International Journal of Neurology

ISSUE DEDICATED TO:

BIOLOGICAL PSYCHIATRY

VOLUME 6 NUMBER 1

INTERNATIONAL JOURNAL OF NEUROLOGY

CONTENTS OF VOL. 6 — NUMBER 1

Editorial

Paralelamente al extraordinario progreso en el conocimiento de afecciones psiquiátricas, vinculado a las investigaciones acerca de los mecanismos psíquicos que comandan la actividad mental normal y patológica, se vienen desarrollando valiosísimas conquistas basadas en el empleo de distintas metodologías biológicas elaboradas para el estudio del soma, en lo atingente a la actividad anímica.

El fascinante capítulo de la Psiquiatría Biológica tiene brillantes cultores, ha obtenido logros extraordinarios y se proyecta al futuro con la promesa de trascendentes contribuciones para el mejor conocimiento del cerebro y sus funciones. Se ha constituido y fundamentado en el rápido y espléndido desarrollo de la electrofisiología, la neuroquímica, la farmacología, la microscopía electrónica y otras ciencias básicas.

Esto no sólo ha proporcionado beneficios por el aporte de elementos significativos nuevos en el planteo de la problemática psiquiátrica teórica, sino que es un importante factor en el apreciable mejoramiento alcanzado en los últimos años en la asistencia del enfermo psiquiátrico tanto en los aspectos relativos al diagnóstico como en la terapéutica. El progreso en el tratamiento medicamentoso de las enfermedades mentales ha transformado los servicios hospitalarios psiquiátricos prácticamente en clínicas de los hospitales generales por la tranquilidad y el silencio que impera en los mismos.

La orientación biológica de la psiquiatría ha promovido investigaciones sobre el origen químico de las enfermedades psiquiátricas y las contribuciones en este campo se destacan por su cantidad y significación. El núcleo indólico presente en la fórmula de los alucinógenos se ha constituido en un elemento sobresaliente en este tipo de pesquisas.

Estos estudios benefician también el conocimiento de la química del cerebro y de sus estructuras especializadas. La adrenalina, la noradrenalina, la serotonina, concentrada en el encéfalo, en el diencéfalo y la formación reticular, son las hormonas del sistema nervioso llamadas aminas biógenas y las indagaciones acerca de su metabolismo, así como las búsquedas sobre ciertas enzimas o diastasas y vectores de energía físico-química, generan información concerniente a la intimidad en las células de los receptores especializados. La memoria y el aprendizaje se estudian actualmente a nivel molecular.

El tratamiento medicamentoso de las enfermedades psiquiátricas viene de la prehistoria. El uso y abuso de sustancias psicotrópicas en la antigüedad, su aplicación en enfermos mentales, son hechos bien conocidos. El opio, mencionado por Hipócrates en Occidente, era manipulado en Oriente. Contra la locura y para inducir el sueño en los niños, en época remota los hindúes usaban la rauwolfia. Los egipcios como somnífero y los sirios contra las "ideas negras" empleaban la belladona. Desde esos tiempos hasta nuestros días, se han documentado variados ejemplos de la índole de los anteriores. Fue en 1952 que se hizo presente el primer aporte a la quimioterapia psiquiátrica con la clorpromazina, a la que siguieron después otras medicaciones neurolépticas, las feno-

tiazinas, los reserpínicos y las butirofenonas y los antidepresivos de los tipos I.M.A.O. y no I.M.A.O.

Los mecanismos colinérgicos merecen atención especial en el estudio de las enfermedades mentales y de su terapéutica, particularmente con el desarrollo de compuestos anticolinérgicos experimentales que determinan efectos muy aparentes en la conducta, síndromes de irritabilidad, desórdenes del pensamiento, cambios perceptuales, alucinaciones, etc., y modificaciones apreciables del electroencefalograma. El efecto de la terapia convulsivante se produciría mediante el desarrollo de un aumento de nivel de la actividad colinérgica en el sistema nervioso central. La imipramina sería benéfica por su influencia anticolinérgica y por el aumento de catecolaminas libres centrales.

Las investigaciones neurofisiológicas que atañen a partes anatómicas definidas del encéfalo (por ejemplo, el lóbulo frontal, el temporal, el sistema límbico, etc.), cuya patología da lugar a sintomatología psiquiátrica, significan también adelantos para el conocimiento funcional del cerebro, así como para la clínica y la neurocirugía. Mencionaremos en relación con esto la cingulotomía frontal en los desórdenes afectivos.

Interesa señalar las observaciones realizadas en la conducta de animales cuando están sometidos a ciertas influencias experimentales. Por ejemplo, si a un animal (un pequeño mono) en una época temprana de su vida o en el período prenatal, se le somete a cierto grado de "stress", manipulándole, se logra que su desarrollo sea psicofisiológicamente superior, que llegue a estar mejor preparado para resistir quebrantos físicos y se adapte más a situaciones nuevas, siendo poco susceptible en estas condiciones para experimentar disturbios emocionales.

La electroencefalografía tiene en psiquiatría valiosa aplicación tanto en investigación científica como en la clínica asistencial para el mejor estudio de ciertos pacientes que presentan anormalidades bioeléctricas cerebrales.

Se señalan particularmente algunos hechos interesantes, por ejemplo las relaciones de puntas monofásicas de frecuencia de 14 y 6 por segundo, con algunos rasgos de personalidad, que aparecen primariamente en registros electroencefalográficos de sueño de gente joven y que se ha ligado a conducta caracterizada por estupidez, grosería, impulsividad y agresividad.

Otro aspecto provechoso de la electroencefalografía en psiquiatría, es el de su utilidad para la confirmación o la predicción de la eficacia de ciertos tratamientos como el electroshock o psicofármacos dados intensamente.

No deseamos extendernos más en la enumeración de brillantes temas que integran el capítulo de la Psiquiatría Biológica, que tratamos en este número.

Agradecemos al Dr. Himwich por su valiosa colaboración en su organización y a todos los partícipes del mismo, cuyos escritos son de marcado interés para nuestros lectores por lo que aportan a la cultura psiquiátrica que debe tener el neurólogo.

VICTOR SORIANO.

Editorial

Together with the extraordinary progress achieved in the knowledge of psychiatric disturbances connected with the investigation of psychic mechanisms commanding normal and pathological mental activity, valuable developments continue in the use of different biological methodologies oriented towards the study of the soma, in its relation with mental activity.

The fascinating field of Biological Psychiatry includes outstanding personalities, it has obtained extraordinary results and promises in the future to produce even greater contributions to the knowledge of the brain and its functions. This field has been constituted and supported by the tremendous development of electrophysiology, neurochemistry pharmacology, electron microscopy and other basic sciences.

This has not only brought great benefit by the introduction of new significant elements in the formulation of theoretical problems in psychiatry. In addition it has been an important factor in the great progress introduced in the assistance to the psychiatric patient in both diagnosis and therapy. Advances in treatment of mental illness have changed hospital psychiatric services by introducing the calm and quiet atmosphere of the general hospital.

Biological orientation of psychiatry has favored research on the chemical origin of psychiatric illness and contributions in this field are surprisingly numerous and significant. The indole group present in halucinogens has become an outstanding element in this type of research.

These studies shall also improve the knowledge of chemical features of the brain and its specialized structures. Adrenalin, noradrenalin, serotonin concentrated in the encephalon, the diencephalon and the reticular formation, are the hormones of the nervous system. They are called biogenic amines and investigation concerning their metabolism, as well as the search of certain enzymes and vectors of physico-chemical energy, furnish information concerning the intimacy of the cells of specialized receptors. At present memory and learning are studied at molecular level.

Treatment with medicine of psychiatric illness stems from the prehistorical age.

The use and misuse of psychotropic substances in the past and its administration to mentally ill patients are well known facts. Opium mentioned by Hypocrates in the Western world was also used by Eastern civilizations. In ancient times the Hindus used rauwolfia to fight against madness and to induce sleep in children. Belladona was used as a somniferous by the Egyptians and by the Syrians to fight "black thoughts". From those remote ages to our days there are many examples similar to those mentioned above.

In 1952 the first contribution to psychiatric chemotherapy was introduced with chlorpromazine, which was followed by other neuroleptic products; phenotiazines, reserpine derivatives and buthyrophenones and antidepressants of the I.M.A.O. and not I.M.A.O. type.

Cholinergic mechanisms deserve special attention in the study of mental illnesses and their treatment, particularly the development of experimental anticholinergic compounds determining significant effects on behavior, irritability syndromes, disturbances in thought, perceptual changes, hallucinations, etc. as well as marked modifications in the electroencephalogram. The effect of convulsive therapy would be produced by the development of an elevated level of cholinergic activity in the central nervous system. Imipramine would be beneficial due to its anticholinergic central action, to which the augmentation of free central catecholamines has to be added.

Neurophysiological research concerned with definite anatomical regions of the encephalon (i.e. frontal lobe, temporal lobe, limbic system, etc.) whose pathology provokes psychiatric symptomatology constitutes an important advance in the functional knowledge of the brain and also in the clinical and neurosurgical aspects. In connection with this kind of investigation we mention frontal cingulectomy in cases of affective disturbances.

It is most interesting to call attention to observations on the behavior of animals submitted to certain experimental influences. For instance, if an animal (a young monkey) is submitted —at an early stage of his life or during the prenatal period— to a certain degree of stress by manipulating him, a much better psychophysiological development is obtained. The animal is thus better prepared to resist physical breakdowns, is less susceptible to emotional disturbances and adapts himself more easily to new situations.

Electroencephalography plays a valuable role in psychiatry, in scientific research as well as in clinical work, for a better study of patients with bioelectrical abnormalities of the brain.

Some particulary interesting facts are pointed out, for instance, the connection between monophasic spikes of 14 and 6 c.s. and certain features of personality, which appear primarily in electroencephalographic records of sleep in young people and is associated to a kind of behavior characterized by stupidity, rudeness, impulsivity and aggressivity.

Another profitable aspect of electroencephalography in psychiatry is its usefulness for the confirmation or prediction of the efficacity of certain treatments as electrosbock or strong doses of psychodrugs.

We do not wish to extend in the enumeration of brilliant subjects integrating the chapter of Biological Psychiatry we treat in this issue.

We are grateful to Dr. Himwich for his valuable cooperation in the organization of this issue as well as to all the other authors whose papers will be most interesting to our readers as they constitute a significant contribution to psychiatric knowledge which every neurologist should possess.

VICTOR SORIANO.

Some Problems of Classification of Psychiatric Disorders in Relation to the Use of Psychotropic Drugs

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The progress of current psychopharmacology promotes not only a successful treatment of new contingencies of patients with mental disturbances, but at the same time enables to solve a number of new problems in the field of neurophysiology, biochemistry, psychology and clinical psychiatry.

The present report is based on the experience of clinical use of psychotropic drugs for the treatment of psychic diseases and of schizophrenia particularly.

The main feature of our method of investigation lies in the study of psychosis, in the dynamics of its development. It refers to all periods of the course of the disease, from prodromal up to the terminal state. Such a study of the course of the disease in a "longitudinal section" by means of a prolonged follow-up study of a large contingency of patients, often during their entire life, with a more profound clinical analysis of the dynamics of the symptoms and syndromes and their change at various stages of the psychosis development gave the possibility to a number of Soviet research-workers to establish certain regularities.

Thus according to the data obtained by A. V. Snezhnevsky and his colleagues, [8, 9, 10, 11, 12] which have been confirmed by many sources and numerous investigations made at other clinics, they achieved convincing results in the field of systematization of schizophrenia, both in delineating it from other diseases and subdividing it according to its course forms. S. G. Zhislin and his collaborators, [13, 14, 15] T. J. Hvilivitski et al. have obtained similar data in relation to manicdepressive psychosis and its atypical variants.

The principal feature of these and many other investigations is the rejection of a widespread point of view about the uncognizability of regularities of the course of a psychosis which is understood by a number of authors as a result of a chaotic occasional combination of multiform and unstable symptoms and syndromes. On the contrary, the course of psychosis is considered in the form of regular change of periods and stages, symptoms, syndromes and states, reflecting the chain reaction of pathogenic mechanisms of the disease process, which retains its fundamental regularities in spite of individual variations. Thus a unity between the clinical picture of the condition at the moment of investigation and peculiarities of the disease course as a whole enables us to solve questions not only of clinical, but of social,

occupational and therapeutic prognosis as well.

We believe this principle to be the most reliable criterion of psychiatric disorders classification, its division into forms and subforms, variants and course types.

Differentiation of manic-depressive psychosis and schizophrenia, which was begun by E. Kraepelin more than half a century ago still remains one of the controversial questions of psychiatry and yields foundation to some researchers to refute the trustworthiness of the nosological principle in psychiatry. The isolation of an intermediate group of "limitrophic", "autochtonous" and "degenerative" psychoses by Kleist, Schroeder and Leongardt et. al. has not solved this problem. We understand the main criteria of division appear as accumulation, in the course of the disease, of changes in the personality according to the schizophrenics type in the first place, and peculiarities of the picture of the state, in the second. The manic-depressive psychosis is characterized not only by the Kraepelinian triad of symptoms and typical somatic disorders, but by defining the leading role of affective disturbances in the structure of the clinical picture of a given phase. It means, for example, that the presence of delusional ideas of relationship and even of persecution and isolated hallucinations (more often bearing the character of illusory hallucinosis), if they result from vitally changed depressive affect and from ideas of self-accusation, guilt and sinfulness at the depressive stage, speaks in favor of the diagnosis of manic-depressive psychosis. And vice versa, the occurrence of the symptoms which are alien by their structure, not connected in a direct manner with depression, for instance, in the form of ideas of persecution, influence, auditory hallucinations, pseudohallucinations, etc. gives evidence of a schizophrenic character of the attack.

In such cases the discerning is often impeded by the general repression of patients which is similar in most cases to paranoid inaccessibility. In other cases this repression achieves far higher degrees including stupor externally similar to a catatonione.

The use of psychopharmacological drugs of the stimulants group has not only a therapeutic purpose but at the same time facilitates in the majority of cases, quick and sufficiently exact localization of given disease in the existing system. Thus we quite successfully use for this purpose imipramine or other drugs from the MAO inhibitors group, which with comparatively rapid increase of doses usually whithin several days clear up the clinical picture of the condition. By their activating, stimulating thymoleptic action gradual decrease of depression and repression in cases of manic-depressive psychosis takes place, or on the contrary, the hallucinatory-paranoid formations never observed before are reinforced which puts out of doubt the diagnosis of schizophrenia. It is worth while to notice that not infrequently an artificial aggravation of the schizophrenic process thus induced does not prevent, but on the contrary, facilitates further treatment with neuroleptics.

In this and in many other observations made during a period of 10 years in the development of psychopharmacology as a field of psychiatry new evidences in support of the nosological principle in psychiatry were obtained in the sense of strict determination of psychopathological disorders within the framework of nosological forms and in the sense of regularities of their course. Thus, the exacerbations observed in the course of schizophrenia under the influence of such neuroleptics as reserpin, piperazine derivatives of the phenothiazine group, haloperidol, and psychodisleptic means, occur together with mobilization of schizophrenic disturbances. Specific extrapyramidal disturbances accompanied by a number of psychic disorders while medicating with Majeptil (Kulenkampf - Tarnow syndrome), with haloperidol and haloanizone (excitomotor crises after Deley and Deniker) do not change after all the contents of pathologic manifestations. In general, any neuro-

leptic treatment causing the course of the psychosis to change, making it more benign, can't change its common regularities, the stereotype development of the disease (V. H. Vasilenko).

The data about the alleviation of schizophrenic defect by means of some neuroleptic drugs and stimulants also support this view. These drugs in no way change the specific features of the mentioned defect, which differ from all other psychopathological disorders, although certain compensation and alteration takes place.

The use of psychothropic drugs facilitates the demarcation not only of nosologically different diseases but enables us to specify the clinical classification within these diseases. The use of the mentioned stimulant drugs permits for example, to differentiate more precisely the inert variants of paranoid schizophrenia from the simple schizophrenia with similar course, but characterized by inexpressiveness of symptomatology (hallucinations and delusions, in particular) and by the preponderance of apathic-abulic disorders. In the former case due to the action of stimulants an exacerbation of hallucinatory and delusionary phenomena which were indistinct before, occur, while in the latter only the activating effect is displayed. This, by the way, serves as an indication for the further use of psychoanaleptic drugs which prove to be in some cases, along with insuline therapy more effective for the treatment of the simple schizophrenia, than neuroleptic treatment.

As one more example we may cite here psychiatric disorders in the course of which stuporous states prevail. We have already mentioned the difference between depressive and catatonic stupors. Within the frames of schizophrenia stuporous states are not adequate. This fact is reflected in the differentiation of stuporous variants of the nuclear, "lucid", incessant and malignant catatonia ("Dementia catatonica" - Kraepelin) and of the benign, remittent, recurrent, oneroid schizophrenia with periodic course (Mayer-Gross, Meduna, Snezshnevski, Favorina et. al.). The spastic stupor with negativism, mutism, prolonged refusal of food, which is characteristic of the nuclear catatonia often proceeds without hallucinatory-delusionary disorders, the so called "empty stupor" (after M. J. Sereiski and G. A. Rotstein) and is confined to motor disturbances regularly combined with a uniform long course without remissions. Contrary to this, the stuporous states of the oneiric catatonia are distinguished by a great changeability of state. The muscle tone, as a rule, is not elevated, on the contrary frequently decreased, and the so called "waxy elasticity" is often observed. By the patient's behavior, his mimical expression, the fragmentary speech we may judge about the presence of copious, oneiric phantastic experiences. In the overwhelming majority of cases such a clinical picture has its corresponding course in the form of acute attacks, interchanging, especially at the first stages of the development of the disease, and often during the course of the whole life of the patient, with deep and complete remissions, which very frequently resemble intermissions.

Such a clinical differentiation of these stuporous states which are often so similar is very important for practical purposes and is confirmed with different reactions to the administration of psychotropic drugs. Thus, a long treatment with aminazine (chlorpromazine), as well as the use of other phenothiazine derivatives with an aliphatic side chain, in fact appear to be ineffective in cases of nuclear catatonia. Frequently they only enhance the inhibition and deepen the stupor, while with the help of the drugs which possess disinhibitory properties (thioproperazine-Majeptil) a much better therapeutic effect is achieved. It is interesting to note that using stimulants of the imipramine type such patients not infrequently achieve a considerable decrease of stupor, although there were cases of the shifts to the catatonic excitement characterized by hebephrenic silliness, impulsiveness and aggression. This

excitement differs considerably from the excitement with confusion of the patients suffering from oneiroid catatonia. Thus, the administration of psychothropic drugs to patients of this kind has not only therapeutic purposes, but at the same time enables us to make a more qualified decision on the questions of systematization.

Similarly to oneiroid catatonia, in the group of patients with schizophrenia characterized by periodic course, the Soviet psychiatrists differentiate the cases of depressive-paranoid schizophrenia the main feature of which is not only a combination of hallucinatory, paranoid and depressive disturbances that one may observe also in the paranoid schizophrenia with an incessant course but which also have a quite different clinical picture. Unlike the paranoid form, in depressive-paranoid schizophrenia, instead of authentic auditory hallucination an illusory hallucinosis is observed, instead of the prevalence of ideas of persecution with a tendency to systematization, the foreground is occupied by ideas of reference, delusion of dramatization — intermetamorphosis, so characteristic for paranoid schizophrenia. The phenomena of the Kandinski-Clerambeau in the depressive-paranoid form are expressed inconsiderably; the syndromes of the "double" are very often observed. Depression which may become very pronounced more frequently is accompanied with agitation, and not infrequently the syndrome of Cotar develops. Like the oneiric catatonia in the clinical picture of this psychosis affective disorders occupy a prominent position; the sensual character of the delusion in rather pronounced.

Some other psychic features also common to the oneiric schizophrenia, for example, serve as a foundation for the differentiation of this variancy with a periodic course from the paranoid schizophrenia with an incessant course. An intertwining of the symptoms of these two diseases is often met with at the height of a depressive-paranoid attack when a dreamlike change of the consciousness of an oneiric type occurs or after the first depressive-paranoid attacks when an oneiric develops or vice versa.

The practice of the use of psychothropic drugs for the treatment of this variancy of the periodic schizophrenia as well has confirmed the justification of its existence and has more fully revealed the peculiarity of the clinical picture. As early as in the period of the use of chlorpromazine it was found out that under the influence of therapy a split of this complex syndrome takes place (Snezshnevski): the hallucinatory-delusionary part of the status undergoes a reverse development, while the depressive not only remains but sometimes even increases, acquiring a vital character (development and increase of distress, reaching the degree of a "physical suffering", development "anaesthesia dolorosa psychica", daily variations etc.). Finally there begins such a "filtration" of the clinical picture that the state of the patients becomes rather similar to a typical depressive one. The attempts to use stimulants (imipramine, iproniazide, marplan, niamide and others) also facilitated the splitting of the clinical picture of a depressive-paranoid attack but in the contrary sense: the decrease of the depression was a comparatively rapid one, while hallucinatory-delusionary phenomena increased, the excitement was gaining force.

The clinical analysis of the action of these two groups of psychothropic drugs gave a possibility to use effectively a combined treatment with chlorpromazine and stimulants by means of such an individual dosage that the chlorpromazine decreasing the hallucinatory and delusionary phenomena does not increase depression, while stimulants decreasing depression do not enhance delusion and hallucinations. During the following years far more successful results were obtained through the use of the drugs possessing both antidepressive and neuroleptic properties of the levomepromazine type (or its combinations with chlorpromazine and imipramine), and also through the use of the phenothiazine derivatives of the trilafone type possessing

along with neuroleptics certain stimulating action (the Soviet etaperazine, the Hungarian phrenolon), and if necessary their antidepressive action was strengthened with the help of imipramine.

Thus, the employment of psychothropic drugs has convincingly demonstrated the independence of this variant of schizophrenia mentioned above and its difference from the paranoid form with an incessant course not only according in the principle of its periodic course, but in relation to a qualitatively different structure of psychosis. From the dynamics given above in the process of administration of various psychothropic drugs it is evident, that the depressive components of the state are not "secondary" symptoms due to the paranoid experiences of the patient, but as if they coexist alongside with them comprising a complex syndrome.

On the contrary to it, in treating with neuroleptics the patients suffering from a paranoid form of schizophrenia the reverse development of the symptoms occurs more harmonically: as hallucinatory-delusionary phenomena decrease the depression accompanying them disappears.

One more serious argument confirming the heterogeneous course of schizophrenia and the necessity to differentiate it into two large groups —both with an incessant and a periodic course— was the data about the increase of periodicity while medicating with neuroleptics obtained at the clinic of Prof. S. G. Zhislin. By means of prolonged follow-up studies it has been established that there was a group of patients who in the process of a protracted chlorpromazine treatment rapidly improved however, they just as rapidly had relapses again, being admitted to the psychiatric institutions with approximately the same although a somewhat mild picture of psychosis. Analysing such cases it has been found that most of them are related to various types of the periodic schizophrenia. The comparison with the course of the disease before administration of chlorpromazine convincingly showed the increased frequency of the attacks in the course of the treatment. There are observations which permit to extend this dependence on other neuroleptic drugs and on the phenothiazine derivatives in the first place.

The cited regularity contrary to some extent to what is observed during the paranoid form with the incessant course enabled us to raise an important practical question about giving up the mediocre maintenance therapy which is prescribed to all patients without any exception who were under the neuroleptic treatment. It means that only an incessant process of the paranoid type needs a maintenance therapy for the purpose of protracted action in a permanent though weakened psychopathological disorder, while with the attacks favourably terminated of periodic schizophrenia the maintenance therapy is not only useless, but often is counterindicated. It seems to us that with this very circumstance, in particular, all data about repeated admissions to the psychiatric institutions during the time of mass neuroleptic treatment are connected. This permits some authors using summary statistic estimation to be sceptical about the use of psychopharmacological drugs.

The solution of the question of the value of this or that therapeutic method is to be sought not in the expanded statistical investigations which combine in one group patients with various prognosis types, variants, stages of the course, but in the thorough clinical studies based on an accurate, clinically proved classification of psychiatric disorders and taking as its aim an establishment of well-grounded indications to the use of this or that psychothropic drug. Only in such a condition one may rely on the trustworthiness of the data obtained through statistic operations, and as well as to avoid the diversity of views characteristic of the psychiatric literature at the present moment, and frequently the controversy of certain authors in relation to the effectiveness of the psychothropic drug therapy.

SUMMARY

The author believes the only reliable criterion for the classification of mental disorders is the clinical principle, according to which the course of the disease is considered to be a pattern like process in which the psychosis and its course display an individual clinical picture. It is on this very principle that Soviet psychiatrists base both nosological classification of mental diseases and their forms and subforms respectively.

The administration of the psychothropic drugs makes it possible not only to give more precise definitions, but also to receive new data important for practical purposes. For instance, with the help of stimulators it appears possible to solve with a higher degree of precision the problems of delimitation of manic depressive psychosis from some forms of schizophrenia with similar outward features. It also gives more precise classification within the nosological forms. Data are obtained on different reacting to treatment with psychotropic drugs of schizophrenic patients with the continuous form (paranoid type) and recurrent course (depressive-paranoid and oneiroid catatonia). This pertains as to the different dynamics of the psychical status during the period of treatment so to the modification of course of the disease with long term of neuroleptical medicaments (intensification of the periodicity).

The contradicting views on the efficiency of therapeutics are, to some extent, due to the fact that the clinical classification of mental disorders in connection with the administration of psychotropic drugs is underestimated while only statistical methods are used.

RESUMEN

El autor considera que el único criterio de apreciación válido para la clasificación de las enfermedades mentales es el principio clínico que consiste en estudiar el curso de la psicosis como proceso regido por leyes determinadas y señala la unidad del cuadro clínico y de la evolución de la enfermedad. Fundándose en este principio los especialistas soviéticos han elaborado una clasificación nosológica general y una clasificación de tipos y subtipos de una psicosis dada.

El empleo de productos psicotrópicos permite la precisión de los criterios clínicos establecidos y además la posibilidad de reunir nuevas informaciones de interés para los médicos. De esa manera por medio de los estimulantes se podrá obtener una mejor solución a los problemas que ofrece la identificación de las psicosis maníaco-depresivas y de las esquizofrenias similares a este tipo de psicosis; también será posible precisar la clasificación dentro del cuadro de las entidades nosológicas. El autor hace observaciones concernientes al carácter diferente de las reacciones al tratamiento según que la esquizofrenia sea de evolución continua (tipo paranoico) o sea de evolución periódica (catatonia depresivo-paranoica y oneroide). Las observaciones han hecho resaltar las diferencias de dinámica del psiquismo durante el tratamiento así como también los cambios ocurridos durante la evolución de la psicosis bajo el efecto de neurolépticos administrados durante años (periodicidad acentuada). La subestimación que deriva del empleo generalizado de productos psicotrópicos, del interés de la clasificación clínica de las psicosis en beneficio de meros estudios estadísticos, es una de las causas de la diversidad de las opiniones dadas por los investigadores de métodos de tratamiento eficaces.

RÉSUMÉ

L'auteur considère que le principe clinique qui consiste à etudier le cours de la psychose comme un processus régi par des lois bien déterminées, et realisant l'unité du tableau clinique et de l'evolution de la maladie, est le seul critère valable d'appréciation d'une classification des maladies mentales. C'est sur ce principe que les aliénistes sovietiques ont fondé leur classification nosologique en général et leur classification des formes et des sous-formes d'une psychose donnée.

