19-year-old school student, did not respond to treatment on low dose – average 2 mg. – but after being stabilized on imipramine and diazepam for eight weeks he was placed on combined therapy i.e. a high fluspirilene dose with imipramine and diazepam. He received a total of 48 mg. in 11 doses, average dose 4.36 mg., spread over a period of 11 weeks. He rated himself weekly on a 13-symptom self-inventory, on Lung Scale for depression and Hamilton Scale for anxiety. The Maudsley Obsessive-Compulsive inventory proved to be of very little help in assessing any change in his condition.

After four weeks on combined therapy i.e. fluspirilene with imipramine and diazepam, it became afferent that he was not responding to fluspirilene even in high doses and thereafter the other two durgs were stopped.

Results: On self-rating scale comparing the score when he was on combined therapy for four weeks with the last four weeks on fluspirilene alone, he showed an overall improvement of 21.04%.

Comparing the same two blocks of treatment, it was found that for the last 4 weeks when was on fluspirilene there had been an overall improvement in anxiety, on the Hamilton Scale, of 25.46% and in depression of 14.14% on the Lung Scale as compared to the 4 weeks when was on both an anxiolytic and an antidepressant – i.e., both anxiety and depression diminished after his basic symptoms began to show improvement without recourse to symptomatic treatment of the former.

On the Mandsley Obsessive-Compulsive Inventory, the patient was found to have lost his unwanted thoughts of harming other people after the fourth dose of fluspirilene.

On his 13-symptom Self-Inventory scores showed that not all symptoms respond at the same rate and whereas some remain static, either constantly or for a considerable period, others are quicker to respond. In his case items such as imagining things moving on floor associated with the compulsive action of turning round to see to reduce the ensuing anxiety and, compulsive reading of parts of newspaper over and over again were the ones which showed the most favourable response: the former stopped altogether after the seventh dose. Such symptoms as unwanted obscene thoughts intruding into his prayer did not show any change over a period of 11 weeks.

Nine out of thirteen symptoms on his self-scale showed graded improvement setting in at different stages of the treatment and it may be argued that with persistences whilst allowing drug-free periods to prevent the development of cumulative effects, the more resistant symptoms, too, might have shown change.

As in cases 1, 2 and 5 the basic change in his case was in the attitude towards the symptoms: instead of fighting the symptoms,he began to take a stand of ignoring them from the fifth week onwards. Incidentally, this patient with a good premorbid personality, having many leisure interests and definite aims in life, did not develop the existential vacuum as his symptoms started lifting off but then, unlike other subjects with less

desirable personalities, his symptoms were perhaps the most stubborn encountered in this study.

His overall assessment of improvement was 51% in respect of obsessive thoughts involving death themes, and about 86% as regards other ruminations.

COMMENTARY

Case No. 1 showed immediate response to the trial drug, given in a moderate initial dose of 4 mg., with an overall 50% subjective assessment of improvement setting in within the first week of treatment and with cessation of checking locks as its main feature. After the second dose, his excessive leg-washing stopped; obsessive thoughts concerning death and disease and other ruminations became appreciably less in the fifth week of treatment — when his other checking rituals were found to be absent — and excessive hand washing disappeared in the ninth week.

Case No. 2, showed a decline in his checking rituals after the first dose of the trial drug and stopped counting the number of times a ritual had to be performed after three days of its administration. His morbid obsessive thoughts disappeared in the sixth week of treatment, insistence on precision and orderliness became significantly less in the eight week when he had begun to ignore this compulsion, and, excessive washing had diminished a great deal in the fifteenth week. However, he was less successful in ignoring the obscene thoughts that kept intruding into his prayers till the end of the trial period when his therapeutic gains had become greatly clouded by the mounting agitation and anxiety

Case No. 3 showed an early favourable response to the drug by beginning to lose his morbid thoughts after its second dose; thereafter, his obsessive thoughts and compulsive actions responded equally well, albeit slowly, to the new treatment. He stopped being unnecessarily concerned about personal hygiene after about 8 to 9 weeks of treatment when losing his fear of being touched by others he could once again enjoy sitting in his mother's lap.

Case No. 5 lost some of his insistence on orderliness and precision together with some reduction in morbid obsessive thoughts within one week of the first dose of fluspirilene; his checking behaviour and other complicated rituals showed even greater response to this form of therapy.

Case No. 6 lost almost completely his checking rituals after the first dose of the trial drug; the effect on obsessive therapy concerning his health was comparatively tardy and not so complete.

Case No. 7 after showing no response to the trial drug in small doses lost at least one obsessive thought and one compulsive action completely when the same drug was given in relatively high doses. His obsessive thoughts based on religious beliefs turned out to be most resistent to treatment; other obsessive thoughts, ruminations and compulsive actions showed varying degrees of response becoming manifest in different weeks of treatment.

This one patient did not show any response to fluspirilene given in a low fixed dose regime.

Of the seven who derived definite benefit from the treatment: four patients showed amelioration in their condition after a single dose, in two this change became apparent after the second dose and one patient took longer (after the fourth dose) to exhibit any positive change in his symptoms. The same four patients who benefitted from the drug within the first week of treatment did so by shedding some of their compulsive actions chief among their being the checking rituals. Only one patient (L.K.T.) lost his morbid obsessive thoughts in advance of any change in the severity of his compulsive actions.

Two patients preferred tricyclic antidepressants and benzodiazepine anxiolytics to fluspirilene therapy because of the pleasantness of the former though persisted with the latter form of therapy because of its efficacy; two patients preferred fluspirilene to the anxiolytic-antidepressant therapy because of its effectiveness in assuaging their obsessive-compulsive symptoms though did not comment on the pleasantness or unpleasantness of either; two subjects while deriving benefit from the new drug became agitated and defaulted treatment, the response of the remaining two patients from this angle could not be ascertained.

DISCUSSION

Feelings of anxiety and tension have been described as characteristic of obsessional neurosis and together with a sense of impending doom are seen as the worst of patients' suffering by clinicians and other investigators alike working in this field. It is therefore no surprise that treatment of anxiety and depression has been considered a fundamental aim in treatment with the added hope that any reduction in anxiety may be followed by a lessening of the main symptoms of the obsessional phenomenon. The latter aim is seldom fulfilled though there is some justification for this form of therapy on the grounds that patients too seem to seek immediate relief from anxiety rather than hoping for any change in their

obsessions and compulsive actions with which by the time they come up for treatment they have learnt to live. The patients in this study repeatedly reported that while on anxiolytics and antidepressants they had felt calmed down and although they liked this form of therapy, their basic symptoms had shown us change. Furthermore they remain aware of the fact that such treatment is at least symptomatic and suffer from the foreleading that it is bound to fail in the end. In contradistinction to this form of therapy treatment with neuroleptics is fought with the danger of precipitating a severe bout of depression as happened in the case of G.K.S.

On the other hand, as pointed out in the case of T.S.D. – the patient who was included twice in the trial – anxiety and depression may fail to respond to conventional form of therapy and begin to diminish only as obsession and compulsions begin to lift off. Obsessive patients treated with fluspirilene seem to lose their anxiety and depression as a function of the effect of the drug on their basic symptoms.

Premorbid personality, leisure interests and the existence of aims in life determine to a variable extent the prognosis in almost all forms of psychiatric illness; in obsessive patients following treatment with fluspirilene, no less than those who have been leucotomised, this aphorism becomes more convincing once the subjects begin to lose their obsessions and compulsions. Anxiety experienced at this stage is quite different from the anxiety seen when the patient is busy fighting his symptoms and is very much similar to the anxiety reported in such conditions as compulsive gambling following successful treatment. If this fact is not taken into consideration, it is likely that further treatment may not be suited to the needs of the patient – who may decide to opt out of the treatment – or the mounting tension and anxiety may be wrongly interpreted as deterioration of condition and the treatment considered a failure both by the patient and the therapist. In this study, four subjects interpreted this agitation as worsening of condition: two patients (L.K.T.& T.W.K.) defaulted treatment when beset with anxiety of this sort and one patient (G.K.S.) could continue with treatment only after a great deal of persuasion. It has been the experience of the present investigator that continued support and other psychotherapeutic measures become more important at this stage of treatment and helping the patient develop a healthy attitude towards his problems instead of adhering to his erstwhile habit of introspection may help him tide over this period of severe agitation.

It may be added that as the effects of fluspirilene in the treatment of obsessive compulsive neurosis varie from patient to patient and not all symptoms respond to the drug at the same dosage level, using high doses and persisting with the treatment for sufficiently long periods, where indicated, may be two important guide lines for further studies. It is felt that in such resistant cases, the dose should be gradually built up starting from a low dose and gaps allowed in treatment to prevent the development of akathisia, agitation and other disturbing side-effects.

It has been mentioned above that the study was uncontrolled – except in the case of T.S.D. – and the subjective assessment by patients may not be conclusive in deciding the efficacy of the drug in the treatment of obsessional states. The very fact that patients suffering from obsessive compulsive neurosis, tend to be extremely parsimonious when describing any positive change in their condition as a result of treatment minimizes any bias from this angle. It has been the experiences of the present author that unlike the patients suffering from schizophrenia and their relatives who almost always begin the interview with "no complaint" and then go on to describe one symptom after the other, the first response of the obsessive patients is "no change" and then any reduction in the intensity of symptoms is admitted with some reluctance.

It is also worth noting that language barrier between the therapist and the patient which was complete in the case of C.C.B. and allowed very little rapport in two more cases (L.K.T. & G.K.S) served a useful purpose in assessing the therapeutic efficacy of the drug as whatever benefit these three patients derived from treatment may only be attributed to the drug.

SUMMARY

Seven out of eight subjects suffering from obsessive compulsive neurosis found relief in their symptoms, without being calmed down, following fluspirilene therapy; the only patient who could find no change in his condition had been kept on a fixed low dose regime. Patients who derived benefits from this form of treatment reported either losing a symptom completely or developing an attitude of ignoring it.

This exploratory strictly suggests that fluspirilene has perhaps some place in the treatment of obsessive compulsive neurosis where it acts on

Summary of Findings

	G.K.S.	J.N.M.	L.K.T.	H.Y.F.	T.W.K.	C.C.B.	T.S.D.
Obsessive thoughts concerning health death and allied themes.	80% (5) ... Absent (8)	80% (4) ... Absent (6)	90% (10)	30% (4)	20% (1)	70% (13) after 3 doses	51% (11) ... of harming others Absent (5)
Other ruminations	90% (5)	15% (2)	–	40% (3)	–	–	86% (11)
Checking rituals (doubts) and repetitions	only checking locks 0% (1) ... Absent (5)	80% (10)	65% (11)	75% (4)	56% (1)	80% (6) after dose	14% (11)
Washing/ purification/ ablution	Excessive leg-washing 0% (2) Absent (9)	75% (15)	87% (9)	–	–	–	37.5% (11)
Complicated rituals and obsessions	–	90% (10)	90% (10)	30% (3)	some 50% others absent (1)	–	14% (11)
Insistence on precision orderliness	–	75% (8)	–	–	Less	–	12.5% (11)
Other compulsions	–	–	90% (9)	–	–	–	some 28.5% other compulsions 71.5% (11)

Percentage denote benefit derived from fluspirilene therapy; figures in parentheses represent the week when assessment was made.

the basic symptoms of the illness and that its efficacy is dose related affecting different symptoms at different dose levels and at different stages of treatment. Furthermore, in this condition its action is antagonzied by the concurrent use of anxiolytics and antidepressant agents.

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THE CONTROL OF POST-CONVULSIVE CONFUSION BY VALIUM

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In a private practice where modified E.C.T. has to be given out infrequently there is a need to reduce this to a reasonably safe and simple procedure.

This need is generally satisfied by the selection of one of the several techniques available which combines a hypnotic and a muscle relaxant to be followed by artificially maintaining the respiration until recovery from the drug effects sets in.

Where a quick turn-over is desirable for various reasons the choice of a hypnotic often falls on one of the shorter acting barbiturates, whereby patients are able to awake soon after the convulsion that they may leave for home without undue delay.

A quite occasional complication is the post-convulsive confusion. Besides delaying departure time it may well constitute a threat to the practice.