L'emploi des produits psychotropes permet non seulement de préciser des critères cliniques établis de la classification, mais encore de recueillir des renseignements nouveaux qui ne manqueront pas d'interesser le praticien. C'est ainsi qu'au moyen des stimulants, on pourra mieux résoudre les problèmes posés par l'identification de la psychose maniaque-depressive et des formes de schizophrenie qui lui ressemblent, et de préciser la classification dans le cadre des nosologiques. L'auteur rapporte des observations concernant le caractère différent des réponses au traitement selon que la schizophrenie soit à evolution continue (type paranoiaque) ou à evolution periodique (catatonie depressive-paranoiaque et oneroide). Les observations ont fait ressortir des différences de dynamique du psychisme pendant le traitement, aussi bien que des changements survenus dans l'evolution de la psychose sous l'effet de neuroleptiques administrés pendant des années (périodicité accentuée). La sous estimation, par suite de l'emploi généralisé des produits psychotropes, de l'intérêt de la classification clinique des psychoses au profit des seules méthodes statistiques, est une des causes de la diversité des jugements portés par les chercheurs sur l'efficacité du traitement.

ZUSAMMENFASSUNG

In der Klassifizierung psychischer Störungen hält der Autor für das einzig sichere Kriterium das klinische Prinzip, das den Krankheitsverlauf als einen gesetzmaβigen Prozess betrachtet in dem sich die Einheit des klinischen Bildes der Psychose und ihres Verlaufes vollzieht.

Gerade auf diesem Prinzip beruht sowohl die nosologische Klassifizierung psychischer Erkrankungen, als auch die der Form und Subform im Rahmen jeder von diesen Erkrankungen. Beide dieser Klassifizierungen werden von den sowjetischen Psychiatern verwendet.

Die Anwendung der psychotropen Mittel erlaubt es, nicht nur die schon festgestellten klinischen Kriterien der Klassifizierung genauer zu bestimmen, sondern auch neue, für die Praxis wichtige Angaben zu bekommen.

Es gelingt, z.B., mit Hilfe der Stimulatoren viel qualifizierter die Fragen der Abgrenzung der manisch-depressiven Psychose von den äuβerlich ähnlichen Varianten der Schizophrenie zu lösen, und die Klassifizierung in den nosologischen Formen genauer zu bestimmen.

So, z.B. werden die Angaben über verschiedene Reagirung auf die Behandlung mit psychotropen Mitteln der Schizophreniekranken mit ununterbrochenem (wahnlicher Typ) und periodischem Verlauf (depressiv-wahnliche und oneroidische Katatonie) angegeben. Es bezieht sich sowohl auf verschiedene Dynamik des psychischen Zustandes im Behandlungsprozess, als auch auf die Veränderung des Krankheitsverlaufes oder auch auf mehrjährige Anwendung von neuroleptischen Medikamenten (Verstärkung der Periodizität).

Die Unterschätzung klinischer Klassifizierung psychischer Storungen wegen breiter Anwendung der psychotropen Mittel

und Gebrauch nur statistischer Methoden ist einer der Gründe verschiedener Stellungnahme der Forscher zum Erfolg der Therapie.

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The Role of Biological Psychiatry in the Modern Treatment of Psychoses

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The introduction of *Wagner-Jauregg's* [51] malaria treatment marked the breakthrough of biological methods of treatment in the era of therapeutical nihilism. This was the first time that a promising therapy had been brought into psychiatry after centuries of merely symptomatic methods of treatment: further milestones on the road toward a more active treatment of psychoses were the electric shock treatment (*Cerletti* and *Bini*) [15], the cardiazol treatment (*Meduna*) [41], and the insulin coma treatment (*Sakel*) [46].

The therapeutic impulse of those times was rooted in certain fundamental concepts on the nature of psychoses. It was a time when at least schizophrenic psychosis was considered a "somatosis", a time during which fundamental work on the hereditary basis of schizophrenia was done by many authors [10, 11, 13, 14, 17, 18, 31, 34, 37, 38, 40, 44, 45, 47, 48, 49, 50, 52].

Almost concurrently, however, the so-called purely psychogenetic school was being developed, based in the main on the work of *Freud* [19], but also on that of *Adler* [1] and *Jung* [36]. Its contemporary exponents belong both to orthodox psychoanalysis and to individual psychology, both to behaviorism and to collective psychology. The Russian views too, based on *Pavlovs's* theory, and the "Daseinsanalyse"[12, 53, 54] (related in its origins to existentialist philosophy) have made significant contributions to our knowledge of the personality set-up of schizophrenic patients and their environment, and of their mutual relationships.

Fundamental misunderstanding arose owing to an indistinct division between "erklärende" and "verstehende" psychology [22] - a division such as *Jaspers* [35] had already called for. This went so far and so deep that the more extremist representatives of each school —on one side the purely psychogenetic school and the organic-hereditary school on the other— faced one another without the faintest spark of understanding. An important contributory factor was that the science of heredity itself had been somewhat compromised by political infiltration so much so that to this day its results are looked upon with suspicion.

Nonetheless these last decades saw a growing convergence of the two schools. Orthodox psychoanalysts like *Rado* [23, 43] and others consider the basic disturbance in schizophrenia as a disturbance in ego development; but it is precisely these men who call themselves genetic psychologists, thereby hinting that they postulate a genetic basis to that developmental disturbance which will in individual life be covered up and shaped by a number of defense mechanisms. On the other hand the exponents of medical genetics are investigating to an increasing extent factors bearing on social environment and psy-

chodynamic development. This step had become the more urgent as even research on twins had shown differences in the theoretically expected concordance in psychotic uniovular twins.

Even though *Kallmann*[37, 38] marks concordance in uniovular schizophrenic twins at 86%,while concordance in biovular twins stands at 23%, this is nonetheless a fairly clear pointer to the genetic fixation of schizophrenic psychosis; but it also shows that the manifestations of a schizophrenic psychosis must depend on other factors besides the genetically fixed ones.

The postulation of the concept of the oscillating expressivity or changing penetrance of a gene in research on heredity in schizophrenia shows that other factors than the primary genetically fixed factor will play their part in releasing the disease (manifestation), in shaping a psychosis (from a psychopathological viewpoint), and in determining the further fate of the sick person (his social re-adaptation).

A few years ago *Bleuler*[11] wrote: "It seems one must accept that hereditary factors and other factors (such as environmental ones) are inseparably interconnected, without being able at present to know more about the interrelation of those two most important factors governing the ethiopathogenesis of schizophrenia".

But in the course of the last decade the introduction of psychopharmaca in the treatment of psychosis (and particularly the confrontation of the therapeutical results of "older methods" and of psychopharmacological treatment) have led to new concepts on the nature of psychosis and on the basic effects of the various therapeutic measures[3, 4, 6, 7, 8, 20, 30, 31].

We thought from the very first that each new therapeutic measure —and this includes psychopharmaca— ought to have its definite and specific place in the overall treatment plan of psychosis. At the same time, this meant that we have had to revise to some extent our ideas about the position of older traditional methods of treatment.

It must be stressed that all these things would hardly be possible without the basis of an exact clinical diagnosis. Such a diagnosis must set out both from psychopathology and from a thorough depth-psychological investigation of the psychodynamics of each individual case. In actual, concrete fact this means that we decide to use this or that therapeutic measure according to the nosological categorization of the great classical subdivisions of endogenous psychoses (according to *Kraepelin*)[19]; according to the predominant symptom — the target symptom—; and according to the given individual psychodynamic development. Let us illustrate the therapeutic views current at our clinic on hand of endogenous depression and the group of schizophrenias.

Let us state from the outset that while upholding a clear dividing line between neurosis and psychosis, we at the same time consider both the group of endogenous depressions and the manic-depressive illnesses as a nosological unit quite distinct from the group of schizophrenias[3, 4, 8, 25, 31, 33].

We mean by depressive moods within the framework of neurosis a secondary reaction of the personality that sets in after the attempt to use existing neurotic defense mechanisms has failed. On the other hand we consider that true endogenous depressive phases are the expression of a genuine biological occurrence, and consequently assign endogenous recidivious depression on principle to the circle of the manic-depressive psychoses. Admittedly, a number of psychogenic mechanisms and neurotic defense mechanisms may dominate to a slighter or greater degree in various stages of endogenous depression. We know, too, that the classical overall symptoms of melancholia are today rather rare and have been replaced to a large extent by neurotically mixed forms of depression. We nonetheless have good reason to hold fast to this diagnostic classification.

It has been repeatedly proven that it is not possible to heal such forms of endoge-

nous depression by psychoterapeutic means. A persistent depressive syndrome holds the possibility of attempted suicide: unfortunately a not inconsiderable percentage of successful suicides of our times are cases of unrecognized depression. During the last 10 years more than 10 percent of all cases of attempted suicide admitted to the clinic were diagnosed as cases of endogenous depression.

According to the dominant principal symptom this group of endogenous depression is subdivided as follows:

a) a form in which impairment of basic vitality, inhibition, and a slowing down of all vital processes predominates. In our experience this group has reacted best to anti-depressive drugs with clearly marked boosting effect, but also with increased psychomotoric activity. These drugs are Imipramin, Desmethyl-Imipramin, Trimeprimin, etc. We also noted that psychopharmaca on their own often did not suffice, and we have had to carry out a series of electric treatments in quite a number of cases. The best psychopharmaca (such as, for instance, Protryptilene) cannot, according to the authors, achieve a remission rate of over 60%, while electric treatment still achieves the higher remission rate of 85%. We shall return later to a combined treatment of psychopharmaca and electric shocks.

b) A form of endogenous depression in which excessive psychic tension, fear, and agitation are the predominant symptoms. This form of depression is the most dangerous from the viewpoint of possible suicide attempts, because inhibition has been broken through to a large extent.

We cannot bear out the opinion of various investigations, which would allow anti-depressive effects to treatment with neuroleptics only. Nonetheless it is precisely in this group of depressions that antidepressiva with a strong sedation effect (such as Amytryptiline) or a combination of antidepressives and neuroleptics can be usefully administered. In more than 50% of all cases this treatment needs to be combined with electric shock.

c) A form of endogenous depression in which hypochondriac developments predominate. Throughout the world results with this particular group have made the poorest showing. These depressive moods are, after all, only phases within the framework of a personality development of long standing which, owing to fixation on body phenomena and focusing on one's own body, are not easily accessible to any form of therapy.

In our experience this group shows the best results in a treatment with MHO-inhibitors: this we carry out in the form of a short concentrated therapy (Stoss-Therapie).

d) Endogenous-depressive phases, where a clear organic background is discernible. This can occur in cerebral sclerosis, general age-conditioned changes within senile dementia, after head injuries, in metabolic diseases such as endocrinopathia, diabetes mellitus, diseases of the heart and the circulatory system. It is obvious that the tendency to relapse of these depressive states will vary with the given possibility of treating the body disease, and with the possible disappearance of a constant releasing factor. From a therapeutic viewpoint it is therefore necessary to treat both the internal and endocrine diseases, and other diseases, while administering antidepressive treatment. For this group drugs with slighter side-effects than those of the highly potent antidepressive are indicated: this means, in turn, that one is faced with a longer period of waiting for the moment of maximum effect.

e) Psychotherapy of endogenous recidivious depression should be considered merely an in-between therapy, particularly indicated with regard to the prophylaxis of relapses. But we think that in an existing endogenous depressive phase a psychotherapy that goes over and beyond the framework of a psychologic treatment or of an environmental therapy is not possible: so suitable contact can be found to the patient because the disease depression erects a barrier between doctors and patient. The more importance must be pla-

ced on the enlightment of the patient's surroundings, the environmental arrangements that are indicated — since each melancholiac has the well known tendency to draw his environment into the melancholic syndrome.

SCHIZOPHRENIA

We hold fast to the unity of the group of schizophrenias and the possibility of dividing it clearly fron the other great psychoses. We take the heredity *for granted*, and moreover assume that a "basic disturbance" on a psychological level corresponds in the "Erlebnisvollzug" to a disturbance on a metabolic level [5, 6, 7, 8, 27, 28, 29, 30, 31, 42].

It is precisely in this group that a number of therapeutic measures reaching from biological methods of treatment to individual and group therapy must be employed in order to get the optimum effect as regards re-integration or at least social re-adaptation.

We also insist on differentiating between the schizophrenic process and the defect after the process has run its course, because this differentiation carries significant therapeutical implications. Of course, nowadays we look upon the schizophrenic defect as being considerably more dynamic, and as the expression of a more or less unstable balance, comprising a reduction in the level of energy, dysdifferentiation and also the re-appearance of pre-formed defense mechanisms during the phase of rehabilitation based on the individual psychodynamic of each individual patient. The inter-action of the various therapeutic measures can be shown quite clearly on hand of the various subdivisions of schizophrenic psychosis.

We continue using as before electric treatment and full insulin shock. In recent years, however, changes in indication have arisen as a result of a new heuristically valuable subdivision of schizophrenic processes. In cases of acutely threatening catatonia (according to *Stauder*) we feel that electric treatment of a special kind (3 treatments at 15 minutes interval each) are vitally indicated.

In other phase-like processes of schizophrenia (those where restitutio ad integram is achieved without formation of defect) a series of electric treatments still remains the quickest and safest way for the complete recovery of the phase. In this group we nowadays often make combined use of neuroleptics during the start of treatment and during the re-adaptation phase. Psychotherapy in open group and occupational work therapy have their well-defined places in the overall plan of treatment.

The full insulin coma treatment is still the necessary basis of treatment in the intermittent progressive form (in remissions and relapses) of schizophrenia corresponding to the former concept of paranoid schizophrenia. We use the combination of cardiazol or electric shock within the framework of the insulin treatment to reinforce the insulin effect.

Both individual and group psychotherapy — and in isolated cases environmental therapy — will be used in the rehabilitation of such patients, according to the phase of remission and the specific situation of the case.

During recent years we have had part successes with Thioproperatin treatment (Majeptil) in primary progressive form of schizophrenia (hebephrenia). Nowadays we succeed, in these processes which were formerly often resistant to every other therapeutic measure, to re-socialize a number of such patients by means of repeated Majeptil treatment. We are of the opinion that treatment with Thioproperatin should be carried out to the point of a clear Parkinsonian syndrome, to the appearance of extra-pyramidal dyskenesis.

In mixed psychoses (a combination of schizophrenia with MDI) neuroleptics will to some extent be used for the sedation of fear and agitation, while antidepressives will be used to a lesser extent as treatment. Treatment with antidepressives always holds the danger of activating schizophrenic symptoms.

In those forms of mixed psychoses which heal with defects a series of electric treatments is frequently used and shows the highest percentage of remission rates.

In those processes which have a progressive character where defect symptoms of a schizophrenic nature can be proven during intervals, we carry out an insulin coma treatment.

Psychic methods of treatment too are being used within the framework of an overall plan of treatment. Our own position can be briefly outlined as the following: We regard active psychotherapeutical treatment in psychosis as a part of treatment, and we cannot say that the psychotherapeutical method alone is successful in the field of psychoses.

We do not make extended use of analytically uncovering methods of the psychogenetic releasers. We are less concerned with individual treatment than with a new pattern in the disturbed family and social relationship of the patient. We endeavor to attain a manageable balance for people who after their disease still carry remnant symptoms of their psychosis; from various viewpoints we hence prefer group therapy.

Nowadays we know that the formation of groups, which started in hospital during the phase of biological treatment, has its continuation in the psychotherapeutic group, in work therapies; after the patient is discharged, in the form of therapeutic clubs that allow the sick person to forge his human relationships in a new form that suits him. It must not be forgotten that these patients' clubs help man in his conflicts with his surroundings by giving him a considerable support, and a feeling of safety through apportenance to his group.

In some cases the setting-up of day and night clinics has helped to prevent the breaking up of social contacts built with such difficulty in the outside world. We are nowadays ready to carry out treatment in the evening (whether it be neuroleptics treatment or electric shock treatment) in order to keep the sick person at his place of work.

SUMMARY

The theoretic concepts on the nature of psychosis and its ethiopathogenesis are outlined. We believe in a multifactorial genesis: while assuming that psychosis has an organic basis, we do not by any means deny that a number of psychodynamic, sociodynamic, and cultural factors play a role in shaping the psychoses.

Hence in the treatment of psychoses too we believe in the necessity of an exact clinical diagnosis. Along the lines of KRAEPELIN we believe in the unity of schizophrenia, in the definibility of MDI and of neuroses. By making use of psychotherapeutic endeavors in the widest sense of the word, by means of environmental treatment and post-institutional social welfare of patients we try to create as wide a framework of treatment as possible. In our opinion an optimum treatment of psychosis is possible only when taking into account ethiopathogenetic factors, and by deciding on a differentiated treatment according to the prevailing symptoms.

RESUMEN

Son señalados los conceptos teóricos acerca de la naturaleza de las psicosis y su etiopatogénesis; creemos que el origen de las psicosis se debe a una multiplicidad de factores. Si bien afirmamos que la base de las psicosis es orgánica, no negamos en absoluto el papel desempeñado por una serie de factores psicodinámicos, sociodi-

námicos y culturales en su caracterización.

De aquí que creamos también en la necesidad de un diagnóstico clínico exacto. Según los lineamientos de KRAEPELIN creemos en la unidad de la esquizofrenia, en la definibilidad de las MDI y las neurosis. Empleando una labor psicoterapéutica en el más amplio sentido de la expresión a través de tratamiento ambiental y la atención social post-institucional de los pacientes tratamos de ampliar al máximo los límites del tratamiento.

A nuestro criterio sólo es posible un tratamiento óptimo de las psicosis si se tienen en cuenta los factores etiopatogenéticos y si se adapta el tratamiento de acuerdo con los síntomas predominantes en cada caso.

RÉSUMÉ

Ce travail esquisse les points de vue théoriques sur la nature des psychoses, leur étiologie et pathogenèse. Notre point de vue est la genèse multifactorielle. Nous supposons une base organique des psychoses sans repousser pour cela l'influence d'une serie de facteurs psychodynamiques, sociodynamiques et culturels.

Ainsi nous basons la thérapie des psychoses sur un diagnostic clinique exact et nous tenons à l'unité de la schizophrénie dans le sens de KRAEPELIN et à la possibilité de la distinguer de la folie circulaire et des névroses. Mais nous essayons cependant de donner au traitement un cadre aussi large que possible en y introduisant des mesures psychothérapeutiques dans le sens le plus large, la thérapie de milieu et la post-cure sociale. Une thérapie des psychoses tout à fait satisfaisante n'est possible qu'en considérant tous les facteurs étiopathogénétiques d'une façon differenciée selon la prévalence des symptômes.

ZUSAMMENFASSUNG

Es werden die theoretischen Anschauungen über das Wesen der Psychose und deren Ätiopathogenese skizziert. Wir stehen auf dem Standpunkt einer multifaktoriellen Genese, wobei wir eine organische Grundlage der Psychose annehmen, jedoch keineswegs eine Reine von psychodynamischen, soziodynamischen, kulturellen Momenten einen Einfluss auf die Ausprägung der Psychosen absprechen.

Auch in der Therapie der Psychosen halten wir deshalb an der Notwendigkeit einer exakten klinischen Diagnosestellung fest. Wir halten auch im Kraepelin'schen Sinne an der Einheit der Schizophrenie, der Abgrenzbarkeit zum MDK und zu den Neurosen fest. Wir versuchen jedoch, durch Einbeziehung von psychotherapeutischen Bemühungen im weitesten Sinne des Wortes durch Milieutherapie und soziale Nachbetreuung der Patienten den Behandlungsrahmen soweit als möglich abzustecken. Unter Berücksichtigung einer ätiopathogenetischen Komponente und durch eine differenzierte Therapie je nach der Prävalenz der Symptomatik, ist unserer Meinung nach erst eine optimale Therapie der Psychose möglich.

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Basic Actions of Psychoactive Drugs

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While the pharmacology of the peripheral nervous system has reached a certain degree of maturity, our knowledge of the mode of action of drugs in the central nervous system is still very incomplete. This may well be due to the difference in complexity between the two systems. There is nothing to suggest there should otherwise be a basic difference in their organization.

As is well known, the points of attack of the great majority of drugs acting on the peripheral nervous system are the neurohumoral transmission mechanisms. With our present knowledge of the biochemistry and physiology of the nerve cell this is not astonishing. The function of the neuron is to release its transmitter —a specific chemical compound of high physiological activity— in the right amount and at the right time. In order to do this it must be able to react properly to incoming signals, which as a rule are the transmitters released from other neurons. These two characteristics of the neuron, *i.e.* specific sensitivity to transmitters on one hand, and the manufacture, storage and release of its own transmitter on the other, form a natural basis for selective attack by drugs. Agents interfering with functions more or less common to all cells, such as oxidative phosphorylation and general membrane permeability, cannot be expected to act with the same high degree of selectivity. In fact, attempts to explain the action of centrally acting drugs apart from unspecific depressants such as the general anesthetics in such terms have proved fruitless.

The introduction of the modern psychoactive drugs has meant a significant step forward in psychiatry. In basic research these drugs have proved important in several respects. One aspect seems particularly impressive: the drugs have become valuable tools in attempts to build a bridge between the peripheral and the central nervous system: *for the first time the principles of neurohumoral transmission can be fruitfully applied to the pharmacology of the central nervous system.* In the present survey this aspect will be emphasized.

Criteria for chemical transmission in the peripheral and central nervous systems

Ever since the experiments of *Loewi* [68], there has been a discussion going on as to which criteria should be satisfied by transmitter substances. There seems to be general agreement that criteria of morphological, biochemical, physiological, and pharmacological nature are all essential. It is but natural that these criteria have been modified somewhat since the twenties, taking into account the development of the research field since that time.

1. *Cellular localization of transmitters.* It is evident that a substance must occur in the axonal terminals of neurons in order to function as their transmitter. Needless to say, the direct demonstration of this point by means of purely chemical techniques is difficult, if not impossible. Until recently, the evidence was indirect only

and consisted mainly in the demonstration of the substance in non-terminal parts of the neurons and in its disappearance from tissues following denervation. For acetylcholine this situation still prevails. With the advent of a new histochemical technique it has become possible to demonstrate the accumulation of some monoamines in the synaptic widenings ("varicosities") of central and peripheral nerve terminals [29, 27, 47, 48, 49]. Such accumulation affords in itself strong support for the assumption that the substance is a transmitter, although additional evidence is necessary to prove the point. The following monoamines have been demonstrated to have such a "transmitter-like" intraneuronal distribution:

noradrenaline (NA): in peripheral sympathetic neurons and in neurons of the brain and spinal cord of mammals,

dopamine (DA): in neurons of the brain of mammals and in neurons of molluscs,

adrenaline (A): in sympathetic neurons of the frog,

5-hydroxytryptamine (5-HT): in neurons of the brain and spinal cord of mammals as well as in neurons of molluscs.

With respect to the *subcellular localization* one further point may be added. In all the known cases the transmitter is stored in particles, by electron microscopists referred to as vesicles but generally known as storage granules [18, 39, 44, 62, 86].

2. *Cellular localization of enzymes responsible for transmitter synthesis.* It is generally considered as a requirement that the neuron should be capable of synthesizing its transmitter. Theoretically this does not seem absolutely necessary, but in all known cases this requirement seems to be fulfilled. The following enzymes must be assumed to occur in neurons, since their activities are very much reduced following neuronal degeneration: choline acetylase [56, 57], DOPA/5-HTP decarboxylase [8], beta-hydroxylase, responsible for the step DA-NA [35]. The neuronal localization of tyrosine hydroxylase and of tryptophan hydroxylase has not yet been demonstrated but is supported by strong indirect evidence.

3. *An enzyme responsible for the local inactivation of the transmitter* is generally required but again perhaps not theoretically necessary in all cases, because inactivation may take place also by escape into the circulation and by reabsorption into the nerve terminal. Inactivating enzymes that have been demonstrated locally, both in the central and the peripheral nervous system, are acetylcholine esterase [see Koelle [67], monoamine oxidase (MAO), and catechol-O-methyl transferase (COMT)]. The cellular localization of the latter two enzymes will be further discussed below.

4. *Stimulation of the neurons should result in release of the substance.* In the peripheral nervous system this has been demonstrated for acetylcholine, adrenaline (frog heart), and noradrenaline (mammalian symphatetic system, see Euler [43]). In the central nervous system the release of a monoamine, *i.e.* 5-HT, following electrical stimulation of descendent spinal axons has been demonstrated [3].

5. *The accumulation of the substance in the synaptic cleft should be accompanied by a change in the activity of the post-synaptic neuron.* In the peripheral nervous system these effects can be demonstrated *e.g.* by close arterial injection or local application. In the central nervous system the problem is more difficult. Close arterial injection cannot be applied, because the transmitters generally do not penetrate through the blood-brain barrier. Local application has been successfully tried in some cases (see below). The following three procedures have also proved successful, 1) administration of precursors (DOPA and 5-hydroxy-tryptophan) alone or in combination with MAO inhibitors, 2) administration of reserpine to animals pretreated with MAO inhibitors, resulting in release of monoamines from the nerve endings into the synaptic cleft —as can be de-

monstrated by means of the new histochemical fluorescence technique (unpublished data of *Hillarp's* laboratory), and 3) administration of large doses of MAO inhibitors, resulting in accumulation, and finally release into the synaptic clefts, of monoamine transmitters. Marked changes in neuronal activity have been observed following procedures 1) to 3).

6. *Drugs interfering with the degradation or physiological activity of the substance should influence the effect of neuronal stimulation accordingly.* There are exceptions to this rule, however (see *Gaddum* [51]). A prerequisite, which is often not fulfilled, is sufficiently detailed knowledge of the mode of action of the drugs in question.

When all these criteria are considered, there can be no doubt that adrenaline, noradrenaline and acetylcholine serve as transmitters in the peripheral nervous systems of vertebrates. As to the central nervous system, a strong case can be made for 5-HT, noradrenaline and dopamine, even if 100 percent proof has not yet been obtained. The case for acetylcholine is perhaps not equally convincing (apart from the branches of spinal motoneuronal axons innervating the *Renshaw* cells, see *Eccles* [41]), but still good enough to be regarded as acceptable for all practical purposes.

Different sites of drug action on the transmission mechanism

For the understanding of the mode of action of psychoactive drugs it is necessary to consider in some detail the events taking place during neurohumoral transmission. Since some of the most important psychoactive drugs seem to interfere particularly with monoamine transmission, the discussion will deal primarily with this group of transmitters.

When a terminal axonal branch of a nerve cell approaches its target cell it undergoes certain changes [27, 42, 47, 69, 85]. The originally smooth fiber becomes uneven through the occurrence of bead-like enlargements, so-called varicosities, which are in close synaptic contact with dendrites or the soma of the target neuron. These varicosities are particularly rich in storage granules (or "vesicles", according to the terminology of the electron microscopists), which contain the transmitter in high concentration. The varicosities are also rich in mitochondria, indicating high metabolic activity. These varicosities are the factories which synthesize, store and release the transmitter. The apparatus necessary for this work (enzymes, granules, mitochondria, etc.) are probably built in the soma of the nerve cell and transferred to the varicosities *via* the axon.