Extra care is required to manage the confused patient. Besides falling he may injure others or do damage to property. He may be a fearsome spectacle and when exposed to other awaiting patients may cause them untold anxiety. Where the patient is big and strong a state of emergency can arise.

My experience in controlling this complication by the use of Valium in about 250 cases is herewith reported.

METHOD AND PROCEDURE

To a syringe containing about 5cc of a 1% solution of Sodium Brietal (Methohexitone) (for an average Asian adult weighing between 50Kg to 70Kg.) is added about a third of a cc of an ampoule of gr. 1/100 Atropine. The patient if cooperative is asked to take deep breaths and the mixture is then given intranveously immediately in order not to allow time for precipitation which begins to come on after 10 mins. or so.

This syringe is then withdrawn from the needle and another syringe containing between 30mg to 50mg (depending on the size of the patient) of Suxamethonium Chloride (Scoline) is connected to the needle and injected when the patient begins to fall off to sleep.

This second syringe is further exchanged for a third containing between 10mg to 20mg Valium depending on requirements. The Valium is not injected until fasciculations have clearly reached the toes in earnest. It is given not too slowly over a period of about 5 – 10 seconds.

The patient is then immeidately given the convulsion treatment which is effected by an Ectonus machine delivering an alternating current of 150 volts over a period of about two seconds.

On the odd occasion where no definite signs of a convulsion (even modified) is evident a repeat dose of the current is given with a longer time interval, say 1 or 2 seconds more.

These signs must include at least a sustained down-going toe with some bilaterally symmetrical clinic movements of the toes or eyelids or lips.

Very rarely (in only a few cases) was there a need to go on to deliver a third dose.

RESULTS AND DISCUSSIONS

With the above procedure a rousable light sleep follows on the tail end of the short acting anaesthesia.

An attempt may then be made to lightly awaken the patient by patting his cheek, pinching his ears or calling his name. On obtaining a response he is allowed to continue with his sleep for a while more. When it is known that his confusion is a particularly bad one he is not awakened at all but is left to sleep on.

When the sleep reaches the stage when he can turn over to one side he can then be more or less left alone or attended to by his relatives where available.

Ten to 20 minutes after the treatment the majority if not all will either awaken on their own or be aroused with ease by relatives, unless the higher doses have been used.

In this way the confusion may be totally avoided. Or course where the first dose of Valium has only led to a partial effect a higher dose is given with the subsequent treatments.

I had no occasion to exceed 20 mg in this series of cases. In my experience almost invariably where the second dose of current is required it was because of one or more of the following interfering factors having been present:–

1. electrodes had become too dry;

2. insufficient Bicarbonate powder had been used (to wet electrodes);
3. electrodes not pressed hard enough against skin;
4. electrodes slipping away due to movements during the start of the convulsions.
5. greasy skin;
6. heavily powdered skin especially with foundation cream.

The need to give a second dose (about 5% of cases) and even a third, appeared to me to be no more than in the cases when no Valium had been used.

This series of about 250 Valium cases constitue a relatively small percentage of all modified ECTs given. Generally the incidence of post convulsive confusion is not very frequent. As such it would appear unnecessary to give Valium to every patient on a preventive basis. The less drugs given the better is the maxim I subscribe to.

However, where there is a reasonable anticipation that this complication may come on then the Valium is given preventively. Among the reasons for this anticipation are exceptionally strong and big-sized patients and curiously when they are relatively not very literate – as farmers, hawkers and labourers and etc.

Of some interest is that Valium is known as an effective anti-convulsant and therefore theoretically it should not be used in a treatment procedure, where the primary purpose is to obtain a grand mal convulsion even though peripherally modified. This is particularly so when we bear in mind the work done by Ottoson et al;(1) that the therapeutic value may well be closely related to the neuronal release or grand mal convulsion produced by the current.

In my experience there has been no difficulty in the large majority of cases in obtaining a modified convulsion with Valium despite its anti-convulsant property.

Where there has been difficulty on the odd occasion almost invariably one or more of the six interfering factors were found to have been present. With their removal the second (and the rarely required third) dose of current would then unfailingly bring on the modified convulsion.

The summative effect of the subsequent doses of current no doubt would have contributed to bringing on the modified convulsion to some extent.

Reducing the amount of Scoline has also helped. This is particularly so where the patient has been under heavy sedation just prior to the treatment. It is possible that the excessive Scoline could have modified the convulsion to such a degree that any minimal muscular flickering that could have been present may have gone undetected.

It is also possible that the short time interval consequent upon my procedure between injecting the Valium and delivering the current may be a contributory cause as to why the anti-convulsant effect of the Valium did not set in.

On an average my injection time for a 10mg dose is about five seconds and a 20mg dose about 10 seconds.

As the Valium is not injected until fasciculations from the Scoline have reached a point of time that the current is ready for delivery the time interval between the end of the injection and the delivery of the current is normally not more than 5 – 10 seconds (the time taken to put aside the syringe, remove the pillow, place the electrodes on to the temporal region and press the button.)

It is possible that the anti-convulsant property of the Valium may not have sufficient time to act fully to prevent the convulsion.

Thus while it has been shown that 10mg of Valium given intravenously will often stop a grand-mal attack both clinically and electro-encephalographically within 10–30 seconds of injection(2) nevertheless it is possible that there could have been an interval of a few seconds between the delivering of the current and the full effect of the Valium coming on.

Further it may be that the stopping of an already started grand-mal seizure of spontaneous origin and the preventing of an electrically initiated grand-mal may not be one and the same thing.

Of course one could give the Valium after the convulsion, but I find this unnecessary as it involves further steps including another vein puncture or if the needle has been left in during the convulsion, the risk of trauma from unexpected jerks or the possibility of clotting within the needle if the convulsion, were to be of some considerable duration.

In my experience there appears to be no difference in the clinical response to the modified convulsion in patients with and in patients without the use of Valium.

The lack of any significantly undesirable side-effects observed by other workers was also experienced in the study.

Consequently, it may be reasonably concluded that Valium may be used quite freely and with

good effect in the control and prevention of the post convulsive confusion despite its known anti-convulsant property in the procedure aforementioned.

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PSYCHOTROPIC DRUG IN THE TREATMENT OF PSYCHIATRIC COMPLICATIONS AND SEQUELAE OF HEAD INJURY

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The incidence of head injury has been increasing every day and the most common cause is traffic accident. Therefore the need for careful review of the medical status of brain disorders associated with trauma has become increasingly evident. On the one hand, the diagnosis, evaluation, and treatment of head injuries have become more complicated. Concurrently, psychiatric syndromes following injury to the head are of growing medical interest because of their frequency, severity, and medico-legal importance. Prior to 1940, psychiatrists and neurologists were concerned primarily with the demonstrable organic damage which resulted from head injury, and with the treatment of gross sequelae, such as epileptiform attacks and major deviations in behaviour. However, over the past 40 years, physicians have gradually come to realise that injury to the head does not necessarily involve injury to the brain. Nor does brain injury inevitably result in demonstrable disabling symptoms or mental disorders.

In brief, current medical concern is no longer restricted to the nature and residual effects of permanent brain damage. It has been extended to apply to all syndromes following head injury, which may or may not involve brain damage. And, concomitantly, clinicians have become aware of the innumerable complex and subtle variables which must be considered in connection with such phenomena. These include the patient's pretraumatic personality, including his capacity for object relationships, and the conscious and unconscious factors which governed his relations with other people, his occupational and domestic history; and, in some cases, the circumstances of the accident itself. Investigation of the patient's post traumatic behaviour is equally crucial, of course. And, in fact, although evaluation of the complex interaction of psychosocial variables is an inherent part of psychiatric practice, perhaps nowhere is a more intricate combination of organic, social, and psychological components encountered than in the stages of adaptation following head injury.

The classification of brain disorders associated with head injury is very confusing. Different authorities and text books have their own ways which are not similar. In our opinion, the classification in the Henderson and Gillespie's Text book of Psychiatry, tenth edition, 1969 is simple and more practical. According to the text book, the classification is as follows.

1. Post-concussional and post-contusional syndromes; including deliria and transient dysamnesic states.
2. Post-traumatic dementia; including personality changes and Korsakoff's psychosis.
3. Other neurological complications and sequelae; including epilepsy, aphasia and subdural hematoma which we shall not mention today.

After a minor head injury with concussion, the mental symptoms are transient, disappearing usual-

ly in a few days. In addition to complaining of headache, the patient may be dazed, irritable, restless and for some time confused. The effects of cerebral confusion are more severe and tend to be much more persistent. The patient may proceed through the phases of stupor, delirium and confusion as he slowly emerges from coma following a major trauma. He may then recover completely, or show residual disabilities of lesser or greater severity. Post contusional Syndrome, in this condition, the patient is apt on recovering full consciousness to complain for some time of a group of symptoms. They are headache, which is usually throbbing and aggravated by stooping and physical or mental stress; dizziness; increased fatigability; impaired concentration; slowing of thinking process and forgetfulness; irritability, and over sensitivity to noise; and a decreased tolerance of alcohol. The patient realises that he is ill and is often anxious and depressed.

The prognosis is determined by a number of factors which we have discussed from the beginning. However, we would like to mention Ritchie Russell's report in 1934 that anxiety about compensation hinders recovery. Ritchie Russell reported that after 18 months, 35 per cent of his compensation cases had not reported fit for work, while in the non-compensation group only 9 per cent had failed to do so. The prognosis is also influenced by age, those over 40 being less successful in getting back to work quickly.

Gross and permanent dementia following head injury is rare and one should not conclude that damage is permanent until at least 18 months after injury. However, transient psychosis is not uncommon in our series. It is found that about 10 per cent of total cases of head injury at our research centre develop psychotic symptoms. This psychosis resembles a mixture of organic and schizophrenic-like symptoms. The duration of the psychosis varies from a few weeks to several months.

There are other big groups of psychiatric syndromes which we would like to call psychoneuroses precipitated by head injury. These syndromes are not significantly different from the conventional psychoneuroses. Most of the patients show anxiety state, conversion symptoms, hypochondriasis and depression.

In brief, psychiatric symptoms following head injury can resemble almost any form of psychosis, psychoneurosis, personality disorders and organic brain syndromes. In many cases, they are transient and in others are permanent. The most effective way of helping these patients requires the cooperation among neurologists, neurosurgeons and psychiatrists. Psychiatric treatment should begin immediately after neurological or neurosurgical treatment. Most psychiatrists agree that all treatment modalities have their places in the treatment of these conditions. Therefore psychotropic drugs are helpful when they are used correctly and appropriately.

We would like to summarize the psychotropic drugs in the following way:—

1. Antipsychotic drugs: Psychotropic drugs of this class have been called ataractic and neuroleptic. For some time they were described as the "major" tranquillizers to distinguish them from the "minor" or anti-anxiety drugs. As the group name implies, drugs of this kind have striking effectiveness in the treatment of psychoses including those from head injury.
   They are phenothiazine derivatives, Butyrophenones and Thioxanthene Derivatives.
2. Antianxiety drugs: As the antipsychotic drugs proliferated, so did a variety of agents with less dramatic and less specific tranquillizing attributes. However this group of drugs are still helpful in reducing anxiety in psychoneuroses following head injury, particularly when used in combination with psychotherapy.
   This group of drugs are Glycerol derivatives, Benzodiazepine derivatives and Diphenyl methane derivatives.
3. Antidepressant drugs: These drugs have proven to be very difficult to define. All share a reputed or demonstrable effect upon depression including depression following head injury.
   They are Tricyclic derivatives, Hydrazide MAO Inhibitors, Non-Hydrazide MAO Inhibitors and stimulants.

In summary, the use of psychotropic drugs in the treatment of psychiatric syndromes following head injury is very helpful when they are used correctly and appropriately. However, one should not overlook the importance of psychotherapy either in individual or in group.

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SOME OBSERVATIONS ON THE GUILLAIN – BARRE SYNDROME IN SURABAYA

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Since the eradication of poliomyelitis, Guillain-Barre syndrome (GBS) remains one of the most crippling neurological diseases. Although many scholars have written about it, treatment remains symptomatic with a mortality rate of 25% (5) The opinions are divided among neurologist regarding the value of treatment with corticosteroids and in one of the recent textbooks it is still written, that the value of treatment with corticosteroids is uncertain.

GBS is frequent in tropical countries, but reports from these countries on this disease are seldom, probably because of the hopelessness of this syndrome.

This is a report of 67 patients seen in Surabaya at the division of neurology, University of Airlangga, school of medicine and the private offices of the author. In this report the author further presents the result of a new form of treatment used in University Hospital in Surabaya.

MATERIALS AND METHODS

As criteria for selection the author used the criteria as mentioned by Mc. Farlan: (4)

1. The paralytic illness may follow a non-specific infection, but there is no preceding or accompanying illness of a type known or thought to be associated with polyradiculoneuropathy.
2. Sensory impairment may occur, but is less severe than motor impairment.
3. Diffuse lower motor neuron paresis is usually rapid in onset, often ascending, usually symmetrical, may be proximal and distal or both.
4. There are ten or fewer white blood cells per cubic millimeter in the cerebro-spinal fluid (CSF).
5. There is protein of 60 mg in CSF or higher.

Between the first of January 1957 until 1st January 1973, 67 patients were seen at the outpatient department of the University Hospital or at the private offices of the author. They were admitted in the University Hospital or the private hospital but were all examined by the author, except during the years of 1962 and 1963 when the author was in the United States.

In all patients, besides a neurologicl examination a complete blood count, differential count, platelet count and urinalysis was performed, Since the diagnosis was based on the CFS findings, in all patients a lumbar puncture was performed. Patients with a positive serologic reaction for syphilis were excluded from this study.

Clinical Findings.

The age and sex of the patients were as follows:

Table I: Age and sex from patients with Guillain-Barre syndrome in Surabaya

Age	male	female	total number
0 – 10	7	6	13
11 – 20	9	9	18
21 – 30	11	12	23
31 – 40	4	3	7
41 – 50	3	2	5
51 – 60	0	1	1
All ages	34	33	67

Seasonal incidence can be seen in table II

Table II: Seasonal incidence from patients with GBS

Month	No cases	Season	Total
January	13		
February	12		
March	9	rainy	37
April	3		
May	2		
June	1		
July	1	dry	8
August	2		
September	2		
October	4		
November	9	rainy	22
December	9		
			67

63 patients stated that they had an infection before the paralysis started. The variety of illnesses preceding the polyradiculoneuropathy may be seen in table III.

Table III: Preceding illness

Type of illness	No. of cases
Upper respiratory infection	34
Gastroenteritis	12
Fatigue, headache	9
Muscle aches	8
None	4
	67

Initial complaints.

The patients complaints at the first interview can be seen in table IV.

Table IV. Initial complaints of patients with GBS.

Symptom	legs	legs and arms	arms	Total number
Paresthesias and weakness	17	12	7	36
Neck pain	1			2
Motor weakness	12	9	5	29
			Total	67

Most patients were seen within 14 days after onset of the disease.

Neurological signs

The findings on the initial neurologic examination are given in Table V.

Table V. Initial neurological findings in GBS

Sign	facial	arm/legs	neck	respiratory	trig.
Weakness	333	67	37	12	77
Tonus – lowered		67	37	–	
Neg. reflex tendon		67			
Anaesthesia–glove–stocking		67			

Spinal fluid findings.

Since the diagnosis is based on the CSF findings, the spinal fluid was examined by all patients. The findings can be seen in table VI.

Table VI. Cerebro spinal fluid findings in 67 patients with GBS

Signs	60–80 mg%	80–100 mg%	more than 100 mg%
Protein – total	29	27	11
Cell – count	always lower than 10/mm3, mostly lymphocytes		
Colloidal gold all abnormal:	first zone	8	
	second zone	52	
	third zone	7	

Time relations:

In 63 patients the illness developed 7 – 21 days after a preceding illness. The peak of the illness was reached in 6–30 days and most patients began to recover 14–17 days after the peak in 56 pat. The typical course therefore was progression for two – three weeks, stabilization for two and then recovery. This is the rule in the patients not treated with intrathecal dexamethasone. (1, 6)

Therapy:

As noted before, the opinions on steroid treatment are divided. (3) The author noted however, that the corticosteroids usually were given orally or Intramuscularly. The author therefore decided to use the intratehcal route, because by giving it intrathecal, the local concentration of streroid in the spinal, roots should be increased during several hours (similar to in spinal anaesthesia). Most investigators now regard the GBS as a primary demyelinating disorder similar to allergic encephalomyelitis. (7). The usefulness of steroids in the last disease is long known.

Since 1971, the author offered this form of therapy to all patients with GBS. 11 patients agreed: 5 mg of dexametasone was given every day

Table VII. Comparison of patients treated with dexametasone – intrathecal and without.

	dexamethasone intrathecal	only support. therapy
Average days in hosp.	14 – 30 days	60 – 90 days
Neurological residual	only paraesthesias (leg and arm)	leg weakness in 60%
Protein value in CSF	lower than 30 mg %	when dismissed in 60% still above 60 mg %

by lumbar-injection intrathecally during ten days. When the protein value in the spinal fluid was lower than 30 mg%, the injections were stopped, otherwise a second series of injections was given. The results of this form of therapy may be seen in table VII.

DISCUSSION

As seen in the first table, there were as many males as females. Mc. Farland (4) found the same ratio, but Wiederholt (6) twice as many male persons. The age distribution showed that GBS was most frequent in the first, second and third decade.

The seasonal incidence showed, that GBS was frequent in the rainy season. The table on preceding illness, showed that an upper respiratory infection, was one of the most frequent disease preceding the neuropathy.

The initial complaints were mostly paresthesias combined with motor weakness (53.7%). 29 patients (43.3%) complained of weakness alone. In the majority of the patients the complaints were centered on the legs.

The neurological findings on examination showed, that the common picture was a flaccid paralysis of all extremities, with sensibility disturbances at the distal ends.

The spinal fluid showed a disturbance of the total protein value and of the colloidal gold.

Although the opinions are divided regarding the use of corticosteroids in GBS, it become apparent from a review of the literature, that:

1. GBS is regarded by many scholars as a primary demyelinating disorder similar to allergic encephalomyelitis and experimental allergic neuritis. (EAN (7).
2. Steroids inhibit the appearance of lesion in allergic encephalomyelitis.
3. Corticosteroids were used orally or intramuscular in GBS, while the rational way of giving steroids locally in slight dosage should be the intrathecal route, similar like in spinal anaesthesia.

The results in 11 patients treated with intrathecal dexametasone showed, that the number of days spent in the hospital was shortened, because the beginning of the recovery state in GBS was accelerated, a fact which was already suggested by Wiederholt. (6). Table VII proved too, that the neurological residual signs were mild in the patients treated with intrathecal dexametasone compared with those who received only supportive therapy. All the protein values were definitely low in the intrathecal treated cases.

7 patients, who took dexametasone orally, but did not show any improvement, were switched to the intrathecal form of therapy, with much success.

In the 11 patients treated with intrathecal injections no side effects were encountered. It should however be emphasized, that when giving a drug intrathecally, the strict precautions of sterility should be taken and that disposable needles and syringes should be used.

Although Fishman (2) mentioned objections, when giving intrathecal therapy for the purpose of reaching the cerebrum or optic nerves, it seems that from the results mentioned above, that intrathecal therapy with the objective of the spinal roots has still a place in the neurological armamentarium.

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Dexamethasone – Oradexon, Organon. The supply of cradexon needed in this study was donated by Organon, Indonesia.

MIGRAINE, RELATED HEADACHES AND PSYCHOTROPIC MEDICATION

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These observations result from previous experience with headache problems in a headache clinic in Switzerland, and from brief experience with headache problems in Malaysia, for little more than one year (by far not enough time for a statistical survey).

I have read two recent papers from this region: The Diagnosis and Management of Headache, by Loong Si Chin, and Complicated Migraine, by T.G. Loh and J.C. Chawla. I would like to comment upon a few concepts from these articles which may be representative of the interpretation of headache problems at an academic level in this region.

"Complicated migraine", say Loh and Chawla, "is not well known.....it is associated with protean ...neurological features...".

Migraine has been described by laymen from ancient Summerian and Egyptian times, and by Western medical authors (as far as their writings are extent) from the second century A.D., when the term was first introduced as "hemicrania" by Galenos of Pergamon, the father of Western medicine.

The best known variant of migraine is that hemicrania which is further characterized by preceding scintillating scotoma and concomitant nausea: the megrim, or sick headache, which had been described by Galenos and, as "heterocrania", by his precursor, Aretaios, wherefore it is often known as "classical migraine". In 1878, Galezowski gave it the self-explanatory name of ophthalmic migraine.

What Anglo-Saxon authors call "hemiplegic migraine", that is, a paroxysmal headache with transient features akin to some or all of the symptoms of stroke, had been named "migraine accompagnee" by Charcot, the founder of modern neurology, in 1887. The majority of cases of "complicated migraine,' can rightly be classified as migraine accompagnee.

The very rare condition of paroxysmal periodic headache with extraocular palsy was first identified by P. J. Moebius in 1884, and it was named "ophthalmoplegic migraine" by Charcot in 1890.

The migraine variant with the highest frequency of attacks which occur once to many times a day within bouts or "clusters" of one to two months is known in medical literature by at least twelve different names (such as: Horton's Neuralgia, Migranous Neuralgia, Erythroprosopalgia, etc.). In the last decades, American and Scandinavian authors have increasingly preferred "cluster headache", again a self-explanatory term.

On a sound historical basis, migraine and its variants can be classified as follows: common migraine, ophthalmic migraine, migraine accompagnee, ophthalmoplegic migraine, and cluster headache. There are other terms which have found less ready acceptance, such as dysphrenic migraine, characteristic migraine, basilar artery migraine. There is another, more comprehensive classification: the list of the ad hoc committee on classification of headache of the National Institute of Neurological Diseases and Blindness of the U.S.A., 1962, which includes facial migraine under a separate heading. However, the simple classification as proposed above takes care of the practically important forms of migraine, and allows us to get beyond the impression of "protean neurological features" and to sort out the "(infinite) variety of migraine" (Friedman) in terms compatible with contemporary literature.

In Anglo-Saxon literature, "Tension Headache"

comprises most forms of chronic headache without demonstrable underlying disease. In continental European texts, the term is usually replaced by "Cephalaea Vasomotorea". I know of only two features that enable us to distinguish this idiopathic chronic headache from migraine forms: namely, lack of response to vasoconstrictor agents, and lack of paroxysmal character. Even these criteria are far from absolute since literally every variant and every case of migraine may turn into the chronic headache syndrome, and lose its distinctive features. Any migraine variant may coexist with chronic headache in the same patient. Some chronic headache forms may respond to vasoconstrictive agents, especially to Dihydroergotamine. Since "muscle tension", most often in the form of cervical tendomyositis, is also one of the most common features of any long-lasting frequent migraine, I feel that we should regard "tension headache" and "cephalaea vasomotorea" as one and the same idiopathic chronic headache syndrome, and as the chronic equivalent of migraine.

Migraine is a paroxysmal disorder for which really significant correlations with other paroxysmal disorders have often been postulated but never demonstrated. It is associated with vasoconstrictive and vasodilatory phenomena, and with significant biochemical especially changes, in the levels of serotonin , and in the serotonin retention of platelets. It is most likely hereditary. It is very common. In 1959, Bo Bille found 3.9% migraine cases among nearly 9000 school children. As the same study showed, less characteristic headache forms were still more common: Bille found 6.8% "frequent nonmigrainous" headache, and 48% "infrequent nonmigrainous" headache. Since out patients tell us, as a rule, that their headaches began only after school age, it is very plain that migraine and its chronic equivalent must constitute one of the most common and ubiquitous groups of disorders.