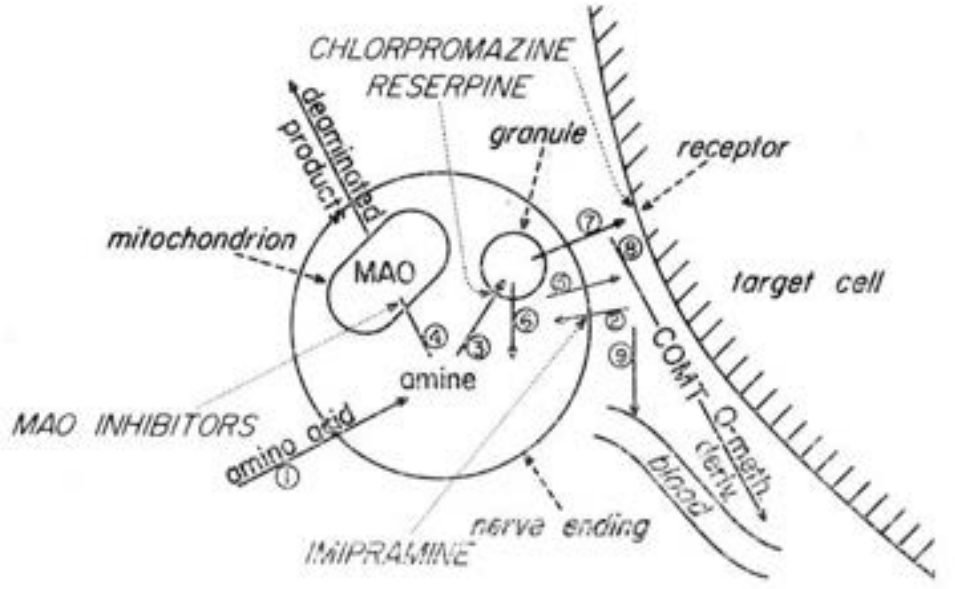

Fig. 1. — *Hypothetical model illustrating the various processes involved in monoamine transmission, and the sites of attack of four different types of psychoactive drugs. - For further explanation, see text.*

The schematic drawing in Figure 1 serves to illustrate how such a varicosity operates. The starting material is an amino acid, tyrosine in catecholamine-storing neurons (*cf.* Figure 2) and tryptophan in 5-HT neurons (*cf.* Figure 3). The amino acid enters the varicosity (arrow 1) *via* a blood capillary and the extracellular space — possibly it also has to pass through a *Schwann* cell (in the peripheral nervous system) or a glia cell (in the central nervous system). By means of a number of enzymes (see Figures 2 and 3) the amino acid is converted to the transmitter ("amine"), which is taken up by the granules and incorporated into a storage complex (arrow 3). (In the case of NA the last step in the synthesis *i.e.* the side-chain hydroxylation of DA, probably takes place in the storage granule). The transmitter is now available for release by the nerve impulse, which by an unknown mechanism acts on the granule to release the transmitter from the storage complex into the synaptic cleft (arrow 7). The transmitter can now combine with its receptor on the target ("effector") neuron and can thus exert its characteristic excitatory or inhibitory action on this neuron. The termination of the effect may be brought about by three principally different mechanisms, 1) enzymatic breakdown, 2) reabsorption by nerve terminal (arrow 2), and 3) diffusion and escape *via* the blood vessels (arrow 9; this route is probably of minor importance in the central nervous system, since the transmitters do not readily pass through the blood-brain barrier). In the case of brain 5-HT monoamine oxidase (MAO) is the dominating, if not the only inactivating enzyme. Also for the catecholamines this enzyme is important, but another pathway is 3-0-methylation by means of catechol-O-methyl transferase (COMT). It appears that MAO primarily serves as a security valve inside the nerve terminal (arrow 4), while breakdown by COMT (arrow 8) chiefly occurs after release into the extracellular space (see Carlsson) [20, 21, 22]. However, also MAO seems to be available for the inactivation of extracellular transmitter. For example, release of 5-HT from the isolated spinal cord into the surrounding Ringer solution could be detected only after MAO inhibition [3].

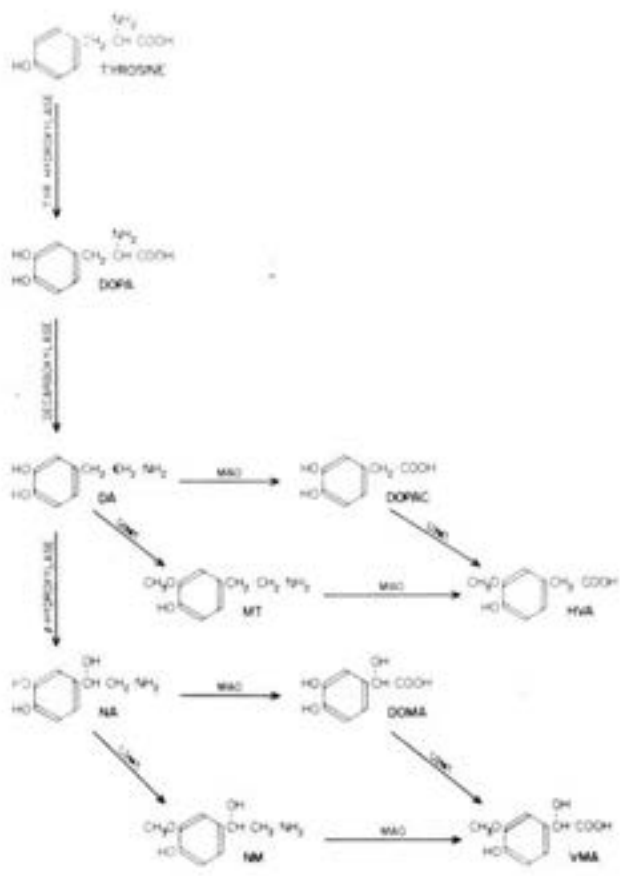

Fig. 2. — *Simplified scheme illustrating the main pathways in the formation and degradation of dopamine (DA) and noradrenaline (NA). - DOPA = 1-3.4-dihydroxyphenylalanine. MT = 3-methoxytyramine. NM = normetanephrine. DOPAC = 3,4-dihydroxyphenylacetic acid. DOMA = 3,4dihydroxymandelic acid. HVA = homovanillic acid. VMA = vanillylmandelic acid. MAO = monoamine oxidase. COMT = catechol-3-methyl transferase. - Certain intermediate metabolites and alternative pathways are not shown.*

These various processes involved in the transmission machinery represent potential sites of drug action. In fact, the detection of these processes and the demonstration of their functional importance is largely the result of drug studies. Below a brief survey will be given of the present status of research with regard to the action of some psychoactive drugs on transmission mechanisms. Four groups of drugs of ma-

jor clinical interest will be primarily considered.

Reserpine and other drugs acting on the storage granules

Reserpine inhibits the transmission mechanism of peripheral adrenergic nerves [31, 60] and probably also of other neurons, whose transmitters are influenced in similar manner, *i.e.* central NA, DA and 5-HT neurons. Reserpine has been found to block the incorporation of transmitter into the storage granules [28, 29, 45, 66], leading to depletion and, consequently, block of transmission. There is, however, no direct correlation between the level of transmitter and the degree of transmission blockade. This is probably explained by the occurrence of two (or more) different pools in the storage granules [61]. One small pool with a high turnover rate appears to be directly involved in the transmission mechanism, while a major fraction serves as a store and is essential only when the synthesis of the transmitter is insufficient [21, 22, 54]. The blockade of transmission caused by reserpine appears to set in and recover before the total transmitter levels are fully depleted and replenished, respectively, but is more closely correlated to changes in the small, functionally essential pool. In similar manner it is possible to explain the fact that the major part of the transmitter l-noradrenaline can be replaced by a less active analog such as d-adrenaline without impairment of transmission [7]. Needless to say, great caution must therefore be exercised in attempts to evaluate the physiological significance of changes in total tissue monoamine levels.

When the incorporation of transmitter into the storage granules is blocked by reserpine, newly formed transmitter as well as transmitter leaking out of the granules (arrow 6, Figure 1) accumulate in the cytoplasm of the nerve ending, leading to increased oxidative deamination by MAO (arrow 4) and accumlation of acid metabolites [11, 74]. Remarkably enough, this accumulation persists longer than would be expected [9, 10]. The cause of this phenomenon is obscure. Possibly mechanisms such as those discussed below under chlorpromazine are at work.

Tetrabenazine and a number of other synthetic benzoquinolizines seem to act es-

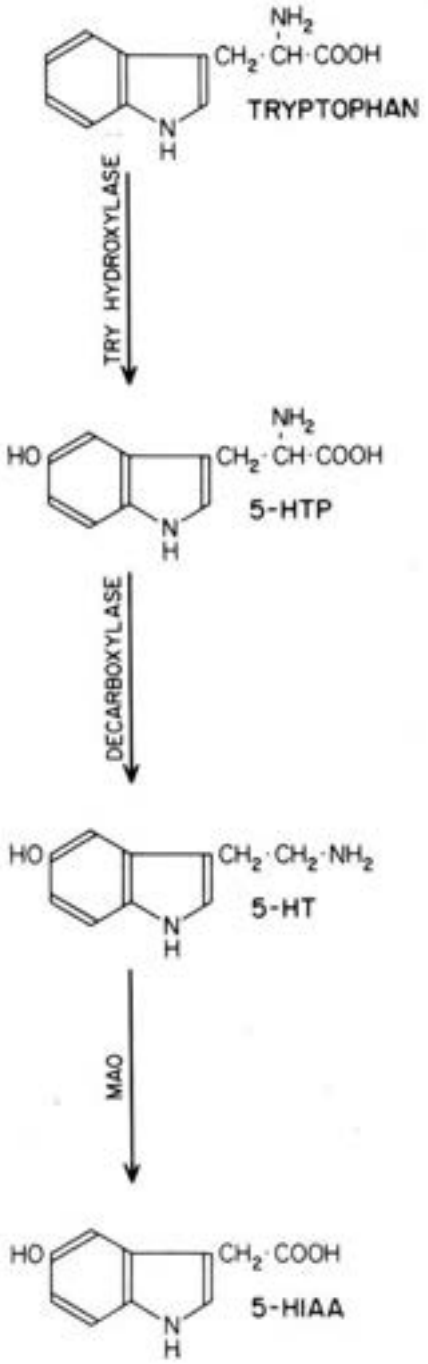

Fig. 3. — *Simplified scheme illustrating the main pathway in the formation and degradation of 5-hydroxytryptamine (5-HT). - 5-HTP = 5-hydroxytryptophan. 5-HIAA = 5-hydroxyindoleacetic acid. - An intermediate aldehyde step between 5-HT and 5-HIAA is not shown.*

scntially as reserpine, except that they have a shorter duration of action and relatively weak effects on the peripheral adrenergic system. In support of identical sites of action it has been found that pretreatment of animals with tetrabenazine protects the animals against the longlasting sedative and amine-depleting action of reserpine [72] *.

A number of benzoquinolizines are able to disrupt conditioned avoidance reactions and produce a number of other depressant central actions in doses which do not affect amine levels. An example of this is benzquinamid. In this case we are probably dealing with another as yet obscure mechanism of action.

Chlorpromazine, haloperidol and related drugs. In spite of the fact these drugs have so many actions in common with reserpine and tetrabenazine, they do not affect monoamine levels.

Their ability to delay a) the monoamine accumulation induced by MAO inhibitors, b) the monoamine depletion caused by reserpine and c) the permeation of *e.g.* tryptamine into the brain, appears to be secondary to the hypothermia caused by large doses of these drugs [63, 70]. Recently another effect of chlorpromazine and haloperidol on monoamine metabolism has been observed. This effect is produced already by low doses and is unrelated to hypothermia. It was first observed that the accumulation of the 3-O-methylated metabolites of dopamine and noradrenaline, *i.e.* 3-methoxytyramine and normetanephrine, respectively (see Figure 2), was specifically enhanced by treatment with chlorpromazine or haloperidol [39]. Later it was found that these drugs, when given alone, caused and increase in the concentrations of the acid dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) [10]. This accumulation of basic and acid metabolites probably reflects an increased monoamine turnover. The mechanism of this effect has not been elucidated. The most reasonable explanation appears to be that we are dealing with a compensatory activation of the transmission mechanism, possibly due to activation of monoamine neurons by a feed-back mechanism. According to this line of thinking the primary action of chlorpromazine would be to block the action of the transmitter by combining with the receptors of the target neuron. As is well known, chlorpromazine blocks peripheral adrenergic receptors of the *alpha*-type and alleviates some of the central and peripheral actions of catecholamines and 5-HT accumulating after the administration of the precursors DOPA and 5-hydroxytryptophan, respectively. Haloperidol appears to share only the central activity with chlorpromazine.

It is noteworthy that chlorpromazine and haloperidol do not cause an increase in the 5-HT metabolite 5-hydroxyindoleacetic acid [10]. This may indicate that these drugs interfere more with catecholamine than 5-HT transmission or that compensatory stimulation of 5-HT neurons is not so readily brought about as in the case of dopamine neurons. As to the effect on noradrenaline metabolites, only the normetanephrine data mentioned above are available as yet.

It may be concluded that not only reserpine and tetrabenazine but also chlorpromazine and haloperidol interfere specifically with the metabolism of monoamines in the brain. In order to clarify the mechanism and functional significance of the effects further investigation is necessary, particularly in the case of the latter two drugs.

Monoamine oxidase (MAO) inhibitors. When discussing the MAO inhibitors it is important to keep in mind that very few of the available members of this group interfere with monoamine transmission only by virtue of their activity as MAO inhibiters. Iproniazid has a well-established adrenergic blocking activity and has central depressant properties– possibly also a result of receptor blockade. Pheniprazine

* According to Quinn et al. tetrabenazine is unable to prevent reserpine-induced noradrenaline depletion. Unpublished experiments of this laboratory show, however, that tetrabenazine protects brain noradrenaline, dopamine and 5-HT to about the same extent.

and tranylcypromine have amphetamine – like properties, and tranylcypromine has been shown to cause release of noradrenaline in brain [32]. Nialamide and possibly also pargyline appear to be relatively pure MAO inhibitors. From the experimental point of view this is, of course, an advantage. From the clinical point of view this does not necessarily hold true. Among psychiatrists there seems to be a wide-spread impression that several of the newer MAO inhibitors are less potent than iproniazid as antidepressants. It might well be asked if a receptor-blocking and sedative component is favourable for an antidepressant. It is interesting to note that there are good reasons to raise the same question in the case of the imipramine group.

In any event, the activating and mood-elevating properties of MAO inhibitors are well established, as are their ability to inhibit MAO and to raise the levels of catecholamines and 5-HT in the brains of several mammalian species, including man [12, 52]. In experimental animals it has been shown that the symptoms of central excitation caused by nialamide do not develop in parallel with the amine accumulation but seem to set in when the capacity of the monoamine stores is exceeded, resulting in overflow of transmitter into the extracellular space. As a sign of this overflow, O-methylated metabolites start to accumulate at an increased rate [32]. This course of events may be explained on the basis of the model of Figure 1. Owing to the intraneuronal localization of MAO, inhibition of this enzyme will primarily result in accumulation of intracellular and thus physiologically inactive transmitter. Only when the capacity of the store is exceeded will overflow into the extracellular space occur. Not until then will the transmitter be available for activation of the receptor and for breakdown by COMT (cf. *Carlsson*[20]).

MAO inhibitors are able to counteract the sedative effect of reserpine, provided the dose of the latter is not too large [13, 19]. In experiments of this kind it is important to keep the animals in a warm environment in order to prevent reserpine-induced hypothermia, which otherwise will retard amine synthesis and thus delay the restorative action of MAO inhibitors [22].

If reserpine or tetrabenazine is administered *after* MAO inhibition, a syndrome characterized by marked central excitation and signs of sympathetic stimulation develops rapidly. The reserpine-induced disappearance of monoamines from the brain is partially prevented. The excitation appears to be due to release of monoamines into the extracellular space, as demonstrated histochemically in *Hillarp's* laboratory (unpublished data). For further discussion of the mechanisms involved in the interaction between MAO inhibitors and reserpine, see *Carlsson* [22].

The imipramine group. The discovery of the powerful antidepressant properties of imipramine at first did not seem to fit in with experimental observations, according to which imipramine appeared to act merely like a weak member of the chlorpromazine group. No doubt imipramine and related antidepressant agents possess a chlorpromazine-like, probably receptor-blocking action, but they also have another effect, which acts in the opposite direction. In the peripheral adrenergic system they potentiate the effect of nerve stimulation or of administered noradrenaline [53, 81, 82]. In all probability this effect is brought about by blockade of the transport of extracellular noradrenaline through the cell membrane into the cytoplasm of the nerve ending (arrow 2, Figure 1). Direct support of this has been obtained by histochemical observations in *Hillarp's* laboratory (unpublished data). Earlier it had been found that the uptake of H^3-noradrenaline by tissues is blocked by imipramine [58, 59]. In all probability imipramine has a similar action in brain. It blocks the uptake of H^3-noradrenaline by brain slices [38] and counteracts several central actions of reserpine and tetrabenazine [22, 40].

Within the imipramine group a certain correlation appears to exist between antidepressant and noradrenaline-sensitizing activities [53,82]. Amitriptyline is less acti-

TABLE 1

Agents causing deficiency of monoamines at receptors

Agent	*Probable mechanism*	
Reserpine group	Blockade of storage granules	
Tetrabenazine group	— " —	
Chlorpromazine group	Blockade of monoamine receptors	
Haloperidol group	— " —	
Dopacetamide group	Inhibition of synthesis	
Alpha-methyl DOPA	— " —	+ ?
Alpha-methyl *m*-tyrosine	— " —	+ ?
Guanethidine	Inhibition of release	
Bretylium	— " —	

ve with respect to the latter effect while removal of one of the two methyl groups on the nitrogen yields more active compounds. Chlorpromazine and several related neuroleptics are able to block the membrane transport of noradrenaline, but this does not necessarily result in sensitization to the transmitter because of a simultaneously occurring receptor blockade. It seems possible that a certain balance between blockade of membrane transport and of receptors results in optimum antidepressant properties. The theoretical explanation of such a paradoxical phenomenon must await further studies.

Other agents. The chief mechanisms by which drugs may cause deficiency and excess of monoamines at receptors are summarized in Tables 1 and 2 respectively, where also some agents of as yet mainly experimental interest have been included. The *dopacetamide* groups have been found to inhibit the first step in the synthesis of catecholamines (tyrosine → DOPA) and 5-HT (tryptophan → 5-hydroxy-tryptophan); they 1) have certain central depres-

TABLE 2

Agents causing excess of monoamines at receptors

Agent	*Probable mechanism*	
DOPA	Precursor of DA (and NA)	
DOPS[1]	Precursor of NA	
5-HTP	Precursor of 5-HT	
o-Tyrosine	Precursor of *o*-tyramine	
m-Tyrosine	Precursor of *m*-tyramine	
Amphetamines	Catecholamine analogs	
Tryptamines	5-HT analogs	
Mescaline, LSD and related hallucinogens	Monoamine analogs ?	
MAO inhibitors	Inhibition of monoamine breakdown	
COMT inhibitors	Inhibition of catecholamine breakdown	
Imipramine group	Blockade of uptake by nerve endings	
Cocaine	— " —	+ ?

1) = *threo*-L-3,4-dihydroxyphenylserine (does not occur physiologically; normally NA is formed from DA).

sant properties 2) cause a decrease in brain monoamine levels, 3) block the amine accumulation and central excitation induced by MAO inhibitors, 4) potentiate the depressant effects of reserpine and chlorpromazine [24, 25]. *Alpha-methyl DOPA* is chiefly used as an antihypertensive drug but may cause sedation, mental depression, parkinsonian symptoms and lactation. This drug thus has several properties in common with the major tranquillizers. As an analog of the catecholamine precursor DOPA it probably acts by interfering with monoamines, but its mechanism of action is not yet known. It was introduced as an inhibitor of DOPA/5-HTP decarboxylase but probably has other more important actions, *e.g.* inhibition of the rate-limiting first step in the synthesis of monoamines (*cf.* the dopacetamides) and interference with monoamines *via* decarboxylation products (see Carlsson [21]). *Alpha-methyl metatyrosine* is closely related to *alpha*-methyl DOPA but seems to be less active in certain respects. *Guanethidine* and *bretylium* are capable of inhibiting monoamine release by the nerve impulse (arrow 7, Figure 1) but do not penetrate into the brain (see *Shore* [79]). Consequently they have only peripheral actions.

The main advantage of the *monoamine precursors* (Table 2) is that they, in contrast to the monoamines themselves, easily penetrate into the brain. Since the DOPA/5-HTP decarboxylase (probably a single enzyme, see *Rosengren* [75]) is mainly localized to the monoamine neurons, the monoamines formed from the administered precursors are chiefly found in the same locations as physiologically, with the reservation that *e.g.* 5-HT may be formed not only in 5-HT neurons but also in catecholamine-containing neurons, and *vice versa*. The fact that the syndromes produced by DOPA and 5-HTP are markedly different, nevertheless indicates that discrimination between the two takes place. Probably this is brought about at the receptor level.

Unphysiological amino acids, such as DOPS and *o*- and *m*-tyrosine, are also substrates for the decarboxylase. The syndrome produced by these amino acids resembles that caused by DOPA and is probably caused mainly by an action of the decarboxylation products on catecholamine receptors. The amino acids themselves are pharmacologically inert [17, 21].

Certain catecholamine and tryptamine analogs (Table 2) are able to penetrate through the blood-brain barrier and to produce central actions resembling those of the catecholamine and 5-HT precursors. The important *amphetamines* probably should be looked upon as catecholamine analogs. *Mescaline, LSD* and related *hallucinogens* probably also act as monoamine analogs, although the mechanisms involved are obscure.

Agents which cause deficiency of monoamines at receptors by different mechanisms (Table 1) in general tend to potentiate each other's actions. The same holds true for agents acting in the opposite direction (Table 2). Furthermore, the drugs of Table 1 in general antagonize those of Table 2, and *vice versa*.

Functional systems involved in the action of drugs interfering with brain monoamines

An as yet rather vague picture of the mode of action of some of the major psychoactive drugs is slowly emerging. This is mainly the result of the accumulation of pharmacological, biochemical, and clinical data. In Table 3 the various symptoms induced by deficiency or excess of monoamines at receptors are summarized, and the neuronal pathways tentatively involved are given. It is evident that the monoamines play a part in a great number of functional systems and at practically all levels of the nervous system. It should perhaps be emphasized that all functional systems are not equally sensitive to a given drug and that drugs acting in the same direction may differ considerably in their actions on different systems. For example, reserpine and other drugs causing blockade of the storage mehcanism and, consequently, of transmission, in general seem to have a wider sepctrum of action than chlorpromazine

TABLE 3

Functional systems involved in the action of drugs interfering with monoamines

FUNCTIONS INFLUENCED BY MONOAMINES	EFFECT OF RECEPTOR-BOUND MONOAMINE LACK	EXCESS	PATHWAYS TENTATIVELY INVOLVED
Higher integrative functions			
Spontaneous motility Explorative behaviour Responses to unconditioned stimuli Responses to conditioned stimuli Emotional reactions Mood EEG activation	—	+	NA and 5-HT (DA?, A?) neurons from mesencephalon to various structures in telencephalon and diencephalon (partly in the limbic system).
Motor functions			
Extrapyramidal functions	—	+	Nigro-neostriatal DA neurons, 5-HT neurons from mesencephalon to neostriatum.
Convulsion threshold	—[1]	+	Ascending neurons from mesencephalon.
Spinal reflexes	—	+	NA and 5-HT neurons from lower brain stem to anterior and posterior horns.
Sensory functions			
Light sensitivity	+	—	Retinal inhibitory DA neurons.
Other sensory functions	?	?	Neurons to various sensory nuclei.
Autonomic functions			
Sympathetic			
Higher centers	—?	+?	NA and 5-HT neurons from mesencephalon to hypothalamic area.
Spinal centers (intermediolateral nucleus)	+	—	NA and 5-HT neurons from lower brain stem.
Sympathetic ganglia	+?	—?	Possibly interneurons of ganglia.
Peripheral organs	— or +	+ or —	Postganglionic neurons.
Parasympathetic			
Higher centers	+?	—?	Neurons ascending from mesencephalon to hypothalamic area?
Centers of lower brain stem and spinal cord	+	—	NA and 5-HT neurons from lower brain stem to parasympathetic nuclei of brain stem and spinal cord.
Parasympathetic ganglia	+	—	NA neurons of unknown origin terminating *e.g.* in intestinal intramural ganglia.
Endocrine functions			
Anterior pituitary (prolaction; ACTH)	+	—	DA (and NA?) neurons from arcuate nucleus to primary capillary plexus of pituitary portal system.
Posterior pituitary	+?	—?	NA (and 5-HT) neurons from mesencephalon to supraoptic and paraventricular nuclei.
Other endocrine glands (*e.g.* islands of pancreas, thyreoid)	?	?	Monoamines in glandular cells.
Chromaffin cells	— or +	+ or —	Catecholamines.
Mast cells	?	?	Monoamines in mast cells.
Enterochromaffin cells	?	?	5-HT in enterochromaffin cells.
Blood platelets	?	?	5-HT in platelets.

1) = threshold is lowered.

and other receptor-blocking drugs. The increased light sensitivity with blepharospasm, the parasympathetic stimulation and the increased sympathoadrenal impulse flow characteristic of reserpine are thus not observed after chlorpromazine treatment. It may be that not all monoamine receptors are sensitive to chlorpromazine, in analogy to the situation in the peripheral adrenergic system. A certain blocking action of chlorpromazine on cholinergic and possibly other receptors may be an additional factor. However, the similarity between the two groups of drugs is more striking than the differences and involves, for example, the following actions: inhibition of spontaneous motility, of explorative behaviour, of responses to unconditioned and —in even lower doses— conditioned stimuli, of emotional reactions, extrapyramidal disturbances leading to parkinsonism, and increase in prolaction secretion resulting in mammary growth and lactation.

The monoamine pathways involved in *higher integrative functions* are now being investigated in detail. In all probability they originate in the mesencephalon where a considerable part of the monoamine neurons are located [36]. In the caudal part of the mesencephalon these cells are almost exclusively of the 5-HT type; they are located predominantly in the raphe nuclei. The NA cells occur almost exclusively in the rostral part, where they are chiefly located in the reticular formation and in a basal medial area dorsal to the interpeduncular nucleus. From the cells of these various mesencephalic areas axons ascend, partly within the limbic system, to widespread regions within the telencephalon and the diencephalon (*Fuxe*, unpublished data). On the whole, these pathways seem to exert a facilitating influence on their target structures. It seems reasonable to suggest that they are activated by various afferent stimuli and thus participate in alerting responses which are so characteristically inhibited by the major tranquillizers (see, for example, the EEG studies of *Pscheidt, Steiner* and *Himwich* [71]). Further investigation will reveal to what extent a closer localization of the different functions —and differentiation between them— is possible.

When the higher integrative functions have been inhibited by drugs such as reserpine or chlorpromazine, they can be largely restored by administration of the catecholamine precursor DOPA but not by the 5-HT precursor 5-hydroxytryptophan, which may partly exert an unfavourable influence [31, 46, 65, 76, 77, 78] (also Hanson unpublished data). The data support the view that catecholamine-containing neurons are involved in these higher functions. Although they provide little information on the role of 5-HT neurons they do not exclude the possibility (which *à priori* seems likely) that also these neurons are involved in higher integrative functions.

The recently discovered nigro-neostriatal DA pathway [1] which is responsible for the high DA concentration in the neostriatum [14, 15] seems to be involved in the *extrapyramidal disturbances* produced by the major tranquillizers or occurring spontaneously. This pathway seems to be characteristically destroyed in non-drug-induced parkinsonism, with severe dopamine depletion in the substantia nigra and in the neostriatum [16] (for further literature see *Carlsson* [23], *Sourkes* [83]). DOPA partially alleviates the motor disturbances of non-drug induced parkinsonism in man [64]. 5-HTP is less active in this respect. In rats the extrapyramidal disturbances caused by major tranquillizers seem to be related to an increased *alpha* and a decreased *gamma* motoneuron activity [84]. These changes are efficiently counteracted by administration of DOPA or 5-HTP [73]. The data suggest that also 5-HT neurons may be involved in extrapyramidal functions. In fact, the 5-HT level is fairly high in the neostriatum [14].

Even though by far the major fraction of brain DA belongs to the extrapyramidal system, it should be kept in mind that DA neurons also occur elsewhere. For example, a compound which in all probability is DA, has been detected in a pathway originating

in the hypothalamic arcuate nucleus and terminating in the primary plexus of the pituitary portal system [60]. It is presumably involved in some of the actions of major tranquillizers on the pituitary. Another DA system has been detected in the retina; it may be involved in the increased light sensitivity caused by the reserpine-tetrabenazine group [55]. Probably other DA pathways exist.