It is astonishing, then, that hardly any doctor's practice is ever filled by headache patients. This is because headache alone is usually not the reason for patients to turn to medical help. It is only the worsening of chronic headache, or the onset of very severe headache, or the appearance of severe additional symptoms, which forces them to consult us. It was my constant experience that such worsening or, the precipitation of very severe attacks or continuous migraine attacks (status migraenosus) did very often coincide with changes in life situation which resulted in let down and frustrated resentment. This emotional background could best be established by taking note of the exact date of the worsening or precipitation, followed by asking about changes in family, job or housing situation at that time, or a little earlier. Once such a coincidence had been found, it was then often relatively easy to discuss the emotional values attached to the coincident change. These informations could then be used as the basis for a problem-oriented relationship which was usually combined with drug treatment. Frequently evidence of discrete or masked depression was found, which led to treatment with antidepressives, alone or in combination with migraine remedies. Migraine remedies were used in prophylactic, or long-term treatment. They comprised Ergotamine tartrate. Dihydroergotamine, Clonidine (Catapres), Sandomigran, Dimetotiazin, Methysergide. This method of treatment was used for both migraine and chronic idiopathic headache (Tension Headache, or Cephalaea vasomotorea).

The relationship of these forms of headache with emotional disturbances has been discussed since antiquity. The predominance of depressive disorders among the causes of headache *problems* has been emphasized before, e.g. by Habib (1972). However, the matter is far from closed; information about this relationship has never been systematically collected.

Loong Si Chin says, in his article in the SMA, 1972: "...treatment...usually presents no problem once a definitive diagnosis is made." I find it difficult to accept this statement. I have found that results of treatment in any not merely ephemeral form of headache can only be assessed after many years. This is why I cannot back up my empirical statements with a convincing statistical analysis. (My experience in my Zurich headache clinic is little more than five years).

Loong goes on to recommend "...tranquillizers or antidepressants for tension headache..." I believe that we should replace this indication by a more precise one, namely, "antidepressants for depressive conditions underlying tension headache and migraine problems." I think that doctors should try to identify these underlying disorders.

If we look closely at the drugs used in the treatment of headache, we find that many or most of them are psychotropic drugs. The indication for antidepressants has already been discussed. Dimetotiazine or Migristene is a phenothiazine derivative with a very marked sedative effect, chosen for its antiserotonine properties, but undoubtedly a true major tranquillizer. Sandomigran, also chosen for its serotonine antagonist properties,

has shown some antidepressive and sedative properties as well as appetite stimulating side effects which are the main reason why it appears to be more useful in Asiatic countries than in the saturated West. Dihydroergotamine had been designed as an agent exclusively related to the autonomic nervous system, but it has since proved to be effective in preventing the dangerous delirium which can arise from the combination of neuroleptics with tricyclic antidepressants. Methysergide, the chemical twin of LSD, chosen for its anti-serotonin properties, has been used for the treatment of mania. Serotonin itself is more and more recognized as one of the biochemical keys to psychic processes. Only Ergotamine tartrate cannot be characterized as a psychotropic drug – however its combination with caffeine is conducive, if used too frequently, to an unpleasant form of drug-dependence which is coupled with permanent daily migraine. In conclusion there is reason to suspect that most specific migraine treatment is at least partly psychotropic treatment, which may be administered without precise indication.

Another form of unwitting psychotropic treatment is the one most often administered by laymen, that is, analgetic treatment with painkillers. In Malaysia's outpatient departments, the Paracetamol reflex is paramount: complaints of headache lead to instantaneous prescription of Paracetamol . Paracetamol has not yet been exposed as having psychotropic properties, but it is clearly useless as soon as a headache has become a problem, that is, chronic or very severe. Other painkillers such as Saridon and APC-like combinations have been shown to be plainly psychotropic due to their combination of stimulating and sedative properties (Kielholz and Ladewig, 1970) which frequently lead to severe addiction. The double-blind controlled effect of these unspecific painkillers is generally in the range of a placebo-effect: for this reason, again, a predominantly psychological mode of action has been suspected, possibly enhanced by mild psychotropic effects.

It appears that we can hardly escape psychotropic medication in the treatment of migraine and tension headache. I believe that we should choose to administer psychotropic medication, not unwittingly, but consciously, and well knowing what it is that we are treating, as far as time limitations allow us.

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CARBAMAZEPINE IN THE TREATMENT OF TRIGEMINAL NEURALGIA

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Carbamazepine (Tegretol^{R}) is by far the most effective drug for the treatment of trigeminal neuralgia. It is an iminostilbene derivative, chemically related to imipramine hydrochloride. Although it is primarily an anticonvulsant, Blom (1963) has shown that it also inhibits the polysynaptic nociceptive linguo-mandibular reflex in decerebrate cats.

Many clinical trials conducted in various parts of the world during the last ten years testify that carbamazepine controls the pain of trigeminal neuralgia in about 70% of cases. In our series of 70 patients, the attacks were completely abolished in 41%, controlled to the patients' satisfaction in 29%, and partially relieved in a further 4% of cases. Analysis of an additional 198 cases reported in the literature prior to 1965 supported our findings (Burke, Grant and Selby, 1965) and more recent publications (Bonduelle and Lormeau, 1966; Krayenbuhl, 1969; Heyck, 1970) provide further confirmation.

Carbamazepine usually relieves pain within 12 to 48 hours and cessation of treatment produces an equally rapid recurrence. The age of the patient, the duration of his trigeminal neuralgia, or the particular division of the trigeminal nerve involved have no influence on therapeutic success.

Long-term follow-up studies have shown, however, that this drug may lose its effect even in large and potentially toxic doses after two years of successful treatment in from 10 to 30% of patients (Heyck, 1970). The reasons why some patients do not respond to carbamazepine at all, and others become refractory to it after months or years, are unknown. The cause need not lie in the pathological mechanisms producing the pain, but may be found in the pharmacodynamics of the drug, such as an accelerated induction of enzymes which metabolise it. Recurrence of tic after previous treatment by alcohol injection or peripheral neurectomy does not appear to influence the emergence of this drug resistance.

Side effects include temporary drowsiness in about 40% of patients, giddiness, and ataxia in 10 to 15%, and skin rashes in less than 10% of cases. A few patients complain of gastro-intestinal upsets, but only two of our 70 patients abandoned the drug because of side effects (Burke and Selby, 1965). Leucopaenia and aplastic anaemia were reported in isolated cases, but can be prevented by appropriate clinical and haematological supervision.

Minor side effects can be minimised by gradual increases in dosage, beginning with 100 mg. twice daily. The average effective dose ranges from 600 to 800 mg. per day and only a few people will tolerate a daily dose of 1,200 mg. If carbamazepine in the maximum tolerated dose does not control pain within 72 hours, therapeutic failure must be conceded. A few patients respond better to a combination of carbamazepine and diphenylhydantoin than to either drug alone.

Carbamazepine is ineffective in post-herpetic dysaesthesiae and in atypical facial neuralgias (Selby, unpublished observations; Krayenbuhl, and the proportion of successful results is lower in symptomatic than in idiopathic trigeminal neuralgia.

This specific effect of carbamazepine on the pain of trigeminal and glosso-pharyngeal neuralgia must be in some way related to the pathogenesis of these diseases.

Trigeminal neuralgia is not a specific disease, but a symptom which can be produced by various pathological processes. A variety of small, benign, slow-growing tumours, as well as vascular malformations and even tiny "aberrant" arteries which compress, distort or encircle the trigeminal root can cause tic douloureux, which is in every respect – including long remissions – indistinguishable from the "idiopathic" form of the syndrome.

As the evidence derived from the often incomplete observations at operation or autopsy failed to reveal structural lesions in most cases, various anomalies of the bone and dura in the region of the petrous apex and Meckel's cave were considered responsible for compressing or stretching the ganglion and root.

The only intrinsic pathological process capable of causing paroxysms of trigeminal neuralgia identical to those of the "idiopathic" form is multiple sclerosis where the plagues of demyelination were always shown to involve fibres of the trigeminal root at their zone of entry into the pons (Olafson, Rushton and Sayre, 1966).

There is still some argument, particularly among electron microscopists, about the validity of ultrastructural changes seen in the trigeminal ganglia and roots from patients with tic douloureux. It may be accepted, however, that partial demyelination and loss of some axons are implicated in the pathogenetic mechanisms. Remyelination could then be considered as an event contributing to the natural remissions characteristic of trigeminal neuralgia. Dynamic forces, such as movements of the head and neck, changes in cerebro-spinal fluid pressure and arterial pulsation, may later cause sufficient minor trauma to the trigeminal root, already compromised by extrinsic compression and intrinsic degenerative changes, to precipitate a new series of pain paroxysms.

The peripheral structural lesions we have so far considered do not provide a sufficient explanation for many of the highly specific features of the pain of trigeminal neuralgia, including:

1. the brief, paroxysmal nature of this pain;
2. triggering of many attacks by minute tactile or proprioceptive stimuli;
3. occurrence of trigger spots located predominantly in the central (most anterior) parts of the face;
4. radiation of pain along linear tracks, usually confined to one or two divisions, but hardly ever diffusing over an entire dermatome;
5. absence of demonstrable neurological deficit.

The paroxysmal character of trigeminal and glosso-pharyngeal tic is unlike any other painful affliction of man, and the only common denominator for these neuralgias is the anatomical convergence of their exteroceptive afferents in the caudal part of the spinal tract and nucleus of the trigeminus.

Kugelberg and Lindblom (1959) have shown that a spatial and temporal summation of tactile impulses is usually necessary to trigger a proxysm of pain. During the refractory period which follows the attack, only stimulation of high intensity will elicit pain, which is then of shorter duration and less severity. The anticonvulsant drugs lidocine caine and hydnatoin raise the threshold for effective stimuli and shorten the duration of the attack by diminishing its tendency to self maintenance.

Physiological studies in animals have shown that stimulation of peripheral branches of the trigeminal nerve evokes both an immediate and a delayed response; the latter arises from cells in the caudal part of the spindal trigeminal nucleus and is conducted centrifugally (antidromically) into peripheral components of the trigeminal nerve. This trigeminal dorsal root reflex can be activated at the same threshold as touch fibres (King et al., 1956; et. al., Crue 1968). These observation indicate that at least part of the patho-physiological mechanism responsible for the paroxysmal pain of tic douloureux is centrally situated, probably in the spinal trigeminal nucleus.

The concept of a trigeminal dorsal root reflex, evoked by tactile stimuli and capable of generating a repetitive, self-exciting after-discharge provides a tentative explanation for the tactile triggers and for the brief, paroxysmal nature of the pain of trigeminal neuralgia. The anatomical substrate for the cutaneous trigger zones in the central part of the face may be the concentric onion-skin pattern of sensory representation in the spinal trigeminal nucleus, where the fibres from central regions of the face are projected to the most rostral part of the nucleus caudalis.

From the clinical and physiological data reviewed above, a working hypothesis of the pathophysiology of tic douloureux can be constructed. Mild mechanical trauma to the trigeminal root, or a plaque of demyelination in multiple sclerosis, results in a partial and differential loss of some large myelinated axons. This reduces the normal inhibitory influence of these fibres on the earliest relays in the nucleus caudalis, which is functionally homologous to the substantia gelatinosa of the spinal cord and may therefore be concerned in the gate control theory of pain proposed by Melzack and Wall (1965). The "gate" has been opened, and the secondary and internuncial neurone pools in the rostral parts of the spinal trigeminal nucleus are now in a deranged, excitatory state. This augments the self-exciting, repetitive discharge of the trigeminal dorsal root reflex, so that a barrage (summation) of afferent impulses is consciously appreciated as a pain paroxysm. The long latent period between the trigger stimulus and the onset of pain, and the subsequent refractory period are consistent with such a hypothesis. It does not explain, however, why a bout of pain terminates, or why during such a temporary remission stimula-

tion of the trigger zone fails to evoke another paroxysm. This is analogous to the enigma of the cession of an epileptic seizure while the irritative epileptogenic focus persists. The balance between excitation and inhibition is obviously very unstable; either exhaustion of the excitatory synaptic transmitter or accumulation of an inhibitory transmitter would provide an explanation. Remyelination and regeneration of a sufficient number of damaged fibres restores the normal inhibitory state and allows for a prolonged remission. A "subliminal" degree of disinhibition of the central neurone pool in the spinal nucleus, however, persists. Further mechanical trauma to the root can thus evoke the next attack more readily, and relapses become progressively more frequent, prolonged and severe.

The precise mechanism of action of carbamazepine in relieving the pain of trigeminal and glossopharyngeal neuralgia is not fully understood, but it is thought to suppress polysynaptic transmission. Physiological experiments in cats after electrical stimulation of the infra-orbital nerve and recording from the ipsilateral spinal trigeminal nucleus and from the centrum medianum of the contralateral thalamus have shown that the drug depresses discharges in the spinal nucleus and abolishes them almost completely in the thalamus (Hernandex-Peon, 1965).

The conscious appreciation of pain and its precise localisation must involve the connections between the trigeminal nuclei and the thalamus and somato-sensory cortex. The role of the various pre- and post-synaptic inhibitory and facilitatory feedback mechanisms on the complex physiology of pain is still obscure.

On present evidence, it would seem that more effective and lasting control of pain in trigeminal neuralgia has to await the discovery of more pharmacological agents which can either suppress synaptic excitation or enhance inhibition in the spinal trigeminal nucleus.

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APPLICATION OF RIVOTRIL (CLONAZEPAM) IN SEEG DEFINITION OF EPILEPTOGENIC FOCI

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Stereoelectroencephalography (SEEG) has been developed since 1949 by Talairach and Bancaud in Paris. This method allows precise localization and identification of epileptogenic foci in the telencephalon. SEEG is indicated in treatment resistent severe focal epilepsy; its purpose is to yield optimal information for subsequent neurosurgical intervention, usually it leads to cortectomy or lobectomy.

The radiologic and stereotaxic equipment used in SEEG has been designed and developed for the task of localizing in the cerebral cortex – the usual stereotaxic equipment is not sufficiently precise for this, in fact, it allows only satisfactory localization in subcortical areas such as the basal ganglia. One main feature of the SEEG equipment is the X-ray focus of 4.7 meters. This extraordinarily long source – object distance allows to get life-size X-ray pictures with only negligible magnification.

SEEG investigation is based upon complete neurological and neuroradiological workup including stereotaxic charting of penumencephalogram, bilateral carotid angiogram and ventriculogram. SEEG can only be performed after at least one full conventional EEG record of a spontaneous seizure has been taken. Of course, interval EEGs will be taken in waking and sleeping and activation methods will be used.

The clinical and conventional EEG results are the basis for a preliminary localization or, at least, lateralization.

According to the X-ray findings, a chart is established showing the areas where the probes will be inserted. The probes are needles with a diameter of 2.4 mm and fitted with up to 15 electrode contacts, each of which can pick up potential differences in the immediate vicinity, that is, from a tissue area within a radius of 3 mm all around the contact ring on the probe.

The patient is placed on the special operating table under fluothane general anaesthesia and fitted with the stereotaxic frame; after applying the boreholes, the fluothane is withdrawn, the patient being under a very superficial general anaesthesia from palfium; then the probes are inserted and EEG recordings are taken from as many as 150 intracranial electrode contacts, and the most rewarding ones are selected for the SEEG study, usually 16 channels record from intracranial contacts, 14 from conventional EEG electrodes, one records the EEG and one the respiration rate. The patient, of course, is awake.

After recording a spontaneous seizure from intracerebral leads, the same leads are used for electrical stimulation.

After observation of provoked seizures, the patient is then given Rivotril (Clonazepam) intravenously in order to decrease cortical excitability to a point where only primary epileptogenic activity will respond to stimulation.

The method will be illustrated here briefly by the example of a 26 years old woman from Naples (Italy), who was explored by SEEG in Zurich in June, 1971. She had had focal seizures from age 17. By the time she came to Zurich, she had had repeated status and besides these, a maximum frequency of 72 seizures in 24 hours.

The main problem to be solved by SEEG was the differential diagnosis between a complex sensorimotor Jacksonian epilepsy and a primary and supplementary motor epilepsy. The former diagnosis would imply surgical removal of parts of both pre- and post-central cortex which would inevitably lead to severe loss of sensory control of the left over extremity, and therefore give rise to severe disorder of gait. Removal of primary and supplementary areas would presumably lead to only motor paresis.

Her SEEG recordings showed bilateral seizure activity with a maximum in the motor cortex region of the left foot, that is, with a pseudoisoelectric tracing from the contact points in that area resulting from high frequency low voltage spike or tonic discharge which is too fast to be reproduced by the writing system. After 3 hours recording – native recording can take up to 10 hours – with two spontaneous fits, the stimulation

programme was performed. For verification of somatotopic representation, through the recording electrodes in the motor area of the left lower extremity rectangular pulses of 0.5 to 3 volts and 1 to 3 millisecond and 1 – 3 cps were applied. The somatotopic representation proved to be correct. The same area was then stimulated by 0.5 to 3 volts, 50 cps, 1 msec series of 4 seconds duration. This led to seizures originating from two contact points, namely in the primary motor area of the foot and in the supplementary motor area of the right hemisphere. The clinical picture of the patient's spontaneous seizures as well as the SEEG pattern were satisfactorily reproduced. Stimulation in the primary motor area with 2 volts gave rise to complete clinical and electroencephalographical reproduction of the spontaneous seizure pattern, while in the supplementary motor area a seizure ensued only from stimulation with 3 volts, and there was clinical but not electroencephalographical reproduction of the seizure pattern.

This difference of excitability threshold was interpreted as indicative of the dominant epileptogenic role of the primary motor cortex area of the left foot, and corroborative evidence was obtained by the I.V. application of 2 mg Rivotril. Stimulation of supplementary motor area with 3 volts led to an abortive seizure while stimulation of the primary motor region with 3 volts led to a mitigated but still fully characteristic seizure pattern, both clinically and electroencephalographically. The record after this stimulation shows a failure of the left hemisphere to take part in the seizure activity, contrary to the spontaneous fits. The tonic discharge was significantly slowed down.

These two final observations are indicative of the correctness of the earlier localization and, incidentally, show that Rivotril – as the other benzodiazepine anticonvulsants – has most likely a direct cortical action as well as subcortical one. This has been experimentally demonstrated by H. Petsche.

The diagnosis was: primary motor epilepsy with secondary involvement of supplementary motor area. Two weeks after this SEEG exploration, a cortectomy was done, with excision of the medial parts of the areas 4 and 6 of the right hemisphere. The patient's left lower extremity was severely paralysed but after 10 days she could walk again, and her gait is now entirely normal (whereas she had had a slight paretic dysbasia before the operation). She has been seizure free since the operation, of course under continued antiepileptic medication with Dilantin 100 mg and Luminal 50 mg tds. Her EEG shows neither lesional nor epileptogenic activity. She is now working in her previous job as a Kindergarten supervisor.

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A COMPUTERIZED RECORDING SYSTEM FOR MENTAL PATIENTS IN INDONESIA

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INTRODUCTION

An integrated recording system of mental patients of all existing mental hospitals and psychiatric facilities in a country, combining recording uniformity, efficiency, quick information retrieval, and easy accessibility is an endeavour fraught with many difficulties.

Psychiatric facilities may provide services which are sometimes so divergent in character, that for some to commit themselves to a uniformly acceptable method of patient recording may hardly be a possibility. Patients' records of university hospitals where teaching is of utmost importance, and where consequently patients' records are very detailed; records used in governmental hospitals, most of them heavily understaffed, which make extensive and detailed recording too time-consuming; units which have provisions for very specialized services, such as drug dependence units, child guidance clinics, facilities for geriatric patients; each of these facilities has its own way of keeping track of their patients.

But psychiatry may get much benefit from the progress modern technology has made. The application of electronic data-processing to psychiatric patient recording may result in higher efficiency, greater speed of processing and analysis of data, accuracy and retrieval. These advantages alone far outweigh the difficulties to be encountered. The justifications for a computerized recording system are valid enough if meaningful research is to be done, or improvements of services linked to changing community demands are to be made. Furthermore, for a central body or for each psychiatric facility to have access to all the recordings in a country constitutes an additional advantage.

This paper describes a computerized recording system for psychiatric in-patients services which has been instituted throughout Indonesia.

Indonesia covers an area of more than 725,268 sq. mi. with about 13000 islands lying between latitude 5 degrees North and 11 degrees South, and between longitude 95 degrees East and 141 degrees East. It has an estimated population of 120 million. There are only about 75 certified psychiatrists in Indonesia and some 65 general practitioners working in State Mental Hospitals. Almost all these doctors work as government officials or in State Mental Hospitals during morning hours and have private practice in the early evening hours.

Basically there are four kinds of psychiatric facilities serving the Indonesian community.

1. *State Mental Hospitals.* These are funded by the Ministry of Health or the Provincial governments. There is a rather uneven distribution: 4 facilities in Sumatra, 3 in Kalimantan, 9 on Java, 2 in Sulawesi, 1 in Irian Jaya (West New Guinea), and 1 on Bali.
2. *University Departments of Psychiatry.* These facilities provide undergraduate medical teaching. Some of them are accredited centres for post-graduate training in psychiatry, such as University Departments in Jakarta and Surabaya.
3. *Private Mental Hospitals.* These are private facilities set up by psychiatrists generally located in some of the largest cities on Java and Sumatra. Included in this group are also Departments of Psychiatry of private general hospitals.
4. *Military Departments of Psychiatry.* These facilities are usually units of general military hospitals.

Obviously, due to the different orientations of psychiatrists, a number of difficulties were encountered when the patient register was devised. In 1970, after extensive and prolonged testing, the basic recording system was accepted by the Indonesian Ministry of Health (Directorate of Mental Health) and the International Committee Against Mental Illness (ICAMI), New York for use on a nation-wide scale.

II. GENERAL OBJECTIVES

A number of general objectives of the recording system is given here:

1. *Provision of an efficient recording and reporting system.*

In the past, patient records and reports were made by conventional methods: records were filled in by hand by attending doctors and periodic reports were laboriously made by administrators. Apart from the illegibility of most doctors' handwritings and the diverse systems of keeping records in different hospitals, to make comprehensive reports from non-integrated and non-uniform records which are not comparable, is an arduous if not a futile task. The use of a General Purpose Psychiatric Questionnaire (GPPQ) which limits itself to factual information, systematically arranged, from which neatly typed narrative print-outs of patients' case histories in summary style can be obtained, provides an obvious advantage over traditional methods. This is especially true for those hospitals which are heavily understaffed and where doctors simply do not have the time to write down patients' histories. Statistical tabulations derived from the wealth of data contained in these questionnaires can be made within minutes, reducing many man-hours of arduous manual work in various hospitals and the Directorate of Mental Health.

2. *New ways for research*
   Since data material is obtained from all areas in the country, comparisons from one area to another can be made. Quality of services can be compared, appraised, and improvements suggested. Hospital based epidemiological research from these data with implications for planning and the development of services, or for further social studies can be made. These preliminary findings may stimulate more specific and sophisticated epidemiological studies. It should be noted, that aside from hospital based studies, community surveys can also be done using this questionnaire.
3. *Information on socio-cultural background.*
   Indonesia has a rich diversity of cultural patterns contained in a vast geographic area. Information concerning different aspects of these socio-cultural groups and their relationship to or the generation of mental illness may shed some light on still unsolved or even unknown problems. More effective community mental health education can be given, directed to groups which seem to be most vulnerable to mental illness.
4. *Uses for administration and planning.*
   Data of interest for hospital administrators may be obtained from these records. Changes in patient load and admissions, seasonal trends, requirements for treatment, manpower requirements can immediately be seen from reports. All this greatly facilitates administrators' work especially for planning and making adjustments.
5. *Uses for education.*
   Completion of these questionnaires is in itself an educative experience. The necessity of framing questions more accurately is a common experience among doctors and social workers. The application of criteria used in the questionnaire may be very beneficial for a more productive communication among psychiatrists or general practitioners.

III. DATA MATERIAL FOR THE GPPQ

The material is divided into two major sections:
Part I: Socio-cultural information (including administrative and personal information.
Part II: Medical information prior to admission.