Space does not permit a detailed discussion of the various functions itemized in Table 3. In general it may be said about the monoamine pathways involved, that with few exceptions they originate in the mesencephalon or in lower parts of the brain stem from where they ascend to various brain regions as mentioned above, or descend to nuclei in the brain stem and spinal cord. The spinal cord seems to contain no monoamine cell bodies. The descendent spinal pathways appear to exert mainly facilitating but partly inhibitory influences on spinal reflexes [4, 5, 6, 33] and to cause inhibition of spinal sympathoadrenal centers [2]. This inhibitory influence of monoamine transmitters may explain certain paradoxical drug actions, *e.g.* the hypotensive action of MAO inhibitors and the signs of sympathoadrenal stimulation observed after administration of reserpine and related agents.

It is interesting to note that parasympathetic bulbar and spinal centers are innervated by NA and 5-HT neurons (*Dahlström, Fuxe, Hillarp* and *Malmfors* [37], and unpublished data). Presumably these neurons exert an inhibitory influence. Blockade of monoamine transmission in these areas may explain some of the signs of parasympathetic stimulation observed after treatment with reserpine and tetrabenazine. However, within the parasympathetic as well as the sympathetic system monoamine pathways may interfere at both higher (*e.g.* hypothalamic) or lower levels (*e.g.* peripheral ganglia or nerve endings). Particularly in the sympathoadrenal system this will result in a complicated picture with stimulation of certain functions and centrally or peripherally induced inhibition of others.

It has been suggested that NA is chiefly concerned with sympathetic ("ergotrophic"), 5-HT with parasympathetic ("trophotropic") centers. The two monoamines would thus antagonize each other [19]. Histochemical data show, however, that both monoamines occur in both systems. It is at present hardly possible to classify the two amines as each other's synergists or antagonists. Most probably the former holds true in some systems, the latter in others. It is noteworthy that, judging by precursor studies, 5-HT has a negative and catecholamines a favourable influence on conditioned avoidance reactions.

There is some support for the view that acetylcholine and catecholamines serve as each other's antagonists in the brain, just as they often do in the peripheral nervous system. Local applications of acetylcholine and NA in the preoptic area have thus been found to cause sleep and alertness, respectively [58]. Analogous observations have been made by *Yamaguchi, Ling* and *Marczynski* [87], who also observed that 5-HT applied locally in certain areas promoted sleep. The central stimulating and even psychotomimetic actions of several anticholinergic drugs are in line with the assumption of a balance between acetylcholine and NA within the limbic system.

The extrapyramidal system provides another example where a catecholamine and acetylcholine probably are antagonists. In addition to the above-mentioned DA pathway a non-monoamine containing nigro-neostriatal pathway exists [1]. Comparison with the data of *Shute* and *Lewis* [80] on cholinesterase-containing systems of the brain suggests that this pathway is cholinergic. The favourable influence of cholinergic blocking drugs on parkinsonism suggests that this pathway antagonizes the DA pathway. The fact that the two pathways run closely together might explain why the production of parkinsonism by experimental lesions has not yet proved successful.

Acknowledgements

The work done in the reviewer's laboratory which is described in this survey was supported largely by research grants from Publich Health Service Research Grant NB 04359-02, National Institute of Neurological Diseases and Blindness the Air Force Office of Scientific Research, OAR (Grant AF EOAR 64-30) through the European Office of Aerospace Research, United States Air Force, and from the Swedish State Medical Research Council.

SUMMARY

Transmission mechanisms have long been recognized as the chief targets for drugs with selective actions on the *peripheral* nervous system. Evidence is accumulating that this holds true also for the *central* nervous system. Several major groups of psychoactive drugs (*e.g.* the reserpine-tetrabenazine group, the chlorpromazine-haloperidol group, the monoamine oxidase inhibitors, the imipramine group, the amphetamines, and certain hallucinogens) in all probability act by interfering selectively with the monoamines noradrenaline, dopamine and/or 5-hydroxytryptamine in the brain. In recent years strong evidence has accumulated that these monoamines occur in neurons, where they are concentrated in the specific storage granules of the synaptic nerve-ending varicosities. This together with biochemical, physiological and pharmacological data constitutes strong evidence that the monoamines serve as transmitters in the central nervous system. The major tranquillizers inhibit and the antidepressant drugs stimulate these transmission mechanisms.

By means of combined histochemical and biochemical techniques it has become possible to map out the monoamine-containing neuronal pathways in the brain and spinal cord and thus to define the morphological and functional systems influenced by the psychoactive drugs. Although this work is as yet only in its beginning, it seems possible to link several of the main actions of the psychoactive drugs with specific functional systems at various levels of integration. For example, the actions of psychoactive drugs on higher integrative functions may be explained by actions on noradrenaline and 5-hydroxytryptamine pathways originating in the reticular formation and other areas of the mesencephalon and ascending —partly within the limbic system— to various telencephalic and diencephalic regions. The extrapyramidal actions of these drugs may be partly explained as due to an effect on a nigro-neostriatal dopamine pathway. Similarly, actions on spinal centers and on autonomic and endocrine functions have been partly elucidated.

RESUMEN

Los mecanismos de transmisión fueron reconocidos durante mucho tiempo como objetivo de drogas de acción selectiva sobre el sistema nervioso periférico. Cada vez son más numerosas las evidencias que indican que esto es válido igualmente en cuanto al sistema nervioso *central*. Varios importantes grupos de drogas psicoactivas (p. ej. los grupos reserpina-tetrabenazina, clorpromazina-haloperidol, imipramina, los inhibidores de la monoamino oxidasa, las anfetaminas y ciertos alucinógenos) muy probablemente actúen interfiriendo selectivamente con las monoaminas noradrenalina, dopamina y/o 5-hidroxitriptamina en el cerebro. Recientemente se han acumulado

poderosas evidencias en cuanto a la existencia de estas monoaminas en las neuronas, donde se concentran en los gránulos específicos de almacenamiento de las varicosidades que se encuentran en las terminaciones nerviosas sinápticas. Sumados a esto los datos bioquímicos, fisiológicos y farmacológicos constituyen una evidencia más en cuanto al papel de transmisores que desempeñan las monoaminas en el sistema nervioso central. Los tranquilizadores fuertes inhiben estos mecanismos de transmisión, las drogas antidepresivas los estimulan. Por medio de técnicas histoquímicas y bioquímicas combinadas ha sido posible determinar las vías neuronales que contienen monoaminas en el cerebro y en la médula permitiendo así la definición de sistemas morfológicos y funcionales influidos por las drogas psicoactivas. Aunque esta tarea está en sus comienzos, parece probable relacionar las principales acciones de las mencionadas drogas con sistemas funcionales específicos a diversos niveles de integración. Por ejemplo, las acciones de estas drogas sobre funciones integrativas elevadas pueden ser explicadas por la acción de las vías conteniendo noradrenalina y 5-hidroxitriptamina originadas en la formación reticular y otras áreas del mesencéfalo y ascendiendo —en parte dentro del sistema límbico— sobre varias regiones telencefálicas y diencefálicas. Las acciones extrapiramidales de estas drogas pueden explicarse en parte como debidas al efecto ejercido sobre una vía nigro-neostriatal conteniendo dopamina. Igualmente, las acciones ejercidas sobre los centros medulares y sobre las funciones autónomas y endócrinas han sido elucidadas en parte.

RÉSUMÉ

Les mécanismes de transmission ont été reconnus pendant longtemps comme but des drogues d'action sélective sur le système nerveux périphérique. Des évidences continuent à s'accumuler qui indiquent que cela est valable aussi pour le système nerveux *central*. Des groupes importants de drogues psychoactives (p. ex. les groupes réserpine - tétrabenazine, chlorpromazine - halopéridol, imipramine, les inhibiteurs de la monoamine-oxidase, les amphétamines et certains hallucinogènes) actuent très probablement en interférant selectivement avec les monoamines noradrénaline, dopamine et/ou 5 hydroxitriptamine dans le cerveau. On a accumulé récemment de fortes évidences quant à l'existance de ces monoamines dans les neurones, où elles se concentrent dans les granules spécifiques de réserve des varicosités qui se trouvent sur les terminaisons nerveuses synaptiques. A ceci s'ajoutent des données biochimiques, physiologiques et pharmacologiques qui constituent une évidence de plus quant au rôle de transmission joué par les monoamines dans le système nerveux central. Les tranquilliseurs forts inhibent ces mécanismes de transmission tandis que les drogues antidépressives les stimulent. Par moyen de techniques histochimiques et biochimiques combinées il a été possible de déterminer les voies neuronales contenant des monoamines dans le cerveau et dans la moëlle et aussi la définition de systèmes morphologiques et fonctionnels influencés par les drogues psychoactives. Bien que ce travail soit dans ses premiere étapes, il parait probable de rapporter les principales actions des drogues psychoactives à des systèmes fonctionnels spécifiques à plusieurs degrés d'intégration. Par exemple, les actions de ces drogues sur des fonctions intégratives élevées peuvent être expliquées par l'action des voies contenant noradrénaline et 5-hidroxitriptamine originées dans la formation reticulaire et d'autres aires du mésencéphale et ascendant —en partie dans le système limbique— sur plusieurs régions télencéphaliques et diencéphaliques. Les actions extrapyramidales de ces drogues peuvent s'expliquer en partie comme dues a l'effet exercé sur une voie

nigro-neostriatele contenant de la dopamine. Egalement, les actions exercées sur les centres médulaires et sur les fonctions autonomes et endocrines ont été partiellement élucidées.

ZUSAMMENFASSUNG

Die Transmissionsmechanismen sind seit langem als die Haupt Angriffspunkte fuer die Medikamente mit selektiver Wirkung beim periferischen Nervensystem anerkannt worden. Es gibt immer mehr Beweise dass diese Tatsache auf fuer das Centrale Nervensystem gilt. Verschiedene Hauptgruppen von psychoaktiven Mitteln (z.B. die Gruppen Reserpina Tetrabenazina, oder die Gruppe Chlorpromazine-Haloperidol, die Inhibitoren der Monamino Oxidase, die Gruppe der Imipramine, die Amphetanamine und gewisse Halluzinogene) wirken sehr wahrscheinlich indem sie selektiv mit den monoaminen Noradrenalin, Dopamine und oder mit der 5-Hydroxitryptamine im Gehirn interferieren. In den letzten Jahren hat man starke Beweise gefunden, dass diese Monoamine in den Neuronen vorkommen, wo sie in den spezifischen Depotkoernchen der synaptischen Nervenendigungs- Varikositaeten konzentriert sind. Dies zusammen mit den biochemischen, physiologischen und pharmakologischen Daten, stellt einen klaren Beweis dar, dass die Monoaminen als Uebertraeger dienen im Zentralen Nervensystem. Die meisten Tranquillisanten inhibieren und die meisten Antidepressionsmittel stimulieren diese Uebertragungsmechanismen. Mittels einer Kombinierten Histochemischen und Biochemischen Technik ist es moeglich geworden, die monaminenthaltenden neuronalen Wege in Gehirn und Rueckenmark festzustellen und so die funktionellen und morphologischen Systeme, die durch die psychoactiven Medikamente beeinflusst werden, festzustellen. Obwohl diese Arbeit erst in seinen Beginne ist, scheint es moeglich zu sein Verschiedenen der Hauptwirkungen der psychoaktiven Medikamente mit spezifischen funktionellen Systemen bei verschiedenen Integrationsniveaus in Zusammenhang zu brigen. Z.B. die Wirkungen psychoaktiver Medikamente auf die hoeheren integrativen Funktionen kann durch die Wirkungen auf Noradrenalin und 5-Hydroxitryptaminwege die in der Retikularen Formation und anderen Zonen des Mesencephalons entstehen, zum Teil im Lymbischen System und in verschiedenen Regionen des telencephalischen und diencephalischen Systems aufsteigen. Die extrapyramidalen Wirkungen dieser Medikamente kann teilweisse als effekt auf die nigroneostriaerten Dopamine— Wege erklaert werden. In aehnlicher Weise sind die Wirkungen auf die spinalen Zentren und auf die autonomen und endokrinen Funktionen teilweise aufgeklaert worden.

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Aspects of Biological Psychiatry in Thailand

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INTRODUCTION

Comparative Psychiatry allows to study the most important aspects in mental health activities. Social status, economic conditions, customs, cultural background, education and religions are analyzed in order to promote a better understanding among people of all creeds and races.

In the Orient, where occult practices have existed for thousands of years and where in some regions witchdoctors are still regarded as belonging to an honorable profession, mental illness is far from being accepted and Psychiatry is at its beginning. Therefore psychiatrists have to explore the social status and cultural phenomena concerning their patients in order to introduce modern psychiatric facilities in that particular society. Among the social factors determining a certain way of life and also adjustment to the environment, religion and philosophy have often proved to be important. As mental health depends on a proper adjustment to the environment, these social factors become the concern of Psychiatry in Thailand.

Thailand is the land of Thai race and Thai means "FREE".

Thailand has been an independent country and enjoys her freedom since a thousand years ago or even more. She is now the main crossroad of the Far East in this supersonic era. Social and cultural changes have modified mental health conditions of some groups of people, mainly youths and young adults, which are of deep concern at present.

The population, now 28 millions, has always been attached to religious principles and has been characterized by cordial relationship and brotherly love.

Incidence of mental illness has increased 5 times in the last 20 years. Psychiatric services in Thailand were established 80 years ago with the opening of the first mental hospital or Lunatic asylum. There has been great progress in these last 2 decades; bars from wards have been removed, detention rooms no more exist and in their place modern treatment including psychotherapy, pharmacotherapy, shock treatment, neurosurgery has been introduced, as well as auxilliary treatment (occupational therapy and recreation services).

At present we have 7 hospitals for mental and nervous disorders with capacity for 6.000 beds, with a separate and independent Neurological Hospital which is entirely devoted to Organic Neurological cases and a Hospital for Mental Retardation. Two child guidance clinics were set up recently to act like mental health centres for pediatric cases. A drug addiction treatment centre was also opened in 1960 to fight against problems of opium addiction and very serious situations in heroine cases.

We have one year post graduate training in Psychiatry at the Mental Hospital, but fortunately enough our physicians had their training in U.S.A. and Europe.

There are 3 agencies working with various professional groups in the promotion of mental health in Thailand. The Psychiatric Association at the Mental Hospital is concentrating on psychiatric facilities for its members and colleagues. The Neurological Society at our Prasat Neurological Hospital is constituted by a group of neurologists from medical schools and various hospitals interested in training and research in neurological sciences. A Neurological Research Institute is now established to work on Neuropathology, Pharmacology, Biochemistry and Physiology of the Nervous System.

The Mental Health Association is a multiprofessional group working for the Public Mental Health Education and cooperates with other social agencies in helping to solve social problems in juvenile cases, geriatric problems and cases of unwanted children.

The main problems to be studied are:

1. High incidence of schizophrenics as compared to other places even though mental illness as a whole affects 1/5 of the patients affected in the Western Countries. The incidence of mental illness in Thailand is 1 in 1000.
2. Problems of drug addiction with almost potential cases of hiding heroine addicts.

SCHIZOPHRENIA IN THAILAND

In Thailand in 1956 of the 4000 mental patients in hospitals, 72% were schizophrenics — a higher proportion than among the hospitalized patients in most western countries. After intensive studies of the various factors which precipitate schizophrenic reactions we have come to the conclusion that psychological and cultural influences are of prime importance.

In order to go further into these matters, the background problem must be outlined. Persons with so-called constitutional susceptibility to schizoprenia [6], according to Freudian concepts are likely to be affected severely by adverse experiences in childhood [4]. On this basis it would follow that psychological studies of child development should receive high priority in research into mental illness in general and schizophrenia in particular.

Westerners always refer to cultural factors producing schizophrenic like personality among the Thai patients [9]. In particular, some of our customs emphasize a quiet way of life that may give rise in some individuals to a lack of eagerness and aggressiveness. Certain aspects of our mother- child relationship and child training may lead to repressive reactions in psychosexual development.

The slow tempo of the old-fashioned life of the country can be seen by open-front shops, and the slow movement of sampans on the river. In Thailand, babies, infants and young children generally seem to be treated gently and with consideration. It is noticeable that they are often in the arms of one or the other of their parents; they are played with and fondled a good deal; their feeding seems pretty close to "demand feeding". Little emphasis is placed on toilet training. Children are taught in an insistent but apparently gentle way to be respectful to their elders. Less wholesomely, they are probably along with this, drilled into attitudes that are submissive and nonaggressive. Toddlers often seem to be extraordinarily quiet and patient: occasionally some are *"too well behaved"*.

Child adoption is a very common custom. This is generally a completely informal adoption by a friend or relative. Sometimes it is done in the case of a child, one or both of whose parents have died, but it is often done simply because the parents are poor and already have all the children they can care for; they will give a child to more prosperous friends or relatives for upbringing and education. This may give rise to conflict when the children grow up and get in contact with others of normal families.

In adult life there is conflict now between the "old fashioned" way of life and the "new fashioned" or Westernized culture. Even on superficial scrutiny it is apparent that the stability and comfort of

our way of life are not complete protection from the effects of this increasing stressful situation.

The old fashioned method of child bearing [3] can be summarized as follows:

In the pre-natal period parents try their very best to prevent any trauma to the foetus. Immediately after birth, the mother wraps herself up with a thick heated cloth for about one month.

Three days after its birth, the baby is placed in the cradle.

At the end of the first month a ceremony is arranged for the baby to have its hair cut for the first time, and this is an occasion for the gathering of relatives. From the age of 3 to 5 the children are trained at home.

From 6 to 10 the children are sent to school, to private teachers or to live with priests in temples.

At the eleventh year of age, the parents arrange a grand ceremony for another hair-cut.

From 11 to 18 is the period for normal secondary education. During adolescence a son's two main duties are:

1. To join the priesthood for at least three months as a symbol of obedience to the parents.

2. To get married, the marriage being arranged by the parents.

The family is hierarchically organized and usually comprises three generations living together in the same home. The most eminent figures are the male members of the first generation: in second place comes the father. From his early years on, the child sees the complete obedience of his father to his grandfather and learns to feel the same way about his own father. The authority of the father is so undisputed that it does not require any extreme form of forcing it; it is instilled in the child so consistently that the facial expression, or an eye wink is sufficient to achieve extreme restrictions in the child's behaviour.

Western culture has scarcely affected the lives of ordinary people, who still live and think in traditional ways. Amongst the small minority who have been more influenced by Western customs, ostentatious social entertainment and automobiles, worrying about money and envy of financial success are most evident. But the attitudes implied in Western way of life meet the profound disapproval of Buddhist principles, and the overwhelming majority of Thais adhere sincerely to the Buddhist teachings. With the encroachment of "Westernization", therefore conflict is inevitable and it is already arousing the anxiety of thoughtful Thais.

Respect to one's elders and for authority is deeply ingrained.

All Buddhists must follow a practical code of conduct, known as the Five Precepts, which prohibit taking life, taking what is not given, illegal sexual pleasure, lying and intoxicants. These rules lead to attitudes of kindness and non aggressiveness.

In developing these basic ideas, Buddhists formed a unique doctrine about the self. If a man comes to a true realization of the self, he loses all craving for worldly pleasures and possessions and can turn toward the ineffable or Nirvana.

As seen by the people of other parts of the world these tenets seen to produce an introvert character. Besides this, in and around many temples all over the country a certain number of people practicize MEDITATION, sometimes sitting in seclusion for days. One can easily see some schizoid pictures in this group of people. *But they are all normal and live a happy way of life.*

When we read the classical studies of two distinguished anthropologists, Dr. Benedict [2] and Dr. Mead [8], who have studied Japanese and Balinese cultures respectively, the Thai character could be considered as being somewhere mid-way between both cultures.

It would appear that in Thailand the common character is moulded to schizoid-like reactions by custom, culture, tradition, economic status and geographical situation.

In 1951 Dr. C. H. Gundry [5], WHO consultant on mental health on an inspection tour to study mental hygiene problems in

Thailand stated in his reports: "...the relative frequency of schizophrenia is a point that attracts one's attention. It would be interesting to try to find out something about the incidence of schizophrenia in the total population... However the high amount of schizophrenia in relation to the amount of manic depressive psychosis is probably significant. It is note-worthy that the schizophrenia generally seems to be quiet and biddable. I was told they did not often develop highly organized affect laden systems of delusions. It may be that the reaction to frustration in this culture is typically one of withdrawal rather than one of hostility".

In my view some of the elements in the nature of the different types of schizophrenia psychoses stem from the anthropological factors.

DRUG ADDICTION

Drug addiction is considered to be a serious problem. It is more malignant than a tumour and more epidemic than cholera, because addiction attacks physical, mental and social status of the individual. It is very widespread, especially heroine addiction in South East Asia. Hongkong, Singapore, Macao and other places in this area are seriously affected.

The etiology of drug addiction is multifactorial and involves sociological, pharmacological and psychological factors. Among the important sociological factors are association with criminals, slum-living, minority group pressures and memberships in gangs.

The pharmacological factors are the effects of opiates which fulfill certain of the potential addict's psychological needs. The most important effects are the reductions in needs or motivations — particularly hunger, pain and sexual urges. Most addicts suffer from a character disorder, constitutional psychopathic inferiority neuroses and a mixture of both.

The use of any opiate results in true addiction, with the development of marked physical and psychological signs if the drug is withdrawn. Because of the physical, mental and social dangers, the government of Thailand abolished opium smoking in 1959 and treatment and research centres on this special problem were established.

1. *Withdrawal Symptoms.* — If morphine or opium is abruptly stopped within 8-12 hours the patients become restless and nervous. Later on they start yawning and exhibit rhinorrea, lacrimation and are more restless; during 12 hours or more they show twitching of legs and arms, chilli-

TABLE I

Statistical data on 100 cases of heroin addicts

1. Age - 70% of cases age between 20-40 years and only 2% for below 20.
2. Sex - 98% male.
3. Marital Status - 56% married.
4. Frequency - 56% 1-3 capsules.
5. Motivations - 58% as substitution for other drugs.
6. Combined illness - 18% T.B., 30% nose & throat infection.
7. Withdrawal reactions: - goose flesh, lacrimation, muscle pain, insomnia, restlessness, tremors & muscle twitching.
8. Results of treatments. Recover: improve & cure of withdrawal reactions 72%.
9. Medication: Drug of choice:
   —Physeptone (Methadone) injection and largactil orally - 88%.
10. Lists of withdrawal symptoms according to severity:
    —Lacrimation, yawning, pain, goose flesh - 100%.
    —Insomnia, restlessness, tremor, twitching, anorexia - 80-90%.
    —Nausea, abdominal pain, cramps, diarrhea - 10-20%.
    —Delirium - 4%.

ness in legs and back. They may have spells of not very serious vomiting and diarrhea. These symptoms remain for 3-5 days and hold on in a less acute stage for 2-4 weeks characterized by some nervousness and insomnia.

In the case of heroin, it is characterized by a rapid onset of signs. (See Table 1).

2. *Neurological Sequelae.* — It was noted on 6 occasions that a patient, who was heavily addicted, suffered seizures ranging between a mild form of epileptic convulsions and status epilepticus with 40-60 convulsion per day.

This heavily addicted patient consumed almost 10 times more heroin than average addicts and the convulsions continued for 6 days. After two months at the hospital he completely recovered and resumed his normal daily living. Cases such as this one may be concluded to be similar to those of abrupt withdrawal of alcohol from chronically intoxicated persons followed by a definite abstinence syndrome which, in some patients includes convulsions of a delirium or both [10].

Treatment. — A number of methods and medication have been introduced, but we could only report on treatment of withdrawal symptoms or a short term therapy, despite the fact that curing of addicts never succeeds without full rehabilitation program. According to Ainslinger "ambulatory treatment of drug addiction should not be tried. Institutional treatment is always required" [1].

According to committee report it was concluded that:

1. Tranquilizers are of enormous value in controlling and subsiding withdrawal symptoms. Among these, chlorpromazine plus amobarmital is the best. Meprobamate alone showed no satisfactory result.

2. Hypnotics: Combination of Pentobarbital and Cabromal seemed to be useful in many cases.

3. Amphetamines: It is necessary for a stage of depression and to stimulate the function of the C.N.S.

4. Methadone or Physeprone 5-15 mg. t.i.d. is the drug of choice and with less torture to patients.

5. Insulin subshock showed remarkable value to strengthen body and mind during convalescence. Anorexia and Insomnia are greatly reduced. Physical improvement is noticed in all cases.

Personality Study. — Provisional studies on 944 cases of opium addiction confirmed findings in the Western countries. They were from the following groups:

a) Inadequate personality.
b) Character neuroses.
c) Dependency.
d) Psychopathic personality.

Motivations. — Urges or drives to become addicts could be summarized as:

a) Persuasion.
b) Social attitudes.
c) Chronic somatic illness.
d) Character or behavior problems.
e) Criminal consequences.

OTHER PROBLEMS IN MENTAL HEALTH

The problem of *Alcoholism* in Thailand is not serious. Evidences show that the problem of Alcoholism is not very high.

At present, the Government is taking a serious action on this problem by organizing a long term plan with coordination of the Ministry of Education, Ministry of Interior and Ministry of Public Health to set up a National Program in health education, law enforcement and medical care for this problem of alcoholism. It is also helped by the Buddhist Association to promote similar groups as Alcoholics Anonymous.

The problem of *Juvenile Delinquency* reaches very small proportions in Thailand, even after careful examination of the figures; but in the light of the present knowledge of the cause of Juvenile Delinquency this is not surprising because family and social structure have not undergone the great changes the advance of industrialization brought about in other countries.

The problem of *Mental Deficiency* was studied by WHO Consultants some years ago with an average incidence of 200.000 cases. Last year, the government considered appropriate to establish the Institute of Mental Deficiency with a capacity of 80 beds and will be increased to 200 beds in the near future. The institute is functioning very well by cooperation of medical service department, Ministry of Education and a private agency, the Foundation for Welfare of Crippled. It is hoped that some other institutes will be organized in the provincial areas.

The problem of *Old Age* was studied carefully for the past ten years and 3 homes for old age were set up in Bangkok, Chiengmai and Korat.

At hospitals this problem is of some concern especially among the priests and people in business life. But on the country, our family system tends to have elders at home, so the problem is not serious.

Even though such a high proportion of mentally sick patients in Thailad are schizophrenic, nevertheless only 1 in 2.000 of the population is mentally ill. In my opinion this is because the Buddhist way of life makes for a peaceful mind. As a Buddhist, may I finish with a poem [7] concerning the Simple Life of the Thai people:

We live and work and dream,
Each has his little scheme,
Sometimes we laugh; sometimes we cry,
And thus the days go by.
There are no stars which we could trust;
There is no guiding light;
And all we know is that we must,
Be good, be right, be just.

I believe in and enjoy this Way of Life and the peace it brings me.

SUMMARY

The author describes the problems of biological psychiatry in Thailand and reviews the development of different services for the treatment of mental and nervous disorders.

In this paper two main problems are studied: the high incidence of schizophrenics and drug addiction.

Some important aspects of social, economical and religious life are analyzed in their influence on mental health; the author points out the existence of a conflictual situation that results from the opposition of the "Westernized" culture and the traditional "old fashioned" way of life.

At the end some other problems related with mental health are mentioned, which are not very serious in Thailand: alcoholism, juvenile deliquency, mental deficiency and the problem of old age.

RESUMEN

El autor presenta los problemas de la psiquiatría biológica en Thailandia y expone el desarrollo de los diversos servicios asistenciales para el tratamiento de las perturbaciones mentales y nerviosas.

En este trabajo se estudian dos problemas fundamentales: la elevada proporción de esquizofrénicos y la adicción a las drogas.