Part I includes the following data:

1. *Personal and administrative information*, such as name, identification number, address, age, sex, place of birth, name and identification number of hospital, date of admission, doctor in charge, source of referral, source of history, etc.
2. *Environmental background*, such as persons residing in patient's family home, place of upbringing, siblings, etc.
3. *Patient's parents*, such as whether they are still alive, divorced, separated, have remarried, etc.
4. *Educational level and schooling.*
5. *Marital information*, such as marital state, divorced, number of marriages, age at first or present marriage, etc.
6. *Employment*, such as primary occupation, income level, work history, patient's household provider, training and ability for present work, etc.
7. *Housing conditions.*
8. *Composition of household*, such as size of family, other relatives living in one household, etc.
9. *Religion*, such as nominal religion, attendance to religious activities, religious observance, etc.
10. *Community activity.*

Part II includes the following data:

11. *Duration of present episode.*
12. *Rapidity of onset* of present episode.
13. *Remissions*, number of prior episodes, prior hospitalization, precipitating factors, suicidal attempts, etc.
14. *Drug or alcohol dependence.*
15. *Intelligence level* of patient and family history of mental illness.
16. *Family attitude* towards patient's illness.
17. *Criminal behaviour.*
18. *Convictions* and types of punishments.
19. *Diagnosis* on admission.
20. *Prognosis.*
21. *Treatment* prior to admission.

Part I consists of 8 pages and can be completed by either the attending physician or a social worker. Part II, however, because of the nature of information required should be completed by doctors only. Although in the beginning the process of gathering information may be time-consuming, after some experience this may be reduced to app. 20 min. Part II which consists of only 4 pages may take only 5 min.

IV. SEQUENCE OF EVENTS

This Recording System Project (RSP) was initiated May 22, 1968, but due to circumstances it was not until October 9, 1970 that a RSP team was organized (*)

During the first initial phases the original English version of the General Purpose Psychiatric Questionnaire (GPPQ) made available by the International Committee Against Mental Illness was adapted to more specific Indonesian needs. The original optical reader form (Appendix I) was redesigned into an Indonesian language data sheet (Appendix II) for use with keypunch cards. Deletions, alterations, and new additions were made. Agencies where automatic data-processing could be carried out were consulted. An IBM 360 model 30 computer with 64 K of memory is used in this project. (**) During this phase a three months' trial period was introduced (January 1, 1971 – March 31, 1971) for all the mental hospitals on Java and Bali. Based on this experience, results were assessed and corrections were made.

During the second phase (April 1, 1971. – March 31, 1972) the project was firmly established on Java and Bali.

During the third phase (April 1, 1972 – November 30, 1972) the project was extended to the other islands of the Indonesian archipelago (Medan in North Sumatra, Banda Aceh in Aceh, Padang in West Sumatra, Palembang in South Sumatra, Pontianak in West Kalimantan, Samarinda in East Kalimantan, Banjarmasin in South Kalimantan, Ujungpandang in South Sulawesi, Manado in North Sulawesi, and Abepura in Irian Jaya).

Corrections in the Novel programme affecting the print-outs were done. Another computer programme which was felt to be more adequate for Indonesian needs was completed. (*) This programme will be instituted at a later date.

V. ADMINISTRATION OF THE SYSTEM

This system is adopted as regular procedure by all the mental hospitals and psychiatric units in general hospitals in Indonesia, regardless of whether they choose to retain their individual methods of keeping records. (**) A central body, in this case, the Directorate of Mental Health, Jakarta is responsible for this project. All data sheets are completed by physicians working in the various psychiatric facilities, sometimes assisted by psychiatric social workers or nurses. These documents are then passed to a local hospital secretary (local GPPQ coordinator) who checks for errors in these data sheets, and mailed to the Directorate of Mental Helath. The record section of the Directorate of Mental Health pools these documents, checks them again for errors, and forwards them to the keypunching centre. Punch cards which contain all the data are then fed into a computer which gives neatly typed narrative print-outs (Appendix III and IV). These print-outs are returned to the hospital of origin. One copy is left in the record section of the Directorate of Mental Health which at present is temporarily staffed by four part-time workers. Two doctors

(*) Members of this team were: Dr. Kusumanto Setyonegoro – Project Supervisor, Dr. Ashton M. Tenney – ICAMI consultant, Dr. Indro Suwandhi – computer consultant, Dr. Heraty Noerhadi – psychologist, and Dr. B. Sadono and Dr. R. Salan – Project managers.

(**) At Present an IBM 360 model 40 with 128 K of memory is used.

(*) This computer program which contains supplementary information on symptomatology and is updated in diagnostic categories is made by ICAMI consultant Dr. Zebulon Taintor.

(**) There are several facilities, formerly, called "psychiatric agricultural colonies", which are temporarily excluded from this project because no doctor is available for the completion of the records.

are in charge of management, budgeting, and correction of errors in the data sheets. One secretary answers incoming mail and makes periodic progress reports, and another assistant collects the documents to be passed to keypunch centre, computer, and returns print-outs to various hospitals. At present print-outs contain case histories in English as well as Indonesian. To ensure a smooth flow of information from the hospitals to the Directorate of Mental Health and back, it is evident that certain community services must be reliable e.g. the postal system.

The project is financed by the Directorate of Mental Health Consultantships are provided by the International Committee Against Mental Illness.

VI. RESULTS AND EVALUATION

The tables presented in this paper cover the period as of January 1, 1972 – June 30, 1972. Since so many expenses are involved in this project and so much effort poured into it, it would be reasonable to ask what conclusions can be drawn from the data presented in these tables, e.g.: What type of patients are admitted to the mental hospitals in Indonesia? What is their general background, educational, environmental, cultural, or otherwise? What kind of diagnoses is made?

Direct and "clearcut" answers to these questions are difficult to formulate due to a number of factors: The number of patients presented here is too small and limited to patients admitted to hospitals during one semester only. It is possible to envision that data which are more conscientiously recorded, and which are gathered over a period of several years, and to which more elaborate statistical analyses have been applied, may give a more accurate and reliable picture. It may very well be that a quite different picture than the one presented here will result. Different geographic areas and cultural patterns will put their own characteristic stamp on the patients, which again can make overall evaluation rather difficult to appraise. Furthermore, the patient population of private mental hospitals can differ in a number of characteristics from the patient population of State Mental Hospitals, military psychiatric facilities, or other specialized units. However, with all these reservations in mind, a very tentative attempt to suggest a generalized idea of the profile of the Indonesian patients admitted to Indonesian hospitals – whatever risk this may involve is very stimulating.

There are more male than female patients admitted to the hospitals. The majority of these patients are Moslems between 16 – 32 years of age. Curiously enough, almost all of them have been brought up in the family home. Their place of upbringing may be either urban, rural, or suburban depending on the location of the hospital. A general characteristic of interest here is that most of these patients are referred by the family. Only a small portion are referred by psychiatrists or family physicians. Almost all the patients speak the areas' dominant language. The occupation's prestige value and income level of these patients may be either low or medium. A relatively small percentage of patients have a high occupation's prestige value or income level. They may be either married or single and there seems to be a low degree of divorce among them. Data also show that the duration of illness of most patients is less than 6 months. Analyses of first admissions will in this context be more meaningful. As to diagnostic category most patients are schizophrenics, but this category may vary depending on the type of hospital, whether these are private or provide specialized care.

The tabulations also show that until June, 30, 1972, twenty-seven facilities have joined the project. However, some facilities were late in submitting the questionnaires, which account for their absence in the tables. This delay has been mainly caused by local administrative difficulties where adjustments to the system have as yet not been satisfactorily accomplished. A system of local GPPQ coordinators who work on a part-time basis does not seem to work very well especially for overburdened hospitals. Experience has shown that checking for errors, and other administrative duties tied to this kind of recording system, such as filing, coding, etc, is a full-time job. It should be reminded here, that much time of the doctors can be saved by having social workers or nurses do the job of completing Part I of the questionnaire. Another difficult matter which is closely related to organization and division of labor in hospitals is the problem of recordings made of patients who were admitted on an emergency basis or after working hours. This problem is more acutely felt by hospitals far away from the residences of the patients' family. These emergency cases are usually admitted in the late afternoon or at night, where doctors or other personnels are difficult to reach. In many cases unfortunately history taking was not very specific. At times, families never visit the patient again, so that the examining physician only meets them at the time

therapy is terminated and the patient is ready for discharge. In such instances the completion of the questionnaire will have to wait long periods of time. Obviously, such rather uncooperative family attitudes do harm the accuracy and the reliability of the data.

VII. CONCLUSION

It is evident that an integrated patient recording system using electronic data-processing on a nation-wide scale is possible and has certain advantages. However, the availability of electronic data-processing hard-ware as well as soft-ware, or agencies which can provide processing services on a computer-time basis is an essential requirement. Since the amount of data-processing of such a project will only take a few hours weekly, the installation of an electronic data-processing unit is impractical and relatively too expensive. It is also clear that such a recording system greatly enhances more systematic communication between the Directorate of Mental Health as central directive agency and peripheral psychiatric facilities. In this manner, a more integrated and balanced approach to mental health problems will develop and their possible solutions will be found.

It is also gratifying to know that the Indonesian government has realized the importance of this project and has given full support for its continuation.

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THE NURSE AND PSYCHOTROPIC MEDICATION

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INTRODUCTION

This paper examines the psychological aspects of the nurses' interpersonal relationships from the standpoint of her role in serving medication. The psychodynamics of interpersonal relationships between medical nursing and paramedical staff with the patients are of tremendous interest and its study can be rewarding for all concerned in the therapeutic community. The author puts together some of the experiences and opinions of assistant, staff and student nurses and sisters in a psychiatric unit. The points mentioned in this paper arises from group and individual discussion in the ward and perhaps a well constructed research could be formulated to study this area of human interaction to promote greater efficacy in "modern milieu therapy" (Abroms, 1969).

Patient-Nurses Relationship

The presence of psychiatric units in a general hospital and the use of effective psychotropic medications in recent years have changed the nurse-patient relationship from one of dominance-submission to one of understanding, emotional

involvement and therapy. Where previously external controls on psychiatric patients were necessary and they were given custodial care, the introduction of phenothiazine drugs gave a form of internalised control to the patient. The act of giving medication very often establishes or maintains relationship between a nurse and a patient. So much emphasis is given nowadays to gain a patient's rapport". In a busy psychiatric unit the positive and negative aspects of this rapport and the transference and counter-transference between nurses and patient can be centred on the deliverance and acceptance of medication.

Responsibility in Serving Medication

To begin with the nurse has to understand the patient's problem and the nature of the medication he receives For example, the nurse would be helped considerably if she reserved the serving of medication to paranoid patients towards the end so that she is not frustrated in the beginning of her rounds serving medication and also the paranoid patient has the opportunity to see other patients taking medication from her. In the case of suicidal patients the nurse have to learn the art of ensuring that the patient swallows the tablet without showing the patient that she does not trust him to do so. The nurse has to be aware of the symptoms and signs of the possible side effects of the drugs and report them to the doctor promptly when detected.

Special problems in the Psychiatric Ward

Unlike other wards where patients are usually physically ill and incapacitated in bed, sometimes with the bed number and names of the patient beside the bed, the patients in a psychiatric ward are ambulant. The nurse has to make an effort to remember the names of the patients. In the case of several new cases in one day she has to counter-check that the patient is actually answering to his own name when called for medication. Similar names and similar faces can result in a patient receiving another patient's medication. Again, during the time of serving medication the patient may be in one of many places, thus the nurse has to look for the patient and those who are not present in the ward, their medication has to be kept aside in a safe place till they return to the ward.

When the patient's identification of the nurse as a significant personality in his own life can lead to his taking medication from one nurse but not from another. The nurse has to be aware of the patient's tendency to project (Teoh, 1972) and she should feel less threatened when a patient refuses her medication. Nurses need also to learn about their own tendency to identify with the part which the patient tries to force them to play. Failure to realise this will unnecessarily foster faulty patterns of behaviour, nurses acting unconsciously as if they were the strict parents, jealous siblings, overpossessive wives, etc.

Sometimes patients have valid reasons for refusing medication – they complain of the side effects – giddiness being the commonest, dryness of mouth, constipation, etc. The nurse is understandably in a difficult position when the patient says, "I will not take this tablet because it will make me feel giddy and when I want to sleep you all will not allow me to have my bed!", or patients begin to question the efficacy of the drug because "I am still the same after taking this medicine". In short, it is not easy to give a satisfactory answer to the patient; the attitude of the nurse in giving medication becomes all important.