También son analizados algunos aspectos importantes de la vida social, económica y religiosa en cuanto a su influencia sobre la salud mental; el autor señala la existencia de una situación conflictual que resulta del enfrentamiento de la cultura "occidentalizada" y la forma de vida tradicional.

Al final se mencionan otros problemas relacionados con la salud mental, que no son graves en Thailandia: el alcoholismo, la delincuencia juvenil, las perturbaciones mentales y el problema de las personas de edad avanzada.

RÉSUMÉ

L'auteur présente les problèmes de la psychiatrie biologique de la Thaïlande et expose le développement des différents services d'assistance pour le traitement des perturbations mentales et nerveuses.

Dans ce travail deux problèmes fondamentaux sont étudiés: la haute proportion de schizophréniques et l'addiction aux drogues.

On analyse aussi quelques aspects importants de la vie sociale, économique et religieuse quant à leur influence sur la santé mentale; l'auteur signale l'existance d'une situation conflictuelle qui est la conséquence de l'opposition de la culture "occidentalisée" et du style de vie traditionnel.

A la fin du travail on fait mention d'autres problèmes en rapport avec la santé mentale, qui ne sont pas sérieux en Thaïlande: l'alcoolisme, la délinquence juvénile, les déficiences mentales et le problème des personnes âgées.

ZUSAMMENFASSUNG

Der Autor beschreibt die Probleme der psychiatrischen Biologie in Thailand und spricht ueber die verschiedenen Heilstellen fuer die Behandlung mentaler und nervoeser Stoerungen.

In dieser Arbeit werden zwei Probleme studiert: die hohe Frequenz von Schizophrenikern und Drogensucht.

Einige wichtige Aspekte des sozialen, oekonomischen und religioesen Lebens werden analysiert bezueglich ihres Einflusses auf die mentale Gesundheit. Der Autor hebt hervor die Existenz einer Konfliktsituation die sich aus der Gegenueberstellung der "verwestlichten" Kultur und der traditionellen "alt-modischen" Lebensfuehrung ergibt.

Schliesslich werden einige andere Probleme, die mit der mentalen Gesundheit zu tun haben eroertert, und die in Thailand nicht sehr ernst sind: Alkoholismus, Jugendverbrechertum, mentale Stoerungen und das Problem des hohen Alters.

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The Treatment of Depressive States

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In being asked to discuss the treatment of depressive states, I am very fortunate indeed to have had all the practical treatment experience made available to me in the past 25 years. This has involved the treatment of some thousands of patients with depression, and it enables me to write with a considerable degree of confidence on this whole subject.

First of all, for instance, in 1934 I was able to work at the old Hanwell Asylum in Middlesex, where Connolly had started the movement to abolish the mechanical restraint of patients in England nearly a hundred years before. Then I was doubly fortunate to be working at the Maudsley Hospital for three whole years and before any of the modern treatments of depression were used there, except for most of the present-day varied forms of superficial and deep psychoterapy. After working for 13 years in all at the Maudsley, I have now spent a further 14 years at St Thomas' Hospital, London, one of England's oldest and largest general teaching hospitals. All this treatment experience has enabled me over this long period of time not only to watch the natural prognosis of untreated and wrongly treated depressions, so to speak, at the bedside itself, but also to get a very good idea from the follow-up study of so many patients under observation and treatment —sometimes for over 20 years— whether it is the treatment that has been effective, or whether one has merely been witnessing the natural process of spontaneous remission, despite any treatment attempted, which is so very common sooner or later in these illnesses.

England, as opposed to so many other countries, has fortunately at the present time not tied herself down to any particular psychiatric ideology or dogma. In Russia, for instance, Pavlovian principles of treatment seem largely to prevail, which has caused such really excellent and useful treatments as even all the newer modified leucotomies to be totally banned. And in the U.S.A. a similar therapeutic and academic preoccupation with Freudian psychoanalysis has also so tragically resulted in many other very valuable treatments being relatively neglected, or frowned upon as "unscientific", and thought of as merely scratching the symptomatic surface of the problem of depression, despite the fact that the patient would be so much better by their use, and saved so much terrible suffering.

In Britain we have been able to use every known form and type of treatment available, and as intensively as possible with only one proviso, namely, that the patient is helped and not harmed by their use. That a patient is really helped by any treatment is, fortunately, in my country considered far more important than any of the present-day psychiatric theories that happen to act attached to it. For surely we should know by now, as in general medicine, how very wrong so many of the theories held so firmly only ten years ago have become today. It is absolutely

certain that it will be exactly the same in psychiatry 25 years hence, when we may have at last learned much more about how the human brain really works.

For those of a younger generation who claim that, apart from certain advances in group psychotherapeutic techniques and in the wider application of, say, Freudian theories in the treatment advances in depression, one needs only to recall the psychiatric scene as I first saw it personally over 25 years ago to be fully reassured. There has been in fact a complete treatment revolution. In those days, except in some reactive depressions, and not always in these, psychotherapy, whether specialised forms of Freudian, Adlerian or Jungian psychotherapy then being practised, or the many purely eclectic forms of psychotherapy, was having extraordinary little effect on the bulk of the depressed patients then crying out for help and skilled treatment. People of excellent previous personality in the involutional period of life, for instance, might remain ill for two to three years and sometimes for up to 20 years, despite all the intensive psychotherapeutic help given them. And when they did finally remit spontaneouly, it was often much too late to salvage the wreckage of their career. Large numbers of patients, as shown by Karagulla's paper in 1949[1] from Henderson's Clinic in Edinburgh, when left untreated by modern methods such as electroshock, or perhaps treated solely by psychotherapy, died due to continuous extreme agitation, sleeplessness and progressive loss of weight. The suffering of these patients used to be terrible indeed to watch. Wards had to be kept closed and locked simply to avoid suicides —as happens in hospitals where psychotherapy alone is still used in such patients. Row upon row of these patients might also have to be kept on special suicidal precautions. And one saw states of deep melancholia with nihilistic delusions, because of the length and severity of their illnesses, which have now almost entirely disappeared from the English scene today, except perhaps in a few backward mental hospitals, or those negiecting physical treatments for psychotherapeutic ones, which was all we had in those terrible days of old.

PSYCHOTHERAPY

In the old days, because one only had these various forms of psychotherapy to help patients, and because the late Professor Mapother of the Maudsley Hospital insisted that everything possible should be done for each patient, one did get a very good knowledge of the real value of psychoterapeutic techniques when unaided by the newer physical treatment methods..

Psychotherapy may help some reactive depressions in which the precipitating cause of attacks is a wrong attitude to life. By altering this attitude and teaching patients to accept the ordinary setbacks and stresses of life, this can sometimes reduce the number of subsequent attacks. Generally, however, when a patient has recovered from an attack of severe depression of any kind with psychotherapy, it is due to the process of spontaneous remission; for, on following up such cases over the years, one will see them relapse and recover just the same, whether they are given psychotherapy or not.

It can also be said quite dogmatically that it is only the advent of the physical treatments that has made the very great difference to the treatment and prognosis of depressions at the present time. In England today, the majority of mental hospital wards can remain open, and patients can be treated on a purely voluntary basis. Many general hospitals now have large open psychiatric wards with no locked doors; and we are treating severe cases of depression in them who in the old days would have started trying to throw themselves out of windows, if left untreated, or if treated by psychotherapy alone, for more than a few days. One can also state fairly dogmatically that there are practically no attacks of depression in patients of good previous personality that cannot

be greatly helped, or even cured when all available treatments are used alone or in combination which can now help patients even though, like so many general medical treatments, we do not yet know exactly how they work.

Because of the natural tendency of most depressions to remit spontaneously with time, the prognosis with treatment is now greatly enhanced by all the methods that are going to be discussed, since they help to break up the fixity of symptoms, and speed up the remission process, providing that death from suicide or agitated exhaustion is not allowed to happen while psychotherapeutic treatment only is being given, or the patient is simply submitted to routine institutional care.

One thing that complicates the present treatment position is that it has proved impossible, with the advent of the new antidepressant drugs, to distinguish clearly the treatment response of many so-called "anxiety states" occurring in good previous personalities, and similar states which are also diagnosed by other psychiatrists as being predominantly depressive in origin. It can be argued, for instance, that the occurrence of what appears to be an anxiety state in a man of good previous personality, and for the first time at the age of 40, practically always proves him to be suffering from a masked depressive illness; and that it is only in people who have been chronically anxious ever since childhood that one can distinguish between an anxiety state and a depressive illness in middle age with a fair degree of certainty. Certainly in this paper one has got to include the treatment of recent anxiety and phobic conditions in patients of good previous personality, along with the treatment of more obviously depressed persons, since both can respond so well to certain of the antidepressant drugs. And Professor Mapother was probably right in insisting that eventually, when effective treatments were discovered to help all these groups of patients, it would be found, especially in people of good previous personality, that anxiety states and depressive illness form one long continuum of illness, and should not be separated one from the other too dogmatically. With the newer physical treatments, one still sees selected groups of obviously depressed patients who are more helped by one treatment than another; but again one also sees a considerable overlapping in these groups in actual treatment practice.

THE ANTIDEPRESSANT DRUGS

Opinion is still somewhat sharply divided in psychiatry with regard to the value of the antidepressant drugs. Here again it is largely because the suitable subgroups of depression have not been as clearly defined for each type of antidepressant drug, as they should be by the protagonists of each group of drugs. However, a careful clinical study, rather than a statistical one, of patients responding to these drugs has generally provided a similar answer wherever patients have been selectively and carefully treated the world over. Those who are unwilling to concede the value of drug therapy, as opposed to psychotherapy, are constantly saying that the value of the new drugs for depression is simply due to the personality of the doctor prescribing them, and the results are solely due to enthusiasm and the psychological effect of giving the drug. This is most unlikely to be really the case when one so constantly sees patients responding to the drugs, say, after only three to seven days or up to a month from starting to take them. And likewise relapses may also occur only 7-10 days or up to 3 week after the drugs have been stopped. If the effects of these drugs were due solely to enthusiasm and personality of the doctor, one would not get these marked differences in the timing of recoveries and relapse in differing types of depression and with differing groups of drugs. But these time lags are constantly being seen when the new drugs are handled in a skilled manner and the right drugs are given to the right patients.

PROPER SELECTION OF PATIENTS

There is no doubt that it has been possible for several years past to differentiate clearly a whole group of patients who are much more likely to respond to the monoamine oxidase inhibitor (MAOI) group of antidepressant drugs than to any others, and in a manner that opens up new hopes for the treatment of certain patients who were previously very difficult to treat by other antidepressives [6]. These embrace not only certain types of reactive depression but also recent anxiety states and phobic states in good previous personalities. Some of these latter, as already stressed, may be diagnosed by some psychiatrists as depressions and not anxiety states, but will mostly be found to have been treated in the past with tranquilisers as anxiety states by general physicians. True endogenous depressions, on the other hand, are much more likely to respond to the phenothiazines than to the MAOI.

Unnatural fatigue despite reasonable sleep is a very common feature of this whole large group responding to the MAOI. The patient generally cannot get to sleep, but sleeps well when he does so. He is often not too bad in the morning, but tends to get worse as the day goes on. Sometimes these patients find that they sleep well, and even more deeply than usual, but the sleep is punctuated by bad dreams. Patients with a *good previous personality*, presenting what appears an almost typical "effort syndrome" picture, with palpitations occurring on effort or in certain "conditioned and anxiety-provoking situations such as closed spaces, railway trains, while crossing bridges or speaking in public, etc., all have their symptoms relieved in a remarkable manner by the use of one of the MAOI, combined with, say, librium or equanil initially. And it will be found that if the MAOI are stopped but the librium or equanil continued, the patients will almost invariably relapse, showing that it is the MAOI rather than the tranquiliser that is bringing about these dramatic results [5]. And these improvements occur in cases which we know were hitherto so resistant to psychotherapeutic treatments and even to sedatives and other depressant drugs, and generally became worse with electroshock therapy.

The author has a whole group of cases exhibiting phobic anxiety symptoms, *with good previous personalities* prior to the onset of the illness, which may have lasted up to even 15 years; one of whom, for instance, had seven years of psychoanalysis with no benefit. They have nearly all responded now with improvement to the use of the MAOI in that, although their fears of entering a room, for instance, may remain, they do not now get the severe somatic symptoms, such as palpitations and tremors, that previously incapacitated them. One may be nervous of going into a room, but it is the shaking hand on taking up a cup of tea which is so distressing to this group of patients, and which can be so easily helped when the right antidepressant drugs are given. Some of these are undoubtedly long-standing depressive illnesses, and a few may in fact respond to electroshock when all drugs have failed. But this is fairly uncommon and will be referred to again later. The main thing is to recognise the symptomatology of this group as described above, and the fact that in the past such cases were generally made worse by ECT, and became dangerously addicted to the prolonged use of barbiturates, which so often had to be given them sometimes even to get them out of the house at all. Now the advent of the new antidepressant drugs has brought these cases, for the first time, into the realm of quite simple physical treatment.

Another group of "depressed" patients greatly helped by the MAOI and who may be made worse by such drugs as tofranil and tryptizol, are those who could well be labelled as having the "tired housewife" syndrome. A person of good previous personality, full of energy and activity, presents, after some sudden or great shock, the typical syndrome of sleeping well but waking up still feeling just as tired or more so, despite their good night's sleep.

They show unusual irritability towards others, perhaps shouting at their children or their husbands in a way quite unknown to them before; they lack all energy and drive, and cannot tackle the simplest problems which were so easy for them before they got ill. It is very tempting to treat these people with psychotherapy, since they have suddenly become unable to cope with their environment, and seem to need help to sort out all sorts of problems that have arisen in consequence. But they will respond far quicker, and in a matter of ten days or so, providing the personality has been good, to the proper use of the MAOI.

It has also become obvious that a group of patients whom one used to have to help by drug abreaction, and by bringing their repressed emotions and experiences to the surface, can now sometimes be much more easily helped by the use of the MAOI group of drugs. These drugs seem to put the emering fears under the surface again, and enable the patient to repress them, as all of us have to do with our fears in ordinary life.

There is undoubtedly an overlapping between groups of depressions responding to tofranil and tryptizol and those responding best to the MAOI. Some endogenous depressions at the end of a particular attack will come out quite easily with the MAOI, but will not respond to this group of drugs early on in their attack. They do, however, respond much more readily to tofranil or tryptizol despite the failure of, say, nardil. In many endogenously depressed patients even better and quicker results may be obtained when one combines tryptizol with, say, marsilid. In Great Britain we have not found the dangerous effects of combining these two groups of drugs that are reported from America, providing, of course, that one realises that doses of both drugs have to be adjusted accordingly. The tendency to postural hypotensive symptoms that can occur with the MAOI alone is potentiated when one combines them with the phenothiazines. But if one uses these two drugs in proper combinations and with adjusted doses[2, 3] the risks have not been found to be serious in hundreds of patients treated over the last few years. There are also "intermediate" groups of depression who seem only to be helped when both groups of drugs are thus combined. Also, we have not had all the deaths from jaudince (some of them probably infective hepatitis) which led to the banning of the drug in the U.S.A. some years ago, though it is still being used successfully and relatively safely in Britain.

But in the general run of endogenous depressions, tofranil or tryptizol will be found far more useful and valuable than the MAOI. Around 50 per cent or more of recurrent endogenous depressions, and involutional melancholias in patients with good previous personalities —showing all the classical symptoms of early morning waking, morning worsening of symptoms, agitation, guilt, self-reproach, blaming oneself rather than others, indecision and retardation— will be found to respond to tofranil or tryptizol when they may not do at all well with the MAOI used early on in their illness. Nearly half of these patients, however, will also need electroshock treatment in addition to drugs. But if the drugs are still continued during the course of electroshock, a lesser number of convulsions is required; and if the drugs are kept on following electroshock treatment, one does not get the old relapses that used to occur when electroshock was used too early on in a attack of endogenous depression, when the patient would improve and then relapse, and then only remit again at the expected termination of the attack. Now, by combining electroshock with both groups of drugs if necessary, one can generally bring patients out of an attack very quickly, and then keep the depressive symptoms under control in subsequent months until the normal phase of the attack is over, when the drugs can be stopped again. Often one has to keep on with the drugs during the whole duration of the expected attack. For in talking to patients one finds plenty of evidence that attacks can still be going on

under the surface, their duration biologically determined, and the drugs are only keeping the symptoms partially at bay while the attack is still on.

ELECTROSHOCK AND LEUCOTOMY

As has already been stressed, there is still plenty of room for the use of electroshock in the true endogenous depressive illnesses. To begin with, it will generally take 3-4 weeks for tofranil or tryptizol to work alone, and then only does so in about 50 % of endogenous depressions treated. Tryptizol has the advantage over tofranil in that one often gets an indication of whether or not the drug is going to work by the fact that sleep starts to return to normal during the first ten days of treatment, whereas this useful pointer does not occur with tofranil. As only around half the patients are going to respond to the drugs, and response may take three weeks or more to occur, there are going to be many patients in whom it is far wiser to give electroshock combined with the drugs straight away. Then one can guarantee that they are likely to be better within a month. Otherwise it might mean waiting a month using the drugs alone, and then another month has to be spent giving additional electroshock so that their illness lasts double the length of time .

There is also the great danger with tofranil or tryptizol alone that while the patients are starting to recover with these drugs, they may go through a phase where they become actively suicidal because of their improvement, since they are now more able to take deliberate and calculated action to end their lives, which they were too retarded and disorganised to do in the deeper phases of their depression. One was inititially afraid of this happening with the early use of out-patient electroshock, but patients seem to go through this particular recovery phase so much more quickly that suicide during the course of out-patient electroshock has proved to be very rare indeed; whereas it is becoming comparatively common again where drugs alone are used instead in cases of deep depression. It was also very common when one had to wait months or even years for spontaneous remission to occur, and when one had only psychotherapy as a means of treatment before the advent of all the new and more effective physical methods of treatment of depressive states.

There is one small but special group of patients, which must be stressed here, who present themselves with what seems to he typical long-standing anxiety in previously good personalities, but who unexpectedly do not respond to the MAOI and are also rarely helped by tofranil or tryptizol alone or combined with, say, nardil or marsilid. But these will do well when electroshock is added to the use of both groups of drugs combined. One can generally pick out these cases by the fact, although their symptoms are those of a phobic anxiety state, yet they have a complete and utter sense of hopelessness of ever getting better. There is also loss of energy and the patients have often given up fighting since they feel they are never going to get better again. It is the feeling of hopelessness that indicates the deep depressive nature of the illness, and it is always worth trying electroshock combined with the antidepressant drugs. Again one may get very surprising results in patients who may have been ill for up to several years by this combination, when in the past one had to do a modified leucotomy in such patients, wich was also generally successful. because of the good previous personality before illness set in. Now this latter treatment is generally avoidable by using the combined method described above.

Turning to leucotomy, and now these operations are mostly confined to the *lower medial quadrants* of the frontal lobes, one can at last guarantee a relief of tension and obsessional rumination with very little of the general personality deterioration that used to happen with the old full operation. The place of modified leucotomy in chronic depression, there-

fore, is now an important one if all other treatments fail. Figures from all over the world show that results as high as 80% can be obtained in states of depression with such operations. And our use of only modified leucotomies over the past 20 years has provided some very useful information on its proper use in this condition.

A large number of depressed patients, who used to be treated with modified operations, presented themselves with a picture of chronic tension rather than a true depression, and they might derive great benefit from a modified leucotomy and be able to return to their old work and to a much more normal life. But some, after operation, were still found to need a few electroshocks to complete their recovery because of a missed depressive component to the illness. Some of these supposedly "chronically anxious" patients have also recently shown a tendecy to relapse, and to show typical mild depressive attacks in later years despite their modified leucotomy. And these later depressive attacks now quicky respond to electroshock or the antidepressant drugs. Many of them, as previously stressed, had originally been diagnosed as chronic tension states and might have had only a short course of electroshock in a long illness lasting six or seven years. Then they had had a leucotomy because they were thought to be suffering from chronic tension rather than a true chronic depression. Follow-up has however, indicated their undoubted depressive nature, since they have had further clear-cut depressive attacks of short duration despite leucotomy. And once we had realised this, we have managed to avoid leucotomy in a large percentage of similar patients still being sent to us for the operation, by making sure beforehand that they are not really masked depressions by more intensive treatment of the depression.

The method now used to do this is as follows. Since most of them have already had one or two courses of electroshock treatment in the past, and generally a trial of one or more of the antidepressant drugs, we straight away put them under a mild continous narcosis regime, obtained by giving 100 mgm largactil and 3 gr. sodium amytal 4 to 6 hourly. Good fluid intake and a very low diet is necessary to avoid complications. They are also then given both tryptizol and marsilid in as full a dosage as they will tolerate (despite all the fears of combining these drugs expressed in the U.S.A.), together with a sufficiently long course of electroshock of up to perhaps 12 treatments or more. So far, we have surplisingly found that practically every case, which previously we would have had to leucotomise, as a long-standing tension state or depression of up to seven years' duration to bring about relief, now responds to this thorough and combined intensive treatment, which should be used when all other measures have failed, and before considering the use of a modified leucotomy operation. Risks have been minimal in a large number of patients, and no deaths or severe complications have been seen. In the few cases in which we have failed with this blunderbuss method and finally had to use a modified leucotomy, the results have generally been extremely satisfactory, just as they were even before we started to use the combined method described above. It must be stressed, however, that leucotomy should only be used in persons of good previous personality and the cut must be confined to the lower medial quadrants. Then one can almost certainly promise the patient that, although his anxiety and obsessiveness will be considerably diminished, his general personality will remain relatively unchanged. In fact, relatives will gratefully report that the patient is often better than before operation and has become much more normal in his attitudes to life, which were previously so obsessively and anxiously determined.

Certainly to leave such patients in the back wards of mental hospitals in states of mental torment, which is still so often their lot for years on end, and without considering a modified leucotomy, is totally unjustified; especially now that neu-

rosurgeons have such progress in modifying the operations as to remove practically all of its deleteriuos side effects, when the right sort of good, anxious and obsessive personality is chosen for its use.

It is only for ideational and theoretical reasons, it seems, both in Russia and the U.S.A., that the use of these modified operations has greatly lessened and that so many patients are perforce left to suffer interminably in mental hospitals. And if Freudian and Pavlovian theories negative such results which have been obtained in actual practice for many years now, then it behoves us to examine the theories themselves rather than give up the means of relieving intolerable and prolonged mental torment which those with good previous personalities undergo in their years of illness.

SIDE EFFECTS

It is only by the skilled handling of all these treatments that one can avoid the side effects that have so often spoiled their use by persons who are either prejudiced against them, or have not had sufficient skill or patience to achieve their full possible benefits. For instance, as already mentioned, I and others have continually used marsilid, as the best of the MAOI, in large numbers of cases for six years now, without getting any of the deaths from jaundice reported from the United States. More deaths have, in fact, occurred in my own series of cases from the use of phenalzine which other people seem to think more harmless. This provides suggestive evidence that some reported deaths from jaundice with marsilid, nardil and the like, occur during epidemics of infective hepatitis; and supposed deaths from the MAOI are generally indistinguishable from deaths due to infective hepatitis during such epidemics. Also, as already mentioned, it has been quite possible to combine the MAOI with tryptizol and tofranil, providing one is careful in the dosage of each of the drugs prescribed. For instance, if one is going to use full doses of tryptizol or tofranil in the region of 50-75 mgm t.d.s., then one has got to start with only small doses of the MAOI —say 1 or 2 tablets a day— and then increase the dose or lower it, depending on whether postural hypotensive symptoms occur. Likewise, it is quite possible to combine marsilid (MAOI) with tofranil or tryptizol, but when using full doses of the latter drugs one should start with only 25 mgm of marsilid t.d.s. and adjust the dose from this starting level.

The states of hyperpyrexia recorded when using combinations of these drugs have also been seen when overdoses of tofranil *only* have been taken. And these hyperpyrexial attacks are likely to be far more common in the U.S.A. where sweating is so much more readily seen in centrally heated rooms in a hot climate than, say, in England. Some of these complications reported are possibly heat-stroke produced by excessive sweating on tofranil, and will respond to appropriate heat-stroke measures once they are recognised. They are much less likely to occur in temperate climates, and in temperately heated rooms as in Great Britain.

Likewise, in prescribing the MAOI alone, one has to warn the patient of the possible occurrence of hypotensive symptoms, such as fainting or giddiness on standing up suddenly. One should tell them not to stop the drugs, but simply to lower the dose, and one must learn to adjust the dosage so that undesirable side effects are not produced in patients, and not simply give up the use of potentially valuable drugs. The severe headaches associated with the MAOI are generally also avoided if one warns the patient about the danger of eating cheese with this group of drugs. Also, one should avoid using the stronger and quickly acting drugs such as parnate, unless necessary, as it contains a benzedrine component wich, while producing much quicker results, runs the risk of producing even more severe headaches and sometimes death from sponta-

neous subarachnoid haemorrhage, especially when cheese is eaten. This also happens with all the MAOI if one accidentally gives intravenous methedrine or benzedrine together with this group of drugs. It can also be very dangerous to combine any of the MAOI with injections of pethedine or morphine.

As in general medicine, nearly all drugs that are really effective in any specific disease process, such as depressive illness, have undesirable side effects if used in the wrong dosage. The art of treating depression by these new and powerful drugs, and the other medical and surgical treatments now available, is knowing all their side effects, and taking all the necessary steps to remove them or reduce them to a minimum. Side effects should be no objection to their use providing one learns how to avoid them by skilled adjustment of individual treatment techniques. This is now generally possible in the ways discussed without destroying any of their therapeutic efficiencies. For instance, although we may all deplore the use of the old full leucotomy operations in destroying the general personality, this is absolutely no excuse for abandoning leucotomy now that we have modified operations confined to the lower medial quadrants which have removed this objection. In fact, one can now say dogmatically that there are very few cases indeed of chronic depression in patients of good previous personality who cannot be helped, providing that all the physical, and only quite simple and supportive psychological, methods of treatment are used, together, consecutively, or alternately. And one must never throw in one's hand, and consign the case to the back wards of the mental hospital, without first playing every card in what is now a very large treatment pack indeed.

SUMMARY AND CONCLUSIONS

Working for the past fifteen years in a great London general teaching hospital, one cannot help seeing states of treatable depression as probably the largest psychiatric group, coming first to general physicians and neurologists, and then being sent on to the general hospital psychiatrist for treatment. Because of their tendency to spontaneous remission, a very great number of these cases are also overlooked and remain undiagnosed. So many of them also refuse to go near psychiatrists, or psychiatric hospitals, and prefer to remain under the treatment of general physicians in general hospitals or in their homes, sometimes for years on end. In England and Wales, 5.000 successful suicides a year, and 20.000 other attempted suicides, are very often also occurring with the very drugs prescribed by doctors to help them, and shows the extent of wrongly treated depressions, both diagnosed and undiagnosed, in Britain at the present time. It is unlikely to be greatly different in other similar industrialised countries.

These mortality figures tragically coincide with the fact that we now have simply physical methods of treatment which providing the previous personality is good, can practically always guarantee recovery or great improvement in most depressive states. The treatment contrast between today and 25 years ago, before the advent of the newer physical therapies and when we only had the psychotherapies to help us, is most striking. There is also little doubt that the effective treatment of depressions will continue to become more and more simple and more biological in both outlook and method. The treatment of depressions will then be united again within the body of general medicine; and in the future many depressions will be treated very simply and easily by the general practitioner, the general physician, or the neurologist. Only in specially difficult cases will it be necessary to refer them at all to the psychiatrist.

This paper shows how this happy state of affairs is already starting to be achie-

ved. It now only needs greater knowledge of the use of these methods by the general physician and the neurologist to make referral to the psychiatrist even now quite unnecessary in many instances. And yet the possibilities of a biological approach to treatment are as yet relatively unexplored compared to the position that is likely to exist in another twenty-five years' time.

RESUMEN

En 15 años de trabajo en un importante hospital universitario londinense se puede comprobar como el grupo psiquiátrico quizá más numeroso, el de los casos de depresión tratable es sometido en primera instancia a la atención de médicos generales para pasar luego a manos de un psiquiatra de hospital general para su tratamiento. Esta tendencia a la asistencia espontánea hace que numerosos casos sean pasados por alto y queden sin diagnosticar. También es corriente que una buena parte de los pacientes se resista a ver psiquiatras o a ingresar en hospitales psiquiátricos y prefiera permanecer en su casa, en hospitales generales o bajo el control de médicos generales durante años. En Inglaterra y Gales ocurren 5.000 suicidios anuales y 20.000 intentos de suicidio, aún a pesar de la ingerencia de medicamentos indicados por médicos, lo cual demuestra claramente la difusión de las depresiones mal tratadas, tanto diagnosticadas como no diagnosticadas, actualmente en Inglaterra. Es altamente probable que la situación sea parecida en otros países llegados a un grado de industrialización similar.

Este grado de mortalidad coincide trágicamente con el hecho de que actualmente tenemos simples métodos físicos de tratamiento que, siempre y cuando se cumplan ciertas condiciones de personalidad, puede garantizar una recuperación o una mejoría considerable en casos agudos de depresión. Hay una oposición total entre los métodos de hace 25 años, anteriores al advenimiento de los novedosos métodos terapéuticos físicos, en que sólo se disponía de los recursos de la psicoterapia. También, hay pocas dudas de que el tratamiento efectivo de la depresión seguirá haciéndose cada vez más simple y más biológico, tanto en cuanto a concepto como a método. El tratamiento de depresiones será entonces incorporado nuevamente a la medicina general, y en el futuro muchas depresiones serán tratadas fácil y simplemente por el médico general o el neurólogo. Solamente en casos especialmente difíciles será necesario recurrir al psiquiatra. Este trabajo demuestra la forma en que esta sastisfactoria evolución ya ha comenzado a realizarse. Se necesita ahora solamente un mayor conocimiento del uso de estos métodos por el médico general y el neurólogo a fin de evitar enviar innecesariamente a los pacientes al psiquiatra. Sin embargo las posibilidades de un enfoque biológico del tratamiento están aún relativamente inexploradas, en comparación con la situación que probablemente existirá dentro de otros 25 años.

RÉSUMÉ

En 15 années de travail à un important hôpital universitaire de Londres on peut prouver que le groupe psychiatrique peut-être le plus nombreux, celui des cas de dépression traitable, est soumis premièrement aux soins d'un médecin général pour passer en second lieu au traitement d'un psychiatre d'hôpital. Cette tendance spontanée à faire suivre cette voie aux patients, fait que plusieurs cas soient examinés superficiellement et restent sans diagnostic. Il est commun de voir qu'une grande partie

des patients se résiste à se faire soigner par un psychiatre ou à entrer dans un hôpital psychiatrique; ces patients préferent rester chez eux, dans des hôpitaux généraux ou bien sous le contrôle d'un médecin général pendant des années.

Il y a en Angleterre et au Pays de Galles 5.000 suicides annuels et 20.000 suicides frustrés, malgré la diffusion des médicaments ordonnés par des médecins. Ceci montre clairement qu'il s'agit dans la plupart des cas de dépressions mal traitées, diagnostiquées parfois, parfois non, en Angleterre. Il est très probable que la situation soit pareille dans d'autres pays ayant atteint le même degré d'industrialisation que l'Angleterre. Ce haut degré de mortalité coincide tragiquement avec l'emploi de simples méthodes physiques de traitement qui garantissent un rétablissement ou une guérison considérable dans les cas de depression aigüe, pourvu qu'existent certaines conditions de personalité. Ces méthodes actuelles s'opposent à celles qu'on employait il y a 25 ans, avant l'avènement des nouvelles méthodes thérapeutiques physiques, où l'on comptait seulement avec les ressources de la psychothérapie. Il n'y a presque pas de doute sur l'affirmation selon laquelle le traitement effectif de la dépression deviendrait de plus en plus simple et biologique, en ce qui concerne le concept et la méthode. Le traitement des dépressions sera alors incorporé encore une fois a la médecine générale, et plusieurs dépressions seront traitées plus simplement; dans les cas particulièrement difficiles il sera nécessaire de recourir au psychiatre.

Ce travail demontre dans quelle forme cette évolution satisfactoire a commencé à se réaliser. On a besoin maintenant seulement d'une connaissance plus poussée de ces méthodes de la part des médecins généraux et des neurologues afin d'eviter l'énvoi innécesaire des patients au psychiatre. Les possibilités d'un envisagement biologique du traitement restent encore assez inexplorées si on les compare avec la situation qu'existera dans 25 ans.

ZUSAMMENFASSUNG

Nachdem man waehrend der letzten 15 Jahre in einem grossen Londoner Universitaets Hospital gearbeitet hat, kommt man nicht umhin als die groesste psychiatrische Gruppe die der behandelbaren Depresion zu sehen, die zuerst den allgemeinen Arzt aufsuchen und auch die Neurologen, und die dann an die Psychiater der Allgemeinen Hospitaeler ueberwiesen werden, um die Behahandlung durchzufuehren. Wegen ihrer Tendenz zur spontanen Besserung, werden sehr viele uebersehen und nicht diagnostiziert. Viele von ihnen weigern sich auch Psychiater zu konsultieren oder in psychiatrische Hospitaeler zu gehen, und bleiben in der Behandlung der Allgemeinen Mediziner in den Allgemeinen Hospitaelern oder zu Hause, manchmal Jahrehindurch.

In England und Wales gibt es 5.000 Selbstmorde und 20.000 Selbstmordversuche, die oft mit den Medikamenten die von den Aerzten verschrieben worden sind, um ihnen zu helfen, durch gefuehrt werden. Sie zeigen wie haeufig die falsch behandelten diagnostizierten und nicht diagnostizierten Depressionen zur zeit in England sind. Die Unterschiede werden in anderen aehnlich industrialisierten Landern nicht gross sein.

Diese Mortalitaetsziffern stimmen tragisch mit der Tatsache ueberein, dass wir heute ueber einfache physikalische Methoden zur Behandlung verfuegen, die wenn die vorhergehenden Persoenlichkeitsbedingungen gut sind, praktisch immer die Heilung oder eine grosse Besserung der Depressionszustaende garantieren. Der Kontrast in der Behandlung zwischen heute und vor 25 Jahren, vor der Einfuehrung der neueren phsykalischen Therapiearten als wir nur ueber die Psychotherapie ver-

fuegten um uns zu helfen, ist auffaellig. Es besteht kein Zweifel, dass die erfolgreiche Behandlung der Depression immer einfacher und biologischer werden wird. Die Behandlung der Depression wird dann mit den Behandlungsmethoden der Allgemeinen Medizin vereinigt werden; und in Zukunft werden viele Depressionen sehr einfach und leicht vom Allgemeinen Praktiker oder Neurologen benhandelt werden. Nur die spezifisch schwierigen Faelle werden dann dem Psychiater ueberwiesen werden muessen.

Die Arbeit zeigt wie dieser gluecklicche Zustand schon bald erreicht ist. Man benoetigt jetzt nur noch eine genauere Kenntnis ueber den Gebrauch dieser Methoden von Seiten des Allgemeinen Mediziners und des Neurologen, um dann die Ueberweisung zum Psychiater in den meisten Faellen unnoetig zu machen. Und trotzdem sind die Moeglichkeiten einer biologischen Betrachtungsweise der Behandlung noch relativ wenig erforscht im Vergleich zu dem was in Weiteren 25 Jahren erreicht sein wird.

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Excretion of Indoleamines in Schizophrenia

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Since Kraepellin [30] grouped mental disorders with various related clinical pictures under the general denomination of "Dementia Praecox", many attempts have been made to clarify the psychopathology and etiology of such conditions. Bleuler's monograph, "The Schizophrenias" [7], consolidating Kraepellin's concepts, was an attempt to establish a primary disturbance common to all subdivisions of this group. Endocrinologic [35], constitutional [31], metabolic [23, 24], anatomopathological [37, 48], developmental [21] and hereditary factors [27, 33, 40, 42] were extensively studied in the past 50 years in attempts to find a specific etiologic connection for the schizophrenias. Wide clinical variations and different kinds of control situations made these studies difficult to interpret. But as a result of various findings, the hereditary factor was the most generally accepted, though the exact mechanisms of hereditary influences in schizophrenia are not fully understood. With the introduction of neuroleptics, reserpine, and chlorpromazine, of thymoleptics including MAO inhibitors like isocarboxazid and iminodibenzyl derivatives like imipramine into psychiatric therapy as well as the development of new biochemical techniques, valuable tools were made available for the search of organic aspects in mental illnesses. During the past 13 years a large amount of experimental work was done concerning the mechanisms of action of psychotropic drugs, chiefly on their electrophysiological, biochemical and behavioral aspects (for review see [8, 17, 32]). As a corollary of these experiments new hypotheses have been offered towards a better understanding of the pathogenesis of schizophrenia [4, 28, 49].

I. Body fluid alterations in schizophrenia

The changes in urinary excretion of indoleamines, catecholamines and their metabolites, when correlated to behavior on a day to day basis, present a valuable method in the research for organic correlates to schizophrenic process since patterns of excretion can reflect not only gross general bodily alterations but also perhaps more subtle changes in the brain metabolism of biogenic amines. On the other hand, such organic parameters in patients free of psychoactive drugs may be the expression of alterations of inborn errors in metabolic pathways or by inadequate diets. Examples of the latter are provided by the psychiatric symptomatology observed in pellagra, Hartnup disease and Wilson's disease (for review see [15, 39]). In all these conditions some metabolic excretory process may be decreased or disappear in the urine and other products can be abnormally in-

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creased. In addition elevations of urinary indole metabolites were first observed by Brune and Himwich [10, 11] in chronic schizophrenic patients before and during an exacerbation of psychotic symptomatology whether the patients were under medication by psychotropic drugs or free of them. These results, namely increases in urinary excretion of indole metabolites with behavioral worsening, were confirmed by Sprince et al. [45]. From these primary observations, a systematic investigation of urinary indole metabolites under various experimental conditions was started in order to find a possible link between the increased excretion of these metabolites and changes in the intensity of schizophrenic symptoms. Working on a different line of attack, Pollin, Cardon and Kety [38] fed essential amino acids to schizophrenic patients and reported that none of these amino acids by themselves induced any changes in the patients' behavior that could be attributed to the amino acids. But exacerbations of psychotic symptomatology occurred when iproniazid, a monoamine oxidase (MAO) inhibitor, was added to the amino acid methionine and to a lesser degree with tryptophan, results that were confirmed by Brune and Himwich [12] and Alexander et al. [1].

The next step in our longitudinal series study was taken to determine whether or not behavioral amelioration could be achieved by reducing the methionine and tryptophan contents of the diets [5, 6]. But no behavioral changes were observed which could be imputed to the diet. Two of these patients, however, had spontaneous exacerbations which were preceded and accompanied by rises of tryptophan metabolites in the urine. Thus indole metabolites exhibited urinary increases before and during behavioral worsening despite the low tryptophan and methionine diet.

Important points for the mechanism of behavioral exacerbation are that during amino feeding in combination with MAO inhibitor, urinary indole metabolites rise before the exacerbation of symptoms and sometimes the most enhanced worsenings are observed when our patients were again placed on the control diet [5, 13, 31], occasionally requiring neuroleptic medication to control the intensification of their symptoms.

On the basis of the primary observations of Brune and Himwich [10, 11] as well as on the experiments of Pollin, Cardon and Kety [38], Brune and Himwich [12] erected the hypothesis that a psychotogenic substance, related to N-dimethyl tryptamine, is formed in the body, the methyl groups coming from the methionine and the indole configuration from tryptophan [4, 12]. This endogenous hypothetical compound is regarded as a mediator for the behavioral exacerbations occurred either spontaneously or in connection with the amino acid feeding associated with the administration of a MAO inhibitor. It is known from other work in our laboratory as well as from other sources that indole substances with N-dimethyl groups, psilocin and psilocybin or diethyl radical like LSD-25 were all psychotomimetic but their non-dimethylated congeners were not [2, 9, 43, 43a, 47, 47a]. It is also important to stress that N-dimethylated indoleamines show a higher degree of solubility in water and lipids than their non-methylated congeners. As a result of these observations it would seem logical to assume that endogenously N-dimethylated indoleamines are able to move across the blood-brain barrier similarly to exogenously administered LSD-25 or psilocybin.

II. General considerations on the indole transmethylation hypothesis

It is necessary in our analysis to emphasize that elevated excretions of indole metabolites are not related to the nosological diagnosis of schizophrenia but rather to the intensity of schizophrenic symptoms in some patients. Thus an activation of psychoses is associated with rises in indole metabolites but when the psychotic process is apparently inactive, urinary indoles fall within normal limits. These variations explain in part the contradictory results contained in the literature where one can

find reports on increased indole products in patients with schizophrenia [3] as well as of no significantly consistent changes from the normal [19, 29]. Former workers have presented averaged results that would tend to hide significant daily variations and in most of the cases a day-by-day behavioral correlation was not carried out. Indeed, Brune and Himwich [11] found that the average tryptamine excretion in patients, whether free of any drug or on reserpine therapy, was within normal limits while that of total 3-indoleacetic acid was only slightly elevated. But when these patients suffered a flare-up of the psychosis the urinary indoles increased in this particular period, suggesting that the alterations in the indole metabolism are not a secondary function of the psychosis since they are present whether or not changes in motor activity and/or anxiety occur.

A final remark regarding the methods used in our studies will be useful in evaluating our results. All patients observed in our longitudinal studies were in good physical health. They had been without psychotropic medication for periods from 1 to 2 months prior to the initiation of the observations and remained without psychotropic medication until the completion of the study, approximately 8 months. To avoid dietary influences in the urinary excretion of indole metabolites the patients were maintained in the metabolic ward on a specially prepared diet, rigorously controlled and excluding preformed indoles and catecholamines. Clinical evaluations of the mental symptoms and behavior were made by a team of physicians during daily examinations and in addition weekly interviews using a rating scale for various aspects of behavior were held.

If our hypothesis is correct, methyl group donor amino acids other than tryptophan and methionine should induce exacerbations in schizophrenic symptomatology when combined with a MAO inhibitor. For that reason we would like to point out a gradual symptomatic worsening observed with the combined administration of isocarboxazid and betaine, a methyl donator, an observation which seems to limit the possibilities to the mediation of a transmethylation process [14].

Similarly, Spaide et al. [44] reported that significant worsening in behavior and exacerbation of schizophrenic symptoms was induced by the combined administration of L-cysteine with tranylcypromine. During and after this combined administration there were large rises in the urinary excretion of tryptamine. The recession of urinary tryptamine excretion to the pre-exacerbation values again occurred in general with a decline in intensity of psychotic symptoms.

As a test of the indole transmethylation hypothesis, N-dimethylated indoles should be sought for in the urinary samples of schizophrenic patients during behavioural

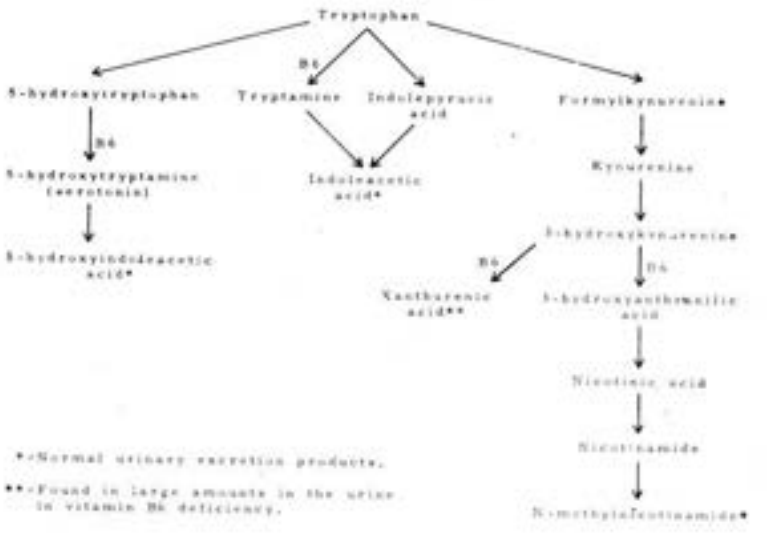

Fig. 1. — *Schema of tryptophan metabolism. As shown in the schema, the normal urinary metabolites include 5-hydroxyindoleacetic acid, 3-indoleacetic acid and N-methylnicotinamide. Besides these excretory products, tryptamine is also found in large amounts in the urine.*

worsening. Indeed, such observations have been made. Bumpus and Page [16] claimed that N-methyl serotonin and bufotenin are excreted in the human urine; Fischer et al. [20] reported that a bufotenin-like substance was found in hallucinating schizophrenia and did not occur in non-schizophrenics; Brune and Himwich [14], using two-dimensional paper chromatography, reported that a bufotenin-like spot was present in the urine of their patients receiving betaine and isocarboxazid, and Heller [25] claims the same results for his hallucinating patients. But the methods used by these workers must be improved before their results can be fully accepted, and Rodnight [39], investigating body fluids in mental illness, could not detect bufotenin or bufotenin-like substances in the urine of his patients.

Perry et al. [37a] failed to detect either bufotenin or N-dimethyltryptamine in the urine of schizophrenic patients. All these investigations, however, were made by paper chromatography. But Tanimukai and co-workers [47b], using thin-layer chromatography, were able to identify bufotenin and N-dimethyltryptamine. Obviously, further work is necessary.

DISCUSSION

The consistent observation of elevated urinary excretion of indole metabolites before and during exacerbations of schizophrenic symptoms occurring spontaneously or induced by amino acid feeding in combination with MAO inhibition is our most striking and intriguing result. In general, the urinary indoles attain increasingly elevated levels with augmentation in the severity of psychotic symptoms. This close correlation between activation of schizophrenic symptomatology and rises in urinary indole metabolites makes it possible, despite individual variations, to conclude that indole metabolism is involved in the intensity of schizophrenic symptoms and possibly also in the schizophrenic process.

Our results on excretion of indole metabolites in schizophrenia indicate that tryptamine exhibits the more consistent and greatest rise on a percentage basis; 3-IAA is usually increased but not as consistently as tryptamine and in the case of cysteine feeding the rise of 3-IAA failed altogether; while 5-HIAA is the least indicative of alterations in indole metabolism, probably due to descarboxylase activity in the kidneys and bacterial degradation of indoles in the gastrointestinal tract.

Moreover, the results of Oates and Sjoerdama [36] obtained by combined administration of tryptophan in association with MAO inhibitor to non-psychotic patients are of interest in comparison with our observations in schizophrenics. These authors reported that for practical purposes chiefly neurological signs were observed such as hyperreflexia and clonus. The subjective symptomatology was dominated by a picture similar to that of moderate ethanol intoxication. No hallucinations, delusional ideas nor schizophrenic symptomatology was reported.

It should also be emphazised that alterations in indole metabolism have been found in unmedicated patients with spontaneous exacerbations of psychotic behavior [6]. Elevations of urinary tryptamine however may or may not be an indication of brain tryptamine level. We found rises in tryptamine excretion [5, 34] during amino acid feeding with or without aggravations of psychotic symptomatology. This observation can be understood if we apply the findings of Erspamer and co-workers [18] in rats as well as man. Erspamer suggested that without MAO inhibition urinary indoleamines were derived largely from the circulating precursor amino acids and reflect primarily the high decarboxylase activity of the renal tissue rather than the amine tissue levels throughout the body. With a MAO inhibitor, however, preventing the action of renal decarboxylase as well as in other tissues, including the brain, the urinary products are more representative of the organs of the body. Suggesting an analogy with our amino acid feeding results we can say that urinary tryptamine in patients receiving an amino acid but not a MAO

inhibitor is produced largely from free plasma tryptophan under the influence of kidney decarboxylase degradation. When amino acids are given, the usual anabolic and catabolic processes go on simultaneously and may balance each other. When, however, MAO inhibitors are added to amino acids, the catabolic process is blocked but the anabolic one continues. The resulting accumulation of indoles leads to increased retentions of indole substances in various organs. Even though urinary tryptamine levels are high during loading with amino acids without a MAO inhibitor, tissue levels of tryptamine, as well as in the brain, are probably considerably lower than with a MAO inhibitor.

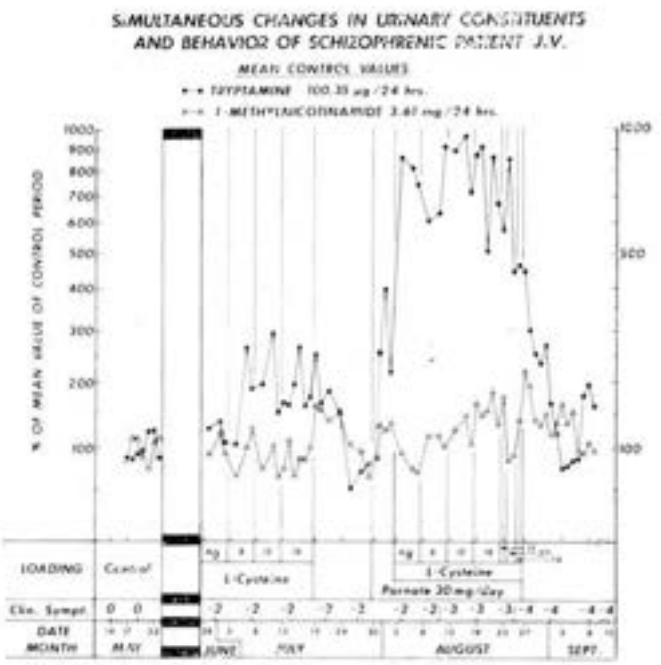

Fig. 2. — *Simultaneous changes of urinary tryptamine and 1-methylnicotinamide in one of our schizophrenic patients (J. V.). Increasing degrees of worsening in the clinical symptomatology are expressed in a rating scale from -1 to -4. The graph is expressed as the percent deviation from the mean of the values obtained during the control period. When the patient was receiving L-cysteine in association with tranylcypromine, a MAO inhibitor, a psychotic exacerbation occurred and the urinary excretion of both tryptamine and 1-methylnicotinamide showed significant increases when compared to control values. Notice that the most severe behavioral worsening occurred immediately after the patient was again placed on the control diet (Taken from Spaide, J., Ginther, R., Tanimukai, H., Bueno, J. R. and Himwich, H. E. Schizophrenic behavior and urinary tryptophan metabolites associated with cysteine given with and without a monoamine oxidase inhibitor (tranylcypromine). Submitted for publication to NATURE).*

The importance of indole metabolism does not seem to be a fortuitous event in the triggering of behavioral changes since not only is tryptamine increased in the urine but also 1-methynicotinamide which is a representative excretory and product of another major metabolic pathway of of tryptophan catabolism [5, 44] (See Figure 1). In the study of Spaide and co-workers [44] (Figure 2), 1-methylnicotinamide was measured to test if an alteration in the metabolic pathway of tryptophan occurs in humans as reported by Sprince et al. for the rat [46]. Because decreases in the excretion of 1-methylnicotinamide was observed in only one of our 4 patients it is not likely that cysteine inhibits the 1-methylnicotinamide pathway of tryptophan metabolism leading to an increased tryptamine excretion.

An increased urinary excretion of creatinine, paralleling the elevations of urinary indoles was also observed during low tryptophan-methionine regime [6] and during cysteine loading [44]. These findings suggest that amino acid loadings can induce a disruption in the normal protein synthesis and initiate an increased breakdown of muscle protein which releases tryptophan and mathionine, among other amino acids, into the blood stream, making them available for the utilization of the body. Furthermore, cysteine is a non-methyl donor amino acid but is part of a metabolic chain starting with methionine going to homocysteine, cystathione and cysteine and the administration of the latter would increase the methionine concentration in the body. Thus in association with the increased muscle protein breakdown, the final amino acids released by cysteine loading will include methionine as well. The breakdown of muscle protein is facilitated by loss of appetite which is frequently an early sign of behavior worsening.

The biochemical picture must be considered in the context of a series of facts. As pointed out by Rodnight and Brune and Himwich [39, 14], urinary changes are of complex origin and reflect among other factors the bacterial action on tryptophan in the intestinal tract, renal metabolism as well as tissue metabolism of the indoles. Thus, when elevations of urinary excretion of indole metabolites are observed we must keep in mind that such findings express the results of interactions of several factors. Moreover, only a minor contribution could come from the brain metabolism. In regard to the formation of tryptophan breakdown products by bacterial degradation the work of Jepson [26] provides information that bacterial synthesis of indoles is important for the metabolism of 5-HIAA but does not represent the leading factor in the urinary excretion of tryptamine and total indole-3-acetic acid. Jepson flushed the intestinal tract with chlortetracycline an found chiefly that the excretion of indoxyl sulphate ceased.

In regard to the behavioral changes, it is well to point out that in a few patients behavioral improvements were seen [1, 5, 10, 38]. These temporary improvements, usually observed following the withdrawal of methionine and MAO inhibitor, are exceptions to the general rule of worsening. Thus far we are without explanation for the improvements. The importance of indole metabolism in the exacerbation of schizophrenic symptomatology is far from settled, but one thing we can say with certainty about our patients — that behavioral exacerbations are correlated with rises in urinary tryptamine excretion.

Though there are similarities in the mechanisms of action between exogenously administerd psychotomimetics and endogenously psychotogenic substances, there seem to be marked differences in the expression of the behavioral aberrations. Taking LSD as an example of exogenously administered psychotomimetic, we know that the alterations in behavior are highly conditioned by the situation and circumstances. In contrast, the endogenously formed psychotogenics, whether occurring spontaneously or facilitated by combined administration of an amino acid and MAO inhibitor, seem to be more limited in expression and are characteristic of the usual behavioral profile of each patient.

We would also like to point out that urinary studies made in a different direction, namely in the field of catecholamines instead of indoleamines by Friedhoff and Van Winkle [22] revealed the presence of 3, 4-dimethoxyphenylethylamine in the urine of schizophrenic patients where they occurred more frequently than in the urine of non-schizophrenics. This catecholamine, however, is methoxylated and therefore

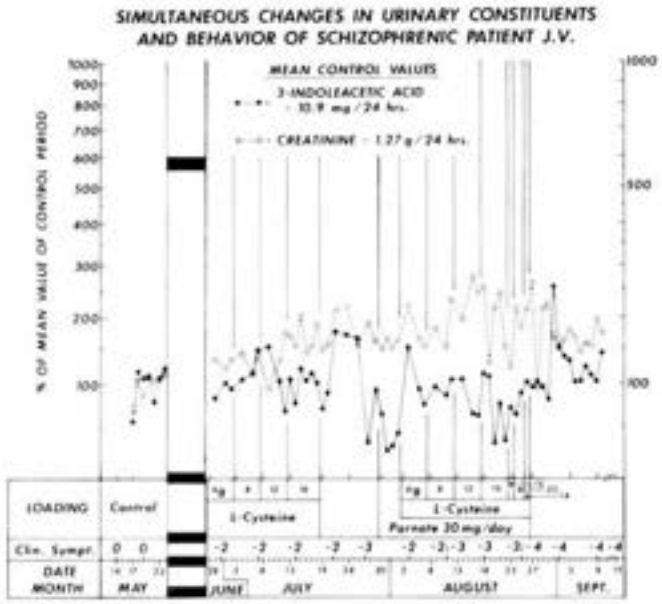

Fig. 3. — *Simultaneous changes of urinary indole-3-acetic acid and creatinine along with the behavioral evaluation of the same patient as in Figure 2 (J. V.). The graph is again expressed as the percent deviation from the control values obtained during the control period and exacerbations in clinical symptomatology are again scored in terms of increasing severity from -1 to -4. During the period of psychotic worsening when the patient was placed on L-cysteine associated with MAO inhibitor, the urinary excretion of creatinine was significant increased while that of 3-indoleacetic acid was not (Taken from Spaide, J., Ginther, R., Tanimukai, H., Bueno, J. R. and Himwich, H. E. Schizophrenic behavior and urinary tryptophan metabolites associated with cysteine given with and without a monoamine oxidase inhibitor (tranylcypromine). (Submitted for publication to NATURE).*

the role of transmethylation in the biologic changes observed in the schizophrenic process may involve transmethylation in a similar way for both the catechol and indole amines. Nevertheless their involvement may not be the same, the indole substances are associated with a mechanism triggering the psychotic exacerbation while catecholamines may be involved in other steps of the process. Furthermore, 3,4-dimethoxyphenylethylamine may be of exogenous origin and may also occur, less frequently in non-schizophrenics. The excretion of 3,4-dimethoxyphenylethylamine is also non-specific for the diagnosis of schizophrenia occurring in other conditions [7a, 23a].