Sometimes the seniority or attractiveness of the nurse also counts. Very often a nurse from a general medical ward transfered to work in the psychiatric unit is very much taken aback by patients disobeying her instructions and labels the patient as 'uncooperative' and difficult. Again the suspicious patient will question the nurse as to the change in the number of tablets, the change in colour of tablets and even the difference in time the medication is served.

Frequently, the nurse who has difficulty medicating patients, tends to be ineffective, vague and uncertain in her proposition. If the nurse acts as a central focal point in the ward for patients, confidence in her is likely to be engendered and patients more likely will trust her. The reciprocal response to an uncertain nurse serving medication is devastating to a paranoid patient.

The nurse has to have the patience and confidence to explain and impress on the patient that he is receiving the right medication in the right dosage and at the right time, that the same drug can be in different colours and two small tablets could add up to the strength of one big tablet. More difficult still is the situation when the patient states categorically that "the doctor gave me a different medicine yesterday" – this almost challenges the whole position of the nurse and can provoke anger in the nurse.

The personal handing out of medication by the doctor to the patient is most effective in patient-doctor contact. It is the intermediary relationship that can be disruptive. If most psychiatrist could

personally serve medication, the cultural impact on therapeutic acceptance is tremendous. However, this is not possible and the nurse has been entrusted to perform this duty with presumably less impact. Hence, when a doctor is asked to serve medication because the patient refuses to take it from the nurse, it is best that he coaxes the patient to take the medication from the nurse, since this would reinforce the therapeutic role of the nurse.

Emotional Feedback on the Doctor

The majority of our nurses have undergone an educational system in which the teacher is always right. The teacher-centred teaching leads them to feel that the doctor is always right and that they work under doctors. The whole question of whether nurses feel comfortable in questioning the medication prescribed by doctors is rather interesting. Where the doctor-nurse relationship is left much to be desired, the nurse adopts the attitude that the doctor will not listen to her. The patient may have shown no improvement to one phenothiazine drug in the last 10 days and in frustration the nurse writes in the progress notes "Patient remains the same. Dieted well. Slept without sedation." When she would have actually preferred to say "Please try another phenothiazine".

In the agitated patient the nurse can be very upset during her night duties if she hears the afternoon nurse reporting that "the patient has been so terrible the whole day but his medication has not been increased. I think you better give him i.m. before he gives you trouble". Nurses should be encouraged to suggest to doctors any change of medication they feel necessary and the doctor in turn has to discuss with the nurse the pros and cons for a change.

It is a paradox that the nurse who spends most time with the psychiatric patient has least therapeutic responsibility, while the physician who spends a few minutes with the patient makes all the major decisions for the patient. Furthermore, we have to take cognisance of the fact that nurses are expected to have initiative and be responsible for making significant recommendations, while doctors accepting advice from non-medical staff is highly threatening to their feeling of omnipotence. Hence the way out of this bind, as is frequently seen, is that the nurse must communicate her recommendations without appearing to be making a recommendation statement and the physician in requesting a recommendation from a nurse must do so without appearing to be asking for it. This "doctor-nurse game" (Stein, 1967) has an inhibiting effect on open dialogue and is stifling and anti-intellectual and obviously is contrary to the concept of psychiatric personnel being counsellors in helping patients communicate effectively in their daily lives.

We have to also take into account the fact that the nurse may hesitate to speak openly of her feelings about the patient's medication, fearing consciously or unconsciously that her prejudice or tendency to have favourites may become obvious to all (Jones, 1968).

Intramuscular Paraldehyde

Where the patient is clearly violent the doctor has no compunction in ordering paraldehyde and the nurse has no hesitation in its administration. However, in the case of personality disorders with hysterical acting out behaviour or behaviour that disturbs the peace of the ward the nurse has to decide whether she should give i.m. paraldehyde which had been prescribed on a prn. basis. A conflict exists in the mind of the nurse as to whether to be punitive in her actions or try a less painful corrective measure. Soon she may lose patience due to pressure of work and she wonders whether her senses have been so dulled that she has become even sadistic in her liberal use of paraldehyde. This can be very disturbing to the emotional stability required of the nurse. She begins to worry about her relationship with other patients as they watch her use physical force to administer the injection.

Where previously the dominance-submission role of the nurse-patient relationship existed prior to phenothiazine therapy, vestiges of such an authoritative control still exists in most large institutionalized hospitals. Chronic psychiatric patients tend to be given a much larger dose of chlorpromazine than is required. It is a sad fact that the Victorian attitudes to mental illness still exists, and nursing staff can utilize a new therapeutic agent – psychotropic medication – not as a means of cure, but as a means of control of psychiatric patients.

The Pharmacy's Role

Doctor's prescriptions having to be sent to pharmacy department for supply poses problems to the nurse. There is the question of whether the drug would arrive in time or even after a long wait to be informed through the phone that the medication is not in stock. Where a new drug is being used, information on the drug should be circulated amongst nursing staff. The success or

failure of a drug trial depends much on whether the nurses are aware of what difficulties the patient may present when placed on this new drug and if so, what special measures are available to handle these difficulties.

Other problems

Apparently minor problems like illegible handwriting on the part of doctors, failure of doctors to obliterate drugs when discontinued and the haphazard use of chemical or proprietary names of drugs can add to the discomfort of the nurse (Martin, 1967). The drugs prescribed for the last admission when the patient was manic could by mistake be continued on his readmission for a depressive episode if the old medication card is used again before the doctor prescribes for the second admission. Constant interruptions during a nurse's medication round can be extremely irritating for her. Night sedation is a thought provoking subject; the over-anxious nurse gives the sedative at 9.00 p.m. and as a result the patient is awake at 3.00 a.m. while at the other extreme the giving of sedation at 1.00 a.m. results in confusion at breakfast time.

The Value of Medication

Nurses in their general training may have the value of medication over-emphasised in their performance of duties. Although psychotropic medication plays an effective role in management of patients it is not the only treatment nor always the best treatment available in psychiatry. The patients should have some idea of the possibilities and limitations of different forms of treatment. If the staff relies too exclusively on physical treatment patients are liable to expect far too much from them. If on the other hand the nurses communicate their awareness of the importance of environmental and psychological factors, many patients will soon realise how many different avenues of help are open to them and make fewer demands for magical cures through medication alone (Martin, 1962). If the nurse understands the patient, the drug involved and the other therapeutic requirements of the patient then she is in a much better position to play her role when administering drugs to their fullest therapeutic value.

SUMMARY

This paper examines some aspects of the role of the psychiatric nurse in administration of psychotropic medication.

The patient-nurse relationship is very much affected by the serving of medication and with emphasis of the therapeutic role of a nurse in a psychiatric unit several factors are worthy of discussion. To begin with, the nurse has her responsibility in understanding the patient and the drug he is served. She has to face the special problems involved with psychiatric patients in the unit – the patient's drug refusal, his identification of the nurse and his preferences between nurses.

Arising from the nurse's difficulty in administration of psychotropic drugs her relationship with the doctor is affected. Whether a nurse is able to disagree with a doctor's prescription or even voice her opinion regarding the efficacy of the drug already prescribed is of importance in the management of the patient.

Problems of another nature arise in the question of giving i.m. paraldehyde night sedation and drug trials. Sometimes doctors presume that what is prescribed will be served by the nurse and accepted by the patient. Many more factors are involved and it is hoped that this paper will add some food for thought into this largely unexplored area in psychiatry.

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USE, MISUSE AND ABUSE OF STIMULANTS IN MALAYSIA

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Identification patterns of abuse and misuse of stimulant drugs of the amphetamine type have been established since their advent about four decades ago. For many persons, these substances have dependence producing characteristics which can bring about serious clinical and personal problems. Abuse of these substances arises from and is perpetuated solely by psychic needs to overcome depression or fatigue or to attain the euphoric and excitatory effects associated with the drugs.

The actual incidence and prevalence of cases of drug dependence of the amphetamine type in Malaysia is obscure. Our clinical experience indicates an increase in amphetamine abuse. The degree to which the abuse of stimulant drugs stems from over prescribing or from illicit source is unknown. However the problem is serious enough to warrant the concern of the medical profession in Malaysia and an examination of use, misuse and abuse of the stimulants. There has also been an increase in the abuse of central nervous system depressants and heroin.

USE AND MISUSE

The indications for the medical use of stimulants are subject to varying degrees of professional dispute. The argument based on both scientific and ethical points, is centred on the efficacy of these drugs as well as on the jeopardy involved in initiating a treatment regime that, in vulnerable personalities can result in the development of psychic dependence and tolerance. Stimulants are presently employed in certain therapeutic regimes entailing prolonged continuous medication. If medical use is not to become medical misuse, any such treatment should be subjected to the discreet assessment and careful management of the patient. The physician should be wary of their dependence producing potential and recognise that some patients may seek other sources of supply either illegally or from another physician.

In the past two decades, a number of amphetamine-like substances have been used as anorexiants and have been prescribed for the treatment of obesity. These drugs also stimulate the central nervous system to varying degrees and therefore have a potential for psychic disturbance and dependence. Particular scrutiny should be given to patients who request amphetamine type drugs for weight control.

Amphetamines appear to be effective for few individuals in acute stress situations with symptoms of mild depression. This mode of treatment is futile without simultaneously instituting other therapeutic efforts aimed at alleviating the underlying emotional disorder. Authenticated evaluation reveal that dextroamphetamine in general is only slightly more superior than a placebo in ameliorating depressive symptoms. The use of stimulants to antagonise drug induced depression in acute poisoning may be desirable but not proper to use for prolonged administration in alcohol or barbiturate dependent persons. This permits the patient to take increasing amount of depressant drugs — a habit which can result in physical and mental deterioration. In fact, the use of amphetamine drugs is contraindicated for alcoholic and other dependent prone persons. When a physician prescribes stimulants, he should do so for a limited time and for a specific purpose.

Not too infrequently are physicians requested to prescribe stimulants for a variety of non-medical reasons. Sports is one field where such requests are made. Amphetamines can drive trained athletes to increased performance in individual events involving strength and endurance but this practice can, by artificially pushing the athlete beyond his normal capacity be detrimental or even fatal. This also violates the principles of sportsmanship.

In the field of horse-racing, jockeys who abuse amphetamines are prone to accidents because of both the excitation produced by these agents and the excessive fatigue which may break through and manifest itself at an inopportune time.

They may also be asked by students preparing for examinations, by executives facing a strenuous business week, some aspiring sexual athletes who wish to enhance their sexual prowess or by taxi and lorry drivers making long hauls, and night-club singers and dancers who are in the show business and career persons on shift duties.

It should be stressed that amphetamines are no

"touch stone" source of extra mental or physical energy. They only goad the user to a greater expenditure of his own reserves, sometimes to a crucial point of depletion and fatigue that is often not appreciated. With or without amphetamines, automobile and truck drivers and air pilots who continue beyond their physical and mental capabilities jeopardise their lives and lives of others. Students who resort to stimulants for all night vigil, not only burn the midnight candle at both ends but do so in the centre as well. This is a breach of sound educational practice. Though stimulants may increase volubility during examinations, there is a concurrent loss of accuracy.

Since occasional use may not harm the individual or lead to antisocial behaviour, it is a matter of conjecture whether this practice should be judged as use or misuse.

However, these situations are of a different order of magnitude and the persons desiring "help" cannot be considered sick and in need of medical treatment in the usual sense. There is also the danger that the efficacy of a stimulant in helping a person achieve a time limited goal may predispose the person to lean upon amphetamine type drugs as desirable rather than dangerous substances and thus may open the door for future abuse.

ABUSE

A startling aspect of drug taking in Malaysia is that there is a great deal of experimenting with amphetamines among youngsters. Many of these persons combine stimulants with other drugs, alcohol (toddy, samsu), ganja (marihuana), Barbiturates, methaqual one (Mandrax), morphine and heroin. Not infrequently serious addicts abuse stimulants by intravenous administration for the express purpose of experiencing the bizarre mental effects, which may result in antisocial behaviour.