In discussion of the mechanisms involving indole metabolism in behavioral worsenings, there are at least three possibilities that should be entertained.

1) Abnormally high levels of a normal product, such as tryptamine, which may evoke abnormal changes in behavior.
2) Many individuals may form psychotogenic indoles in subliminal amounts in regard to behavioral effects, but schizophrenics may either produce larger amounts or are more susceptible.
3) The third suggestion is that only schizophrenics can make such an abnormal product whether with or without a MAO inhibitor, but again the latter facilitates this accumulation in schizophrenic patients.

We feel that at present the second of these three possibilities is the most likely in view of the observations of Axelrod [2] that in addition to the lungs, the adrenal glands, the kidney, spleen and liver all have the ability to transmethylate and therefore form N-dimethyl indole products. These results taken in association with the permeability of the brain to tryptamine and N-dimethyltryptamine compounds allows for the passage of such substances through the blood-brain barrier. This idea that the difference between schizophrenics and non-schizophrenics is not qualitative — that schizophrenics may possess the same characteristics of normal individuals — but rather quantitative, is in agreement with the conclusion of Schneider [41] who found that the normal individual and the psychotic do not belong to different categories, but there are all degrees of gradation between them. It is not a case of only black and white, but a matter of intermediate shades of grey. If this is correct and we accept a genetic component in the schizophrenic process, then a schizophrenic patient inherits a predisposition, a predisposition making for the excessive production of greater susceptibility mentioned above. The mechanism by which this psychotogenic indole substance in formed is as yet unknown. Nevertheless based on the facts presented above, a hypothetical chain of events may be postulated as follows: (a) first comes the initiating cause, unidentified thus far but probably an inherited predisposition either to synthetize larger amounts of this psychotogenic substance or a greater sensitivity to such a compound; (b) a second step is the release of amino acids including perhaps methionine as results of muscle protein breakdown. This process is facilitated by loss of appetite which is among the earliest

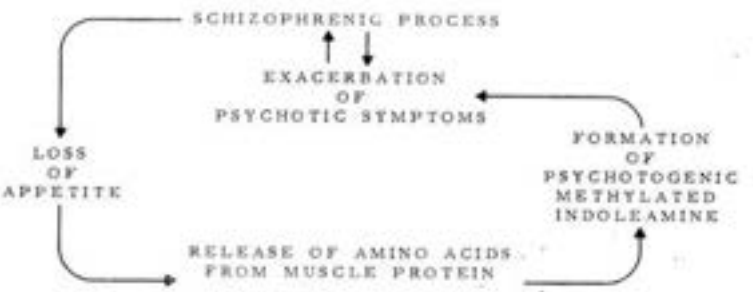

Fig. 4. — *Schematic representation of a hypothetical chain of events observed during an exacerbation of psychotic symptoms either occurring spontaneously or induced by a monoamine oxidase drug* with either methionine or cysteine.*

* Isocarboxazid (Marplan) — Tranylcypromine (Parnate).

signs of beavioral worsening with a consequent decrease in food intake including an amino acid imbalance. This condition can be reproduced by loading methionine and tryptophan in association with MAO inhibitors since indoleamines are catabolized by monoamine oxidase; (c) the third stage is the formation of the psychotogenic methylated indole amine that will trigger the behavioral exacerbation. This hypothetical chain of events is schematically represented in Figure 4.

Another factor making for confusion is the diagnosis of schizophrenia that probably represents more than one condition. The psychopathology and phenomenology of the schizophrenic diseases need further studies to provide better diagnostic classification. Furthermore, even in individual patients the clinical symptomatology may vary greatly during the evolution of the disease, and it is possible that different biochemical situations may prevail in the various clinical states. It is not impossible that using biochemical methods like those we have described above, a criterion for the classification of the schizophrenias may be achieved. Specific excretory pattern of monoamines could then be used not only as a diagnostic tool but also as a guideline for an improved chemotherapic management of these mental disorders.

SUMMARY

From a more extensive review we are emphasizing some results indicating progress towards a possible mechanism underlying the aggravation of psychotic symptoms whether they occur spontaneously or are provoked by feeding amino acids during medication with a monoamine oxidase inhibitor. Originally we found increases in the urinary excretion of derivatives of tryptophan, an essential amino acid, in schizophrenic patients, whether on placebo or drugs. These increases preceded and accompanied the exacerbations of schizophrenic symptoms. Then Kety and associates reported that feeding methionine and to a lesser extent tryptophan produced aggravations of symptoms in schizophrenic patients when given in combination with a monoamine oxidase inhibitor. These important behavioral observations were confirmed in our laboratory. Again, we were able to correlate worsenings of psychotic symptoms with increases in urinary indole metabolites. These findings were also confirmed by Sprince and associates and especially for elevations of urinary tryptamine. On the basis of the above mentioned experiments, Brune and Himwich suggested that psychotogenic indoleamines mediated the aggravation of the symptoms in schizophrenic patients. Some authors have reported the presence of bufotenin-like compounds in the urine of schizophrenic patients. Others failed to do so but in either case, the methods used were open to criticism. Recently, Dr. H. Tanimukai, working in our laboratory, devised new modifications to obtain higher sensitivities than those previously employed. Using his methods we confirmed the presence of bufotenin and other psychotogenic tryptamine derivatives in each of 4 schizophrenic patients examined. Increases of these psychotogenic compounds appeared in the urine before the mental symptoms of the schizophrenic patients worsened and continued there during periods of behavioral exacerbations.

RESUMEN

Señalamos particularmente algunos resultados que indican el progreso alcanzado en el estudio del posible mecanismo determinante de la agravación de los síntomas psicóticos tanto cuando ellos se producen espontáneamente como también cuando son

provocados por el suministro de aminoácidos durante la medicación con un inhibidor de la monoamino oxidasa. Al principio encontramos aumentos en la excreción urinaria de derivados del triptofano (un aminoácido esencial) en pacientes esquizofrénicos, estuvieran éstos bajo tratamiento de placebos o drogas. Estos aumentos precedían y acompañaban la exacerbación de los síntomas esquizofrénicos.

Posteriormente Kety y sus colaboradores informaron que el suministro de metionina, y en menor grado de triptofano, agravaba los síntomas de los pacientes esquizofrénicos cuando se suministraba en combinación con un inhibidor de la monoamino oxidasa. Estas importantes observaciones del comportamiento fueron confirmadas en nuestro laboratorio.

Una vez más pudimos comprobar una correlación entre la acentuación de los síntomas psicóticos y los aumentos de los metabolitos indólicos en la orina. Sobre la base de los mencionados experimentos, Brune y Himwich sugirieron que las aminas indólicas psicotogénicas son factores en la acentuación de los síntomas en los pacientes esquizofrénicos.

Algunos autores informaron sobre la presencia de compuestos similares a la bufotenina en la orina de pacientes esquizofrénicos. Otros autores no llegaron a la misma conclusión pero en todo caso sus métodos eran discutibles. Recientemente el Dr. H. Tanimukai ideó en nuestro laboratorio nuevas modificaciones a fin de obtener un mayor grado de sensibilidad en los métodos de estudio de estos fenómenos. Mediante el uso de sus técnicas confirmamos la presencia de bufotenina y de otros derivados psicotogénicos de la triptamina en los 4 pacientes examinados.

Los aumentos de estos compuestos aparecieron en la orina antes de los síntomas mentales de los esquizofrénicos, se acentuaron y continuaron durante los períodos de exacerbación del comportamiento patológico.

RÉSUMÉ

Nous signalons particulièrement quelques résultats qui indiquent le progrès atteint dans l'étude du mécanisme qui probablement détermine l'aggravation des symptômes psychotiques qui se produisent tantôt spontanément, tantôt provoqués par l'administration d'aminoacides pendant un traitement avec un inhibiteur de la monoamino oxidase. Au commencement nous avons trouvé augmentés dans l'excrétion urinaire, les derivés du tryptophane (un aminoacide essentiel) chez des patients schizophréniques qui étaient traités avec des "placebos" ou des drogues. Ces augmentations précédaient et accompagnaient l'exacerbation des symptômes schizophréniques.

Plus tard Kety et ses collaborateurs informèrent que l'administration de méthionine, et à un moins haut degré si c'était du tryptophane, aggravait les symptômes des patients schizophréniques s'il était administré combiné avec un inhibiteur de la monoamino oxidase. Ces importantes observations du comportement furent confirmées dans notre laboratoire.

Encore nous avons pu prouver une corrélation entre l'aggravation des symptômes psychotiques et les augmentations de métabolites indoliques dans l'urine. Sur la base de ces expériments, Brune et Himwich suggérèrent que les amines indoliques psychotogéniques constituent des facteurs dans l'aggravation des symptômes chez les patients schizophréniques.

Quelques auteurs rapportèrent sur la présence de substances similaires à la buphoténine dans l'urine des patients schizophréniques. D'autres n'arrivèrent pas à la même conclusion mais en tout cas leurs méthodes étaient discutables. Récemment le Dr. H. Tanimukai introduisit de nouvelles modifications en travaillant dans notre laboratoire afin d'obtenir un plus haut degré de sensibilité dans les méthodes d'étude de ces phénomenes. L'usage de

ses techniques nous permit de confirmer la présence de buphoténine et d'autres dérivés psychotogéniques de la tryptamine chez les 4 patients examinés.

Les augmentations de ces substances apparurent dans l'urine avant les symptômes mentaux des schizophréniques, ils s'accentuèrent et continuèrent pendant les périodes d'exacerbation du comportement pathologique.

ZUSAMMENFASSUNG

Bei einer ausgedehnten Uebersicht, legen wir den Hauptwert auf einige Ergebnisse, die einen Fortschritt darstellen in Bezug auf einen moeglichen Mechanismus der die Basis der Verschlimmerung psychotischer Symptome ist, die spontan oder provoziert durch Fuetterung von Aminosaeuren waehrend der Behandlung mit einen Monoaminooxidasenhemmer sein koennen. Wir fanden urspruenglich Vermehrung der Urinausscheidung von Derivaten des Tryptophanes bei Schizophrenikern, sowohl mit Placebos als auch mit Drogen behandelt. Dieser Vermehrung ging voran und begleitete die Verschlimmerung der schizophrenischen Symptomen. Dann teilten Kety und Mitarbeiter mit, dass wenn man mit Methionin, und weniger stark mit Tryptophane, verfuetterte, sich eine Verschlimmerung der Symptome bei Schizophrenikern einstellte, wenn man diese kombiniert mit Monoamino oxidasehemmern gab. Diese wichtigen Beobachtungen ueber das Verhalten wurden in unserem Laboratorium bestaetigt. Darueber hinaus konnten wir eine Korrelation zwischen der Verschlimmerung der Symptome und der Vermehrung Indolabbaubestandteile im Urin feststellen. Diese beobachtungen wurden auch von Sprince und Mitarbeitern bestaetigt, vor allem die Vermehrung von Tryptamine im Urin. Auf Grund dieser Experimente, brachten Brune und Himwich den Gedanke, dass die psychogenetischen Indoleaminen die Verschlimmerung der Symptome anbahnten.

Einige Autoren haben das Auftreten von Bufoteninaehnliche Substanzen im Urin von Schizophrenikern mitgeteilt. Andere waren nicht mit diesen Ergebnissen einverstanden, aber in jedem Fall waren ihre Methoden diskutierbar. Kuerzlich arbeitete Dr. Tanimukai in unserem Laboratorium neue Aenderungen aus, um eine hoehere Sensitivitaet als die frueheren zu erzielen. Mit seinen Techniken konnten wir das Auftreten von Bufotenin und anderen psychotogenetischen Tryptaminederivaten bei 4 schizophren Patienten bestaetigen. Die Vermehrung dieser psychotogenetischen Verbindungen trat im Urin auf, bevor die psychotischen Symptome sich verschlimmerten, und waren waehrend der ganzen Zeit der Verschlimmerung ihres Verhaltens vermehrt.

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Psychotropic Drugs Used in the Management of Schizophrenia

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The advent of psychoactive drugs initiated a new era in the management of schizophrenic disorders: a significant and continued decline for the last decade in the population of mental hospitals in all countries in which these drugs are used was one of the first practical results. As a corollary, a great improvement in the atmosphere in mental institutions was brought about. The so-called somatic or physical treatments in psychiatry such as convulsive therapy, insulin hypoglycemia and psychosurgery are still available forms of therapy for schizophrenia but they are being progressively replaced by psychotropic drugs and the other somatic methods are being reserved for circumscribed situations.

The neuroleptics or tranquilizers, in contrast to barbiturate drugs, allow the physicians to treat their patients without a significant interruption of consciousness. This situation has permitted ward doors to be opened and patients can now pursue prescribed activities in a therapeutic community. Greater optimism pervades all ancillary medical services, resulting in greater effort by the staff and correspondingly better therapeutic results. While the psychoactive drugs by themselves could not have brought about these improvements yet the outlook for schizophrenic patients prior to their introduction was, on the whole, quite dismal.

In the present report we shall review the actions of three different groups of psychoactive drugs in relation to the management of the schizophrenic process; reserpine, phenothiazines and butyrophenones and their principal derivatives. These drugs shall be referred to as tranquilizers or neuroleptics interchangeably, since nomenclature differences reflect only psychiatric school dissimilarities without any marked change is basic concepts.

I. RESERPINE AND DERIVATIVES

Though reserpine nowadays is considered to be of secondary importance among the neuroleptics, the drug is largely of historical interest but remains as a useful tool in research for a better understanding of brain functions. The drug had been used in the field of psychiatry since 1931, in India [45-47]. Despite its increasing importance in India, only in 1953 [24] did Western psychiatry become interested. Since then, an enormous amount of clinical and psychopharmacological work has been accomplished. The original observations of Kline [36] aroused a great deal of interest and since then reserpine experienced a zenith in psychiatric therapy followed by more

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discrete enthusiasm and, finally with gradual replacement by other more potent neuroleptics, so that today in many countries the drug is mostly used in antihypertensive therapy.

A. *Mechanisms of action.*

The exact mechanism of action of reserpine is still controversial. The drug has biphasic effects on EEG recordings from animals and with behavioral correlates, namely an early shorter period of behavioral and EEG activation followed by a longer period of sedation or tranquilization and enhancement of resting EEG patterns [27].

It is interesting to notice that when reserpine is first administered to patients it may produce a period of worsening in the psychotic symptoms, a period of turbulence [3] which is usually more marked and longer acting than that evoked by phenothiazines and is a sign of extrapyramidal dysfunction.

In animals, the initial period of EEG and behavioral activation corresponds closely to the time interval during which free biogenic amines are increased at the expense of amine stores which are diminished by the action of reserpine. The intracellular stores of brain biogenic amines such as serotonin, noradrenaline and dopamine, under the action of reserpine, release the neurohormones into the cell sap and thence to the intercellular space with a consequent increase in the free-form of these brain biogenic amines at receptor sites of effector organs. In addition, newly synthetized monoamines are not bound in the stores but remain in the free-form. (See Figure 1).

In contrast to the earlier behavioral and EEG activation, the later appearing resting EEG patterns and behavioral sedation occur with a reduction in the concentrations of the free amines after the stores have been depleted. With the more moderate dosage administered to patients it is not unlikely that the comparatively short early period of activation of the psychotic symptoms corresponds with the time when the free brain amines are increased above the usual levels while the tranquilizing effects

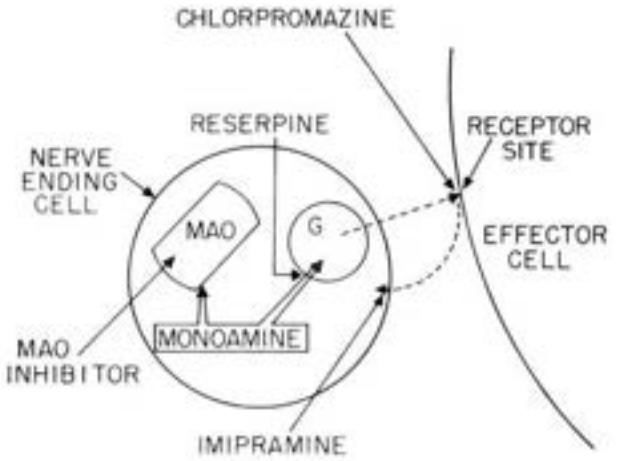

Fig. 1. — *Sites of action of representatives of four groups of psychotropic drugs. This figure is the schematic representation of a cell of a sympathetic nerve ending and of an effector organ and the gap between these two structures through which biogenic monoamines, here represented by noradrenaline, are released from the nerve ending following a nerve impulse. The structure of the mitochondria is intimately bound with the monoamine oxidase activity of that enzyme. Monoamines are stored in granules (G) in a labile form. Noradrenaline liberated from the labile fraction may be utilized in four ways: (1) incorporation into a stable form, (2) after the nerve impulse the monoamine is released into the gap (straight dotted line) and stimulates the effector cell at the receptor site, (3) outside the nerve cell noradrenaline may also be transformed to normetadrenaline by the COMT enzyme, or (4) re-enters the nerve ending (curved dotted line). Inside the cell the free monoamine may be oxidized by the MAO enzyme. Reserpine and chlorpromazine diminish the effectiveness of the response of the effector organ to nerve stimulation: reserpine blocks the incorporation of the monoamine into the granule. Accordingly the monoamine is exposed to oxidation of the MAO enzyme and its amount is therefore decreased. Chlorpromazine has a similar effect but in another way, for that drug blocks the receptor site so that the monoamine cannot contact it. This blocking action is similar in effect to that of atropine in regard to acetylcholine. The MAO inhibitor prevents the MAO enzyme from oxidizing the monoamines and therefore increases their concentrations. Imipramine accomplishes the same purpose by preventing the return of the free monoamines into the cell, thus raising the levels of free monoamines available to react with the receptor site. (This figure is reproduced with the permission of Prof. Arvid Carlsson).*

are associated with the long-continued low levels of bound brain amines and specially of the free amines [42].

Brodie and Shore [6] forwarded the hypothesis that the tranquilizing effects of reserpine are a result of serotonin depletion which increases the free amount of this amine in the brain. But more recently, Bueno, Pscheidt and Himwich [7] proposed that a balance between the brain contents of serotonin and norepinephrine may be an important factor since EEG and behavioral activation was achieved in animals with high levels of brain serotonin usually associated with a 50% decrease in the brain norepinephrine.

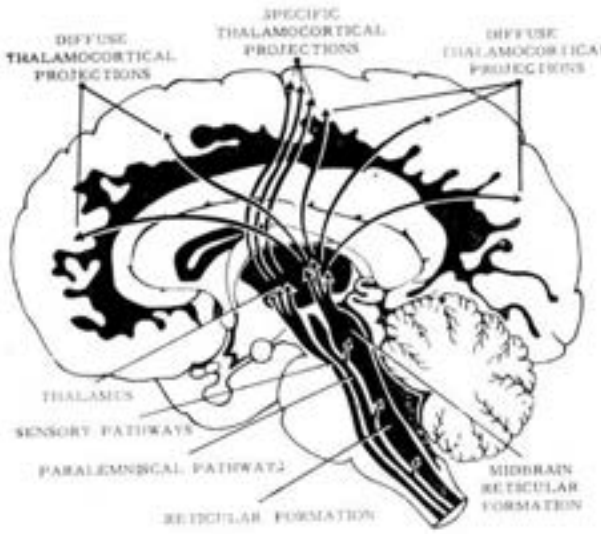

Fig. 2. — *Mid-saggital view of the right hemisphere showing a schematic representation of the mesodiencephalic activating system (MDAS) and of the pathways connecting the MDAS with the Papez circuit (see Figures 3 and 4) as well as with the cerebral cortex. Sensory stimuli ascend the lemniscal sensory pathways and stimulate the specific sensory nuclei of the thalamus from whence impulses are transmitted to the cortical somatosensory areas. The ascending functions of the mesodiencephalic activating system may be said to start with impulses in collaterals from the paralemniscal sensory pathways to the reticular formation which is thus aroused and send signals to the unspecific thalamic nuclei where the diffuse thalamocortical projections to the cortex take their origin. The paralemniscal pathways are represented by the spinoreticular, spinotectal and Lissauer's tracts.*

Other neurophysiological actions of reserpine are even more complex (See Figures 2, 3, 4). There is a decreased response to exteroceptive stimulation which is correlated with a block in the mesodiencephalic activating system (MDAS) while the limbic structures are stimulated by reserpine where that drug may evoke spontaneous seizures [33]. These complex actions of reserpine, a tranquilizing effect without the hypnotic properties of the barbiturates may find an explanation in the hypothesis of Himwich [28] who states that the neuroleptics affect to a greater extent subcortical functions of areas in the brain which are regarded as the anatomic substrate of the emotions and are involved in mechanisms of crude awareness and emotional responses while affecting to a lesser extent the neocortex, which is chiefly

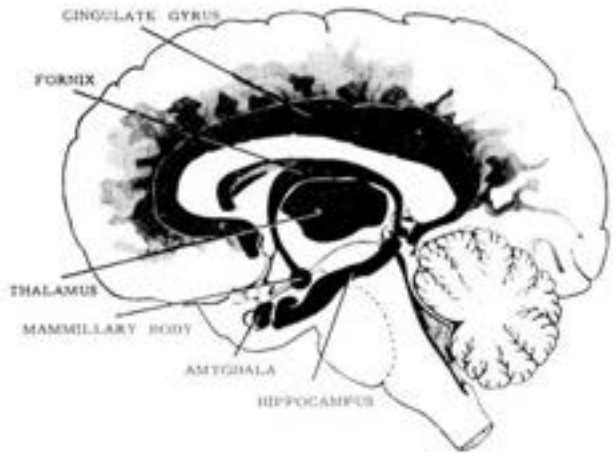

Fig. 3. — *Papez circuit. On stimulation of the hippocampus, that structure relays impulses via the fornix to the mammillary bodies of the hypothalamus and from that area they are transmitted in turn to the anterior thalamic nuclei and the cingulate gyrus of the cerebral cortex. The functional circuit is completed by fibers leaving the cingulate gyrus and returning to the hippocampus via the hippocampal gyrus. These subcortical areas, together with the mesodiencephalic activating system (MDAS) represented in Figure 2 are regarded as the anatomical substrate of the emotions and are involved in mechanisms of crude awareness as well as in emotional responses (Himwich, H. E., Morillo, A. and Steiner, W G., Drugs affecting rhinencephalic structures. J. Neuropsychiat., 3: S15-S26, 1962).*

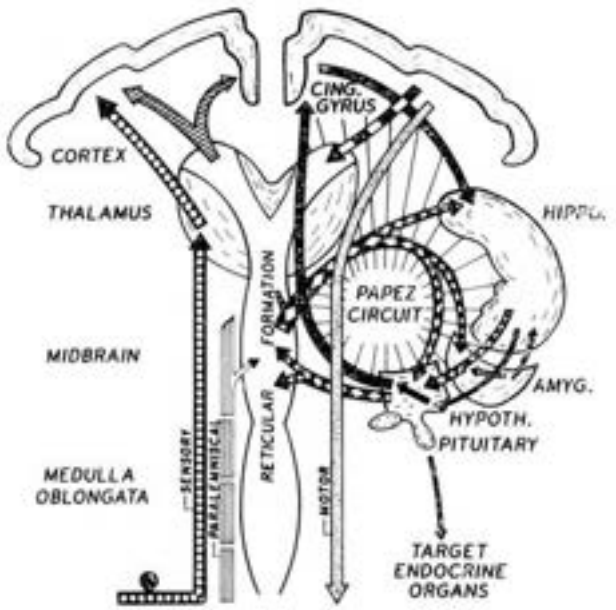

Fig. 4. — *Diagrammatic transverse section of brain. The left half of the figure portrays lemniscal sensory pathways to the specific sensory nuclei and the specific sensory areas of the cortex (white dots on black arrows) as well as paralemniscal ones (black and white vertical stripes) and collaterals (black and white arrow) to the reticular formation (white) which in turn relays impulses to the cortex via the diffuse thalamocortical projections (shaded). On the right side of the figure a feedback from the cortex in the corticoreticular projections completes a reverberating circuit between the cortex and reticular formation. The Papez circuit (in black) is portrayed connecting the hippocampus, hypothalamus (mammillary body) (anterior thalamic nuclei are not represented), cingulate gyrus and returning to the hippocampus. The connections of the Papez circuit with the amygdala and reticular formation are indicated by arrows containing white diamond shapes. Fibers originating in the nuclei of Gudden and Bechterev, situated in the reticular formation, pass directly to the hypothalamus, to the septal area (not indicated) and the hippocampus and amygdala. These structures send impulses to the reticular formation to complete reverberating circuits. These areas represent a portion of the anatomic substrate of behavioral adjustements occurring especially with strong stimulation of the organism. The motor pathways from the cortex to the spinal cord (stipled arrow) are included in the right half of the diagram. The reticular formation also possesses important descending motor activities, including extrapyramidal regulation. (This figure is adapted by Himwich, H. E., Functional organization of the brain, past and present. J. Nerv. Ment. Dis., 130: 505-519, 1960 from Galambos - IN Herrick, C. J. The Brain of the Tiger Salamander, University of Chicago Press, Chicago, Illinois, 1948).*

involved in integrative mechanisms and discrete awareness. In fact, this statement may be generalized to all tranquilizing drugs in contrast with the barbiturates that have a more widespread action throughout the entire brain.

B. *Clinical Uses.*

In the early stages reserpine was tested in a variety of psychiatric and neurologic conditions: schizophrenia, epileptic psychosis, manic-depressive and involutional psychosis [36], epilepsy [30], and extrapyramidal disorders [35], depressions [34, 21], choreic disorders [5], enuresis [38] and in the neuroses [40].

After the initial enthusiasm, Kinross-Wright [34] noticed that reserpine could aggravate depressions and many of the reported data were subjected to re-evaluation. Afterwards, the reports then became more restricted, in full agreement with the original observations of Sen and Rose [45] that the drug is "effective only in a certain type of insanity which is common, insanity with violent manical symptoms with such somatic signs as a full, hard phletoric pulse, violent movements and insomnia". At present, reserpine is still used in the management of violent, hyperactive schizophrenics and for the treatment of overactive, brain-injured children [28a].

C. *Side Effects.*

Amidst the most common side effects of reserpine are: nasal stuffiness, hypersalivation, intestinal hypermotility, lethargy and drowsiness, Parkinsonism, bradycardia, hypotension, aggravation of bronchial asthma, reactivation of duodenal ulcer. The potential danger of a reserpine-induced depression is also present, chiefly in predisposed patients. These side effects are dose-dependent and a decrease in dosage usually is adequate for their alleviation. On other occasions the combined administration of a cholinolytic drug or an anti-Parkinson

agent is also highly effective without the necessity of diminishing the daily dosage.