A professional resigned his job on the spot by foregoing a month's pay, sold his car for a song and flew to San Francisco where he made such a social nuisance of himself that he was immediate ly deported. More often they are taken orally in the form of amphetamine barbiturate (purple hearts) or amphetamine-methaqualone (Biji Kena) Patterns of self medication with amphetamine-type drugs are varied. Some start taking stimulants to neutralise effects resulting from abuse of barbiturates or alcohol, thus developing cyclical pattern of sedation-stimulation, in which to a degree, each type of abuse counterbalances the effects of the other. Other persons try to achieve both effects simultaneously. In these cases, the clinical problem is of a dual nature. Other dependent persons, who became chronic abusers were introduced to stimulants as ahorexiants or to combat fatigue or depression. When the rubber price was at its lowest ebb, some rubber tappers resorted to stimulants to work long hours at more than one occupation to bolster the income. After a hard day's toil, they used to wake up early in the morning to tap as they believed that the yield is greater if tapped in the pre-dawn era. Some developed a mild form of psychic dependence in which, although believing that the drugs are essential to maintain their daily routine, they do not increase the dosage much beyond usual therapeutic limits. The more prevalent pattern of abuse is the one in which the person self-administers the drug with increasing frequency and increasing amounts to get the desired euphoric effects. The paramount danger of self medication is that the abuser often is incapable of accurately evaluating his performance and likely to overmedicate – a habit that in neurotic or dependence-prone persons, often leads to chronic abuse.

PSYCHIATRIC CONSIDERATIONS

Abuse of the amphetamine-type drugs almost invariably reflects some underlying forms of psychopathology. Amphetamine dependence is a symptom complex that usually reflects some form of psychological and behaviouristic disorder that has preceded and predisposed the patient to drug abuse. The stimulant is commonly used as an 'adjustive' mechanism to help the person "cope" with problems of living and emotional difficulties. Abuse constitutes a "reaching out" for something without which the patient feels relatively helpless and there is a continuum between what constitutes ill advised "self medication" and full abuse.

The underlying reason for drug abuse varies from person to person and the drug may serve different purposes at diverse times for the same patient. Usually the amphetamine-dependent patient is consciously or unconsciously, seeking to attain one or more of the following effects: relief from fatigue, increased mental alertness, heightened sense of well being and relief from the emotional tone of depression.

Dependence of amphetamine like substances is generally a chronic relapsing disorder. The treatment goal should be abstinence. Irrespective of the relapse, continual treatment of the patient's state and underlying emotional disorder is essential. Withdrawal of drugs of the amphetamine type is never threatening to life and requires psychological rather than somatic therapy. Although there

is no characteristic abstinence syndrome, abrupt withdrawal can reveal a masked depression or it may precipitate a Depressive Reaction with a suicidal potential in some cases. Because of the ever increasing frequency of multiple dependence patterns, the physician should make every effort to ascertain the patient's drug history before attempting withdrawal. As indicated, the amphetamine abuser often is taking barbiturates or heroin in combinations or separately and if so, procedures should be instituted to withdraw him from them.

Amphetamine intoxication can precipitate a schizophrenic episode in some, especially latent psychotics. In other persons, an acute and florid paranoid psychosis is produced called amphetamine psychosis. This is characterised by variable amounts of anxiety, auditory and visual hallucinations and feelings of reference. They do not exhibit the specific dissociated and autistic disorganization of thinking associated with schizophrenia. Without definitive or supportive treatment and after care relapse is frequent resulting in hospitalisation. Fluphenazine Enanthate, Thioridazine and Diazepam are used in varying doses as per physical tolerance and clinical response. This phenomenon was recognised as early as 1938 and there is an excellent report on this subject by Connell.

AFTERCARE

Psychiatric help should be sought be obdurate cases where indicated and feasible. In the absence of such referral, the general practitioner should administer those forms of psychotherapy that he is qualified to provide. In cases in which it is not possible to give specific therapy, the general physican can function effectively in a supportive and rehabilitative role. Physician leadership is essential to sound community education and prevention programmes and also in creating a climate where drug dependence is regarded as a medical problem as well as one involving social and law enforcement agencies.

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IMPORTANCE OF CEREBELLAR DYSFUNCTION IN TREMOR MECHANISM

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Introduction of l-Dopa for treatment of parkinsonism has given us the new powerful weapon for analysing the mechanism of symptoms, such as rigidity, tremor and akinesia, in addition to experiences of the stereotaxic neurosurgery

Here specially, the generation of tremorous movement will be discussed.

1. Attitude of tremor in response to l-Dopa therapy is observed quite differently in each case. In about half of the cases of parkinsonism with various grades of tremor, tremor is abolished or markedly reduced. But in other cases, tremor is not changed or influenced at all or even seems worsened. In such uncommon instances, amplitude of tremor becomes larger and less easy to control voluntarily. We had then the working hypothesis, whether the phenotype or pattern of tremor would be dependent on the grade of muscular rigidity, the latter being more definitely improved or alleviated by l-Dopa therapy.
2. In about twenty years experience of human stereotaxic surgery on the thalamus of parkinsonism, we are very confident that rigidity and tremor are slightly differently located.

Rigidity is easily increased or decreased (abolished) by stimulation or destruction of the ventrolateral nucleus (VL) of the thalamus and tremor is by Ventralis Intermedius nucleus (Vim). VL specially, mainly receives fibres from the pallidum and the Vim, which is posteriorly located to VL and anteriorly to the thalamic sensory nucleus, receives more fibres from the cerebellar dentate nucleus. These may lead to the assumption that interrelation between these two different anatomo-physiological systems may be important for the phenotype of tremor. And it is also hypothetized that a certain level of hypertonus must be important for manifestation of tremor.

3. To prove these, the series of monkey experiments were performed. Three monkeys were cerebellar-hemispherectomized including their deep nuclei (mainly dentate nucleus) and one unilaterally. In all four, the midline vermal structures with deeplying fastigial nuclei remained intact.

   These monekys were then kept and fed chronically at least for four months.

   When the harmaline was applied intramuscularly, normal control monkeys did show stiffness of muscles with forebent posturing and shivering-like shaking. But when the same dosage of medicine was given to the chronic operated monkeys, they start to show marked tremorous movement resembling parkinsonian one, as will be shown on the 16mm film.

   On the other hand, for the purpose of facilitating the pallidothalamic system, the VL nucleus was electrically stimulated by 60 c/s, 8 – 12V, and 1 msec, and the typical 5 to 6 c/s resting tremor started to appear, which could not be obtained in normal control monkeys.

4. These experimental observations in animal and experiences in human cases suggest the understanding that tremor may appear on the combined basis of some facilitated state of pallido-thalamic system and also of chronic dysfunction of the cerebellar hemispheric circuit. The latter may involve the rubro-olivo-dentate-rubral pathway, as suggested by Poirier.

PSYCHO-SOCIAL AND THERAPEUTIC PROBLEMS RELATED TO EPILEPTIC PERSONALITY

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As we know, epilepsy, under all aspects, may produce grave difficulties on the patient's relationship to his environment, psychologically as well as socially. These problems will be easily or hardly solved according to the extent of tolerance of society. Hence, we just deal with the out-patients (not the institutionalised ones)—those who, although quite able to live in family or society, show some abnormal personality traits and characteristics. We consider 2 cases.

1. Characteristic Abnormalities Observed in:
   A) *Epileptics with Clinical Seizures:* Among them 40 – 90%, according to the duration of their disease, have the following traits and characteristics.
   a) *Instability on mood and activity* is the predominant disorder. Epileptic children are often overly aggressive, restless, overactive, moody, stubborn, over-sensitive, while the adult patients have a rigid, unpleasant, irritable personality and may then manifest sudden emotional outbursts in response to apparently slight stimuli, and unconsciously provoke conflicts in their family and office.
   b) *Viscous affection to objects*, persons and traditions related to a certain mental slowness from which a contraction of

interests is originated, will develop a self-centred personality. So, the patients often suffer with or without reason, from frustration, social rejection, constant anxieties.

These feelings make them become maladjusted in their environment and may create anti-social tendencies.

B) *Epileptics Who Have Neither Clinical Syndrome (Seizures) Nor Constant Typical Records of EEG but an Abnormal Behaviour*

It must be remembered that some outpatients, never suffered from seizures of any kind, show minor dyschythmia in the EEG and in the others (the percentage seems greater) the EEG is almost absolutely normal. So we can think about possible epilepsy, through their abnormal behaviour, before obstinate patients indefinitely discussing, unable of any control, obsequious, becoming easily exuberant or in the contrary taciturn, often honeyed and clinging, endlessly calling for attention and care, and suddenly manifesting violent and explosive reactions.

II. *Psycho-Social Problems related to Epileptic Personality*

A) *In Family Life*

Conduct disorders observed in Epileptic children are often produced by faulty attitudes such as rejection or overprotectiveness, on the part of their families. Consequently, it is necessary to bring them up in a way as normal as possible. Of course, it is not easy because parents should be able to react, with the knowledge of the elements of the child's personality which still remains intact. So they must receive from pedo-psychiatrist and social workers, advice concerning the education of these epileptic children.

Epileptic Adults often show feelings of inferiority, frustration, discouragement and hopelessness arising from a bad home environment. They live with a permanent tension, in an emotional world to which they cannot adjust themselves and which also hardly accepts them. For the married patients, familial conflicts are related to these reasons:

1. The fear or the mistrust of the partner who often has not been prepared to face the difficulties caused by the patient's character.
2. the feeling of inferiority and guilt of the epileptic
3. the rejection of the relations
4. the fear of giving birth to a possible epileptic child by heredity.
5. the side effects of medicine, particularly to sexual activities, such as impotency in the husband and frigidity in the wife.

B) *In Office*

The patient's work efficiency diminishes because of

1. the risk of accident (fall, burn) in manual career. Known as dangerous and involving responsibilities (driving a car). It can be reduced by a judicious choice of job and a severe medical control.
2. Intellectual deficiency
3. Non-adapting character
4. Prejudices of their colleagues

These above facts lead epileptics to

- absenteeism
- conflicts with their co-workers or even their boss under the form of fighting or frequent job alterations
- alcoholism used for relief of emotional stress which has been induced by their professional troubles. But the abuse of alcohol is known to provoke seizures, aggressive behaviour leading to delinquency, so that an absolute abstinence is necessary.

III. *Therapeutic Aspects:*

Many epileptics, thanks to actual medicine, may live as normal citizens, provided that they should follow appropriate treatment, and most important, have to be accepted heartily by their family and society.

In the view-point of therapy, 2 aspects have to be considered:

A. *Supportive Psychotherapy* aims to maintain contact with the patients and relieve them of their emotional difficulty by reviving their feelings of security and self-esteem, helping them to adjust themselves with their environment.

B. *Psychotropic Medication* used to modify behaviour:

a) *Major Tranquillizers:* among them chlorprothixene (Taractan) seems to be the most effective against characteristic abnormalities on the epileptics (15–60) mgm

per day)

b) *Minor Tranquillizers:* We distinguish

1. *Benzodiazepines*
   - Chlordiazepoxide (Librium: 10–30 mg per day)
   - Diazepam (Valium: 10–30 mg per day) have been used for relief of anxiety and tension and occasionally to subdue seizures.
2. Carbamazepine (Tegretol: 400–1000 mg per day) seems, besides its anti-convulsive effect, to give excellent results against Epileptic characteristic abnormalities especially on Psychic slowness, mood changes, irritability and anxiety. So it increases the patient's ability to deal with difficult situations and consequently helps them to adapt themselves in their family and society. This report is the result of a one-year study (April 1972 – April 1973) of a metropolitan out-patient clinic which is in charge of:
   - treating new patients
   - transferring agitated ones to the Psychiatric Hospital of Bienhoa
   - following up discharged patients.

The total number of patients treated in one year is 3,216 and is allotted as follows:

male adult patients	1,460
female adults patients	1,458
male children patients	143
female children patients	155
Total	3,216

Among those patients, we see about 106 epileptics. Apart from their common personality traits and characteristics we found:

96 Epileptics with clinical syndrome (3.5%)

10 without clinical syndrome and this consists of
4 with minor dyschythmia in EEG
6 with normal EEG

The above figures are not highly accurate because of restricted time spent for observation. It is just worthwhile as indicative value. There were difficulties in obtaining regular medical supplies, therefore any appropriate medicine available had to be used. Only 20 out of 106 epileptics had been treated by Carbamazepine (Tegretol) for a short period of time. Therefore the results could not be considered as definite.