II. THE PHENOTHIAZINES

The phenothiazine derivatives constitute the largest and most versatile group of psychotropic drugs. From the clinical viewpoint there are important quantitative differences between their actions, but the qualitative similarities of the various phenothiazines facilitate their discussion as a group. The phenothiazine derivatives have in common a chemical structure consisting of the phenothiazine nucleus and a three carbon chain in the –Y– position as shown in the model in Figure 5. In the –X– position the phenothiazine can have a hydrogen, a halogen atom or a halogen-methyl group or yet a sulfo-radical. In the –Y– position, these neuroleptics can have a dimethylamino group like chlorpromazine, a piperadine ring as exemplified by thioridazine or a piperazine nucleus as in the configuration of trifluoperazine. (See Figure 5).

The potency of the various representatives of the phenotiazine family is determined by the different radicals present at X and Y positions; the piperazine group at –Y– position generally increases the potency of the drug as do halogen atoms or halogen-methyl groups in the –X– position.

A. *Mechanisms of action.*

The basic psychopharmacological properties of the phenothiazines reveal correlations with clinical findings. The phenothiazines block the conditioned response associated with noxious stimuli without interfering with the unconditioned escape response. Spontaneous motor activity is also depressed by these neuroleptics, and another of their characteristics is a drug-induced catalepsy. Anti-emesis, barbiturate potentiation, cholinolytic [48] and adrenolytic actions [8a, 26a, 5a] are also common features of this large group of drugs which also exhibit a slight antihistaminic action.

Phenothiazines may also induce a depression of respiratory centers but only in high doses and possess a hypothermic action in more usual doses [15]. The biochemical investigations with phenothiazines are not so numerous as with reserpine. The phenothiazines, by interfering with enzymatic process, decrease the sugar and oxygen consumption [15] and also have a moderate blocking action on the uptale of norepinephrine in central adrenergic neurons [41]. It would be interesting to know, in humans, the phenothiazine action on transmethylation of transmethoxylation processes, since methylated indoles [56] or *o*-methylated catechols [19] possess psychotogenic properties and are probably involved in the mechanisms of hallucinatory-delu-

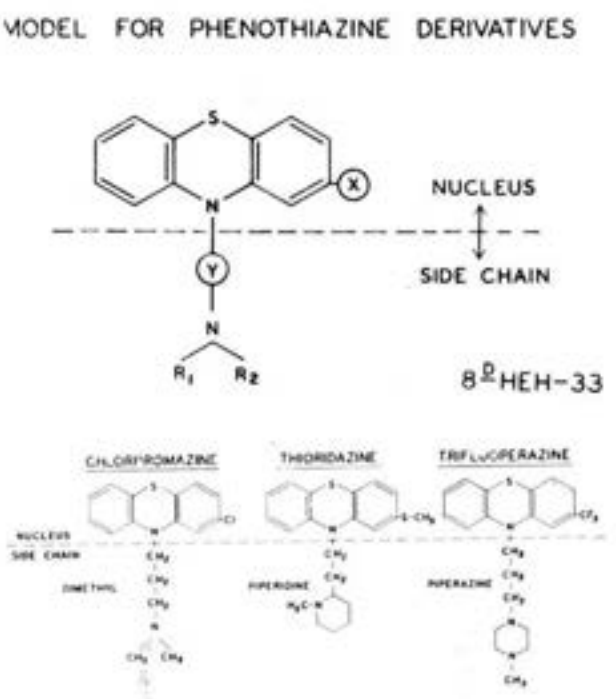

Fig. 5. — *In the upper portion, the phenothiazine nucleus and the positions -X- and -Y- are represented. Phenothiazines with psychoactive properties have a three-carbon chain in the -Y- position. The -X- position usually has a halogen atom, a halogen-methyl group or yet a sulfo radical. In the lower part are represented examples of each of the three groups of phenothiazines which are distinguished by their side chains at -Y- position. The dimethylamino group is represented by chlorpromazine, the piperadine by thioridazine and the piperazine by trifluoperazine.*

sional symptomatology. In animals, Axelrod [1] reported on the enzymatic N-methylation of serotonin and other amines and both chlorpromazine and imipramine are able to block this enzymatic process, perhaps accounting for the tranquilizing and antipsychotic actions of these drugs.

The electrophysiological actions of phenothiazines are multiple and complex. Following the acute administration of phenothiazines the EEG patterns show increases in spontaneous EEG activation [20a].

Phenothiazine tranquilization correlates with depression of the hypothalamus and midbrain reticular formation, areas containing relatively high concentrations of the neurohormones (serotonin, noradrenaline) whose actions are inhibited by these drugs in part due to their blocking of receptor sites [48]. This group of drugs also reduces to some degree the excitability of the extrahypothalamic limbic structures [33] (See Figure 4). The tranquilization produced by the phenothiazines would therefore seem to be associated with both direct and indirect influences on the hypothalamus and also against the neurohormones serotonin and norepinephrine.

The complexity of these actions of phenothiazines correlate with those of the clinical field where there are tranquilizing effects, an action that seems to be unspecific and in addition, antipsychotic properties such as anti-hallucinogenic and anti-delusional actions which are specific of this group of drugs in psychotic patients.

Besides, phenothiazines also have some antidepressant properties as exemplified by levomeprazine [21a] and thioridazine [41a]. It is probable that their successful clinical use is associated with their complex activities in the brain as reflected by their many sided clinical effects.

B. *Clinical Uses.*

After the first report by Delay and Deniker [9] stressing the favorable results in acute schizophrenia, the clinical uses of chlorpromazine and of the other newly synthetized phenothiazine derivatives experienced a great increase. As with reserpine, phenothiazines were first employed in a large variety of psychiatric and neurological conditions. Kinross-Wright [31] reported the use of chlorpromazine in schizophrenics, depressions and manic states using up to 4000 mg daily. The best results were obtained in acute schizophrenia and manic states while depression did not respond as well. With the introduction of phenothiazines with a piperazine ring on the side chains, the tranquilizing action of this group of phenothiazine derivatives became less striking. Moreover, this piperazine group of phenothiazine derivatives produces greater psychomotor stimulation than the other phenothiazines [16].

The response to a phenothiazine derivative will vary from patient to patient and even at different times in the same patient. A patient who does not exhibit a beneficial response to one phenothiazine may improve on another. Hyperactive patients in general are treated more effectively with non-piperazine phenothiazines. On the other hand, the piperazine group is more active in apathetic, underactive, psychotic patients.

The dosage schedule for phenothiazine therapy is also somewhat different from one psychiatric school to another. In one side a group prescribes in accordance with the psychopharmacological actions of a given drug and the dosage is adjusted in accordance with the symptomatic response of the patient. They also point out that the patients' symptoms may become aggravated in the presence of marked extrapyramidal side effects. As a subgroup of this school are included those who prescribe a low daily dosage for a longer period in an attempt to avoid the undesirable neurological side effects. On the other side are psychiatrists who usually prescribe higher daily dosages, looking for extrapyramidal side effects as an indication that the drug is acting at the central nervous system level, "saturating" the nervous structures and exerting its beneficial effects. After the appearance of the Parkinson-like syndrome, however, the daily dosage is gradually decreased towards a maintenance level, the impregnation medicamenteuse

of the French authors [10]. In this second group, there is a subgroup which considers the phenothiazine-induced extrapyramidal syndromes as essential for the treatment and exerting therapeutic effects [25]. This "neuroleptic syndrome" was the subject of many studies and correlations between the neurologic signs, and psychic modifications were reported by Delay and coworkers [11, 12, 13] who also observed an increased suggestibility in patients under neuroleptic therapy, exhibiting a hysteric-like syndrome. But, independently of the different methods of administration utilized for neuroleptic treatments, their therapeutic effects are unquestionable and the introduction of such drugs enlarged not only the possibilities of the patients' recovery and social readjustment but also extended the horizons of psychiatric research.

C. *Side Effects.*

Now-extrapyramidal: Phenothiazines, in general, induce a variety of side effects that disappear on decreasing the daily dosages or after discontinuation of treatment. The most common ones are dryness of the mouth, myosis, nasal congestion, constipation, hypotension, tachycardia, disturbances of temperature regulation, increase of appetite, somnolence, menstrual disturbances, photosensitization, dermatitis, and drowsiness. With a lower incidence, but important due to the widespread use of phenothiazines are agranulocytosis, lowering of the convulsive threshold in epileptic patients as well as in patients with brain injuries [28a] and obstructive jaundice, but Hollister [28b] reported that non-specific histological abnormalities of the liver are relatively frequent among chronically hospitalized patients who have never been treated with antipsychotic drugs.

More recently, other side effects were described such as lower levels of serum Vitamin B_{12} during continuous administration of chlorpromazine [26] and an increased melanogenesis that, however, has also been observed in schizophrenic patients without phenothiazine therapy [23].

Extrapyramidal: The most common side effect occurring during phenothiazine therapy, however, is the Parkinson-like syndrome which is correlated to the potency of the drug used (Table 1). The motor symptomatology has been divided in 5 succeeding phases by Deniker [18]: (1) akinetic phase, (2) hyperkinetic syndrome, (3) akinetohypertonic syndrome, (4) hyperkinetohypertonic phase and (5) neuro-

TABLE I

Side effects of phenothiazines

Drug	*Comparative dosage*	*Side effects other than extrapyramidal changes* *	*Extrapyramidal side effects*
Chlorpromazine	1	Stronger	Weaker
Triflupromazine	1/2	↑	↓
Perphenazine	1/12		
Trifluoperazine	1/20		
Fluphenazine	1/40	Weaker	Stronger

* The six principal side effects are dermatitis, jaundice, agranulocytosis, sedation, orthostatic hypotension and convulsions. Thioridazine, with a dosage range similar to that of chlorpromazine, is not included in the table because both types of side reactions to this drug are milder (Taken from Himwich, H.E. Psychoactive drugs. Postgraduate Medicine, *37*: 35-45, 1965).

vegetative syndrome. This Parkinson-like syndrome is reversible and can be counteracted by anti-Parkinson drugs. Older persons are more susceptible to Parkinsonian changes while the dyskinesias, for example occulogyric crisis, are more common among younger patients. The akathisias, including motor restlessness, are not related to the patients' age. In general, however, women are more sensitive to all side effects than are men. A perusal of Table 1 reveals that the more potent members of this group induce the more severe extrapyramidal side effects. This generalization, however, does not apply to other side effects.

III. THE BUTYROPHENONES

The butyrophenones constitute the newest series of clinically tested neuroleptics. They possess a chemical structure not related to the phenothiazine nucleus nor to the reserpine configuration. The structures of the two most widely used butyrophenones, haloperidol and triperidol, are shown in Figure 6. They were synthetized by Janssen [30] who reported that the butyrophenones are more potent in a dose-effect relationship than the phenothiazines [32]. In addition they induce more severe neurological, especially extrapyramidal, changes than do the phenothiazines.

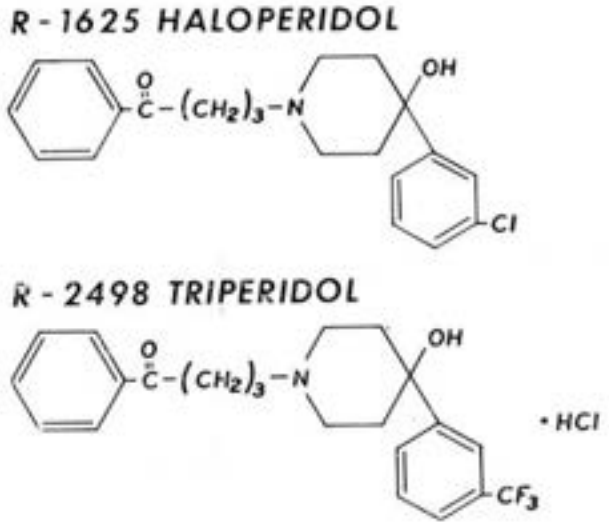

Fig. 6. — *Chemical structures of haloperidol and triperidol, the two representative of the butyrophenone series, which are most widely used. Notice that the configuration of these neuroleptics is completely different from that of phenothiazine derivatives.*

A. *Mechanism of Action.*

The butyrophenones have many of the same basic psychopharmacological properties described above for the phenothiazines. They act chiefly on conditioned psychomotor behavior but proportionally less to alleviate undesirable emotional behavior [22]. Their cataleptic properties, inducing immobility with alertness, are pronounced and like the phenothiazines, butyrophenones decrease spontaneous activity in animals [30, 31-39]. The same authors also reported a potentiating action on barbiturate anesthesia, as well as anti-emetic and antispasmodic properties of the gastrointestinal tract in association with adrenolytic and antiserotonin actions. On the EEG pattern, haloperidol behaves like chlorpromazine, preventing the EEG alerting reaction following acute administration and increasing EEG activation after chronic treatment [20a]. The biochemical aspects of the butyrophenones have not been extensively studied, but van Rossum [49a, b] has reported that haloperidol exerts a specific inhibiting action against dopaminergic fibers of the striatum. Malmfors [41] observed that the same compound has no or very little inhibitory effect on the uptake and storage of norepinephrine in adrenergic nerves. The interactions between butyrophenones and dopaminergic receptors may provide an explanation for the severe extrapyramidal symptomatology observed in the clinical use of these drugs. Thus, the drug induced less of the inhibitory effects of dopaminergic fibers on extrapyramidal activities is a primary factor in the production of the extrapyramidal disturbances associated with this drug. (See Figure 7).

B. *Clinical Uses.*

The butyrophenones, like the piperazine derivatives of phenothiazines, exert a neuroleptic action which does not notably reduce the psychomotor activity of the

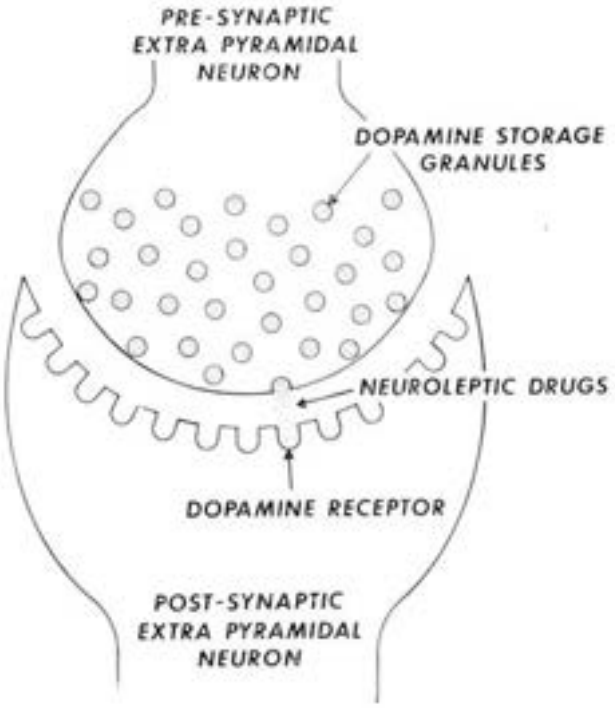

Fig. 7. — *Schematic representation of dopamine actions on the extrapyramidal system. Dopamine is stored in granules inside the presynaptic neuron. The postsynaptic neuron contains receptors which are specific for dopamine. The continuous liberation of this monoamine exerts inhibitory actions on extrapyramidal functions, for dopamine may be an inhibitory transmitter. Neuroleptic drugs can block the receptors inducing the loss of the inhibitory effects and as a result we have the production of extrapyramidal disturbances. Haloperidol is a specific blocker of dopamine receptors. Phenothiazines also block these receptors but do not do it so specifically as the butyrophenones.*

patient and, in therapeutic dosages, leave consciousness clear.

Utilizing the Wittenborn scales, Delay et al.[17] reported that haloperidol significantly decreases the severity of psychotic symptoms as measured by the phobic-obsessional scale for schizophrenic patients. Another interesting point is the highly specific action of haloperidol in manic syndromes and in psychomotor excitement [29, 43]. The first clinical trials on butyrophenones were made by Divry and co-workers [19, 20] who pointed out some advantages of butyrophenone therapy and described a specific action of this series of drugs, namely the neurodyslepsy, characterized by dysleptic myoclonias, parestesias and anxiety. This neurodysleptic action of butyrophenones can be acutely induced by intravenous injection and was employed by Madalena [46a] as a therapeutic measure to activate refractory chronic schizophrenic patients.

Haloperidol and triperidol are indicated chiefly to hallucinatory and delusional patients [44, 19, 20, 17]. To Bishop and Gallant [4] triperidol is of superior efficacy in both paranoid and non-paranoid schizophrenic patients and the authors stress the better and more rapid therapeutic effect in comparison with phenothiazines, while Ban and Stonehill [12] state that disorders of perception and thought content and thought processes respond well to haloperidol. Bueno [8] using triperidol in acute and chronic patients, reported 67% of excellent and good results, chiefly among the acute schizophrenics and stresses the diminution of the hospitalization period as characteristic of the drug when compared with phenothiazines or even with haloperidol, thus allowing for earlier discharge and consequently increasing the possibilities of social readjustment. The drug was equally effective in paranoid as well as in non-paranoid schizophrenics. It is our opinion that the butyrophenones have a definite position among the neuroleptic drugs but they require further studies due to their comparatively recent introduction and dearth of extended follow-up studies.

C. *Side Effects.*

The side effects observed during butyrophenone therapy are similar to those reported with the phenothiazines. But extrapyramidal signs are stronger and more frequent. The neurodysleptic syndrome is also a characteristic of the butyrophenone group though both changes can be elicited by piperazine derivatives of the phenothiazine group such as thiproperazine [12]. The alterations in blood pressure are usually negligible. Liver tests and urinalysis show no or little evidence of organ toxicity. Blood counts reveal an initial lymphocytoses but normalization of the blood picture occurs during treatment. Anxiety,

insomnia, akathisia, and neuro-vegetative symptoms are frequently seen during the early stages of treatment.

DISCUSSION AND SUMMARY

The three groups of psychotropic drugs used in the management of schizophrenic disorders — reserpine, phenothiazines and butyrophenones are reviewed. All three groups share in common neurologic actions: activation of the extrapyramidal system but to different degrees. The diethylamino phenothiazines are weaker than the piperazine derivatives of this group which, in turn, are less potent than reserpine in this regard. Butyrophenones exert the strongest extrapyramidal actions. This side action has a dose-effect relationship and is generally reversible. They seem to be the result of the blockade by neuroleptics of the dopamine modulatory action on the extrapyramidal system. Some psychiatric schools (chiefly the European and South American) use this activation of the extrapyramidal system as an indication that the drug is acting at maximum levels in the central nervous system and the name of these drugs as neuroleptics derives from this extrapyramidal action. It is interesting to notice that during this saturation syndrome (impregnation medicamenteuse) the patients display a higher degree of suggestibility and can often simulate symptoms observed in hysteria. In North America, however, a group of psychiatrists use the tranquilizing and anti-psychotic actions of these drugs as guidelines to dosage level.

Irrespective of the method used, the overall improvement brought by the proper use of neuroleptics in the treatment and prognosis of the schizophrenic disorders is most striking. The neuroleptics do not provide a cure for the disease but the good results obtained with a long-term treatment facilitate social readjustment, thus justifying their use. In addition, these drugs provide a better rapport between the doctor and the patient even whitout mentioning the improvement of the therapeutic atmosphere of the hospital. The clinical usage of neuroleptics is impaired by our present ignorance of the pathogenesis of schizophrenic disorders. But, as pointed out by Delay et al. [14], there are various difficulties in the accurate evaluation of their clinical effects in schizophrenia — the indefinite limits of the diagnosis of schizophrenia, the criteria used to assess remission rate and the protracted clinical course of some cases of schizophrenic disorders. It is not impossible that the understanding of the mechanisms of actions of the neuroleptics will be of great aid in the elucidation of the schizophrenic pathogenesis. On the other hand, biochemical, behavioral and electrophysiological investigations have afforded important basic correlations but further studies are needed. In order to evaluate the mechanisms of actions of these and similar drugs, one must keep in mind that the central nervous system acts as a unit while much of the research thus far is concerned with the particular. It is not impossible that from the particular, a unitary concept clarifying explanations may develop.

We feel that the neuroleptics are a highly specific group of drugs exerting not only tranquilizing actions but also antipsychotic ones. They should be used under close medical supervision and for that reason the physician should gain an intimate knowledge of their psychopharmacology and clinical potentialities including their abilities to induce side effects. The large number of patients treated suggest that these side effects are generally reversible and dwindle in importance to their relation with the crippling effects of schizophrenia. Many pregnant mothers have been under neuroleptic therapy and no teratogenic effects have been reported thus far.

The tranquilizing and anti-anxiety properties of the neuroleptic drugs are unquestionable but since the introduction of weaker drugs with less potent side effects, such as chlordiazepoxide and meprobamate, and with relative specificity in their anti-anxiety actions, the use of the neuroleptics should be restricted to the psychoses where their potent action is necessary. To follow

this simple distinction will avoid the misuse of the more potent drugs with their strong, side effects in patients unsuitable for neuroleptic therapy. It would be wise for physicians to keep in mind that the neuroleptics are supposed to be used with water and not like water.

And what of the future? The history of psychopharmacology starting with the use of phenothiazines and reserpine in the management of schizophrenia was followed by the appearance of MAO inhibitors and iminodibenzyl derivatives, and these two groups of drugs have been proven of value in the treatment of the depressions. In the meantime the weaker tranquilizers like chlordiazepoxide, meprobamate and oxazepam were successfully introduced for the management of neurosis. Last to appear on the scene thus far are the butyrophenones. What the future holds is unclear but it seems likely that progress in the field of psychopharmacology will undoubtedly continue.

RESUMEN

Los tres grupos de drogas psicotrópicas que se emplean en el tratamiento de las alteraciones esquizofrénicas — reserpina, fenotiacinas y butirofenonas — son objeto de una reseña. Estos grupos tienen desde el punto de vista neurológico en común la activación del sistema extrapiramidal aunque en diferente grado. Las dietilamino fenotiacinas son más débiles que los derivados de la piperacina de este grupo, que a su vez son menos potentes que la reserpina en este aspecto. La acción más poderosa sobre el sistema extrapiramidal es ejercida por las butirofenonas. Esta acción secundaria está basada en una relación dosis-efecto y es generalmente reversible.

Parecen ser el resultado del bloqueo de la acción modulatoria de la dopamina sobre el sistema extrapiramidal por parte de los neurolépticos. Algunas escuelas psiquiátricas (principalmente las europeas y sudamericanas) emplean esta activación del sistema extrapiramidal como un indicador de que la droga está actuando a niveles máximos en el sistema nervioso central; la denominación de estas drogas como neurolépticos deriva de esta acción extrapiramidal. Es interesante observar que a lo largo de este síndrome de saturación (impregnation médicamenteuse) los pacientes presentan un mayor grado de sugestibilidad y muy a menudo simulan síntomas observados en la histeria. En Norteamérica sin embargo, un grupo de psiquiatras usa las acciones tranquilizante y antipsicótica de estas drogas como guía para la dosificación.

Sin perjuicio del método empleado, la mejora general obtenida por el uso adecuado de los neurolépticos en el tratamiento y el pronóstico de los disturbios esquizofrénicos es sorprendente. Estos neurolépticos no proporcionan una cura de la enfermedad pero se obtienen resultados satisfactorios mediante un tratamiento a largo plazo, que facilitan el reajuste social, justificando por lo tanto su aplicación. Además estas drogas hacen posible una mejor relacion entre el médico y el paciente y por supuesto su uso se traduce en la mejora del ambiente terapéutico en el hospital.

El uso clínico de neurolépticos se ve alterado debido a nuestra ignorancia actual acerca de la patogénesis de los disturbios esquizofrénicos. Pero, como lo señalan Delay y col. [14] se plantean diversas dificultades para la evaluación correcta de sus efectos clínicos en la esquizofrenia — los límites imprecisos del diagnóstico de la esquizofrenia, los criterios usados para establecer el porcentaje de mejora y la prolongada evolución clínica en algunos casos de disturbios esquizofrénicos. No es imposible que la comprensión de los mecanismos de acción de los neurolépticos sirvan como ayuda en la elucidación de la patogénesis esquizofrénica. Por otro lado las investigaciones bioquímicas, electrofisiológicas y de comportamiento han proporcionado im-

portantes correlaciones básicas que no descartan sin embargo la necesidad de profundizar estos estudios.

A los efectos de evaluar los mecanismos de acción de estas drogas y sus similares, debe tenerse presente que el sistema nervioso central actúa como una unidad, mientras que la investigación hasta ahora está dirigida a lo particular. Es posible que de lo particular surja un concepto unitario y claro. Creemos que los neurolépticos constituyen un grupo de drogas altamente específicas que ejercen no sólo una acción tranquilizante, sino también antipsicótica. Estas deben ser usadas bajo estrecha vigilancia médica y por esa razón al médico se le hace necesario adquirir un íntimo conocimiento de su psicofarmacología y de sus potencialidades además de sus propiedades tendientes a provocar efectos secundarios. El elevado número de pacientes tratados sugiere que estos efectos secundarios son generalmente reversibles y pequeños en importancia en relación con los efectos invalidantes de la esquizofrenia. Muchas mujeres embarazadas han sido sometidas a una terapéutica neuroléptica y no se han observado efectos teratógenos hasta el momento.

Las propiedades tranquilizantes y antiansiosas de las drogas neurolépticas son incuestionables pero desde la introducción de drogas más débiles con efectos secundarios más leves, como el clordiazepóxido y el meprobamato, y con relativa especificidad en su acción antiansiosa, el uso de los neurolépticos debe ser restringido a las psicosis en que su potente acción es necesaria. Estableciendo esta distinción se evitará el uso equivocado de drogas potentes con fuertes efectos secundarios en pacientes que no toleran la terapéutica neuroléptica. Sería acertado que los médicos recordaran que los neurolépticos se toman con agua y no como agua.

Y en cuanto al futuro? La historia de la psicofarmacología comenzando con el uso de fenotiacinas y reserpina en el tratamiento de la esquizofrenia fue seguida por la aparición de inhibidores de la monoaminoxidasa y de derivados del iminodibencil; ambos grupos han demostrado ser valiosos en el tratamiento de las depresiones. Mientras tanto tranquilizantes más leves como el clordiazepóxido, meprobamato y oxazepam fueron introducidos con éxito para el tratamiento de las neurosis. Las últimas en aparecer fueron las butirofenonas. Lo que el futuro reserva es incierto aún pero es indudable que continuará el progreso en el campo de la psicofarmacología.

RÉSUMÉ

Les trois groupes de drogues psychotropiques qui s'emploient au traitement des altérations schizophreniques — réserpine, phenothiazines, butyrophenones — sont décrits.

Ces groupes ont un trait commun du point de vue neurologique: l'activation du système extrapyramidal, à un degré différent selon le groupe. Les diethylaminophenothiazines son plus faibles que les dérivés de la piperazine de ce groupe, qui à leur tour sont moins puissantes que la réserpine. L'action la plus puissante sur le système extrapyramidal est exercée par les butyrophénones. Cette action secondaire est basée sur une relation dose-effet et elle est généralement reversible.

Elles seraient le résultat du blocage de l'action modulatoire de la dopamine sur le système extrapyramidal de la part des neuroleptiques. Quelques écoles psychiatriques (principalement les européennes et les sudaméricaines) utilisent cette activation du système extrapyramidal comme indicateur du fait que la drogue agit à des niveaux de maximum sur le système nerveux central; la dénomination de neuroleptiques pour ces drogues se doit à cette action extrapyramidale. C'est intéressant à observer que tout le long de ce syndrome de saturation (impregnation médicamenteuse) les patients présentent un degré plus elevé de suggestibilité et très souvent ils simulent des symptomes observés à

l'hystérie. En Amérique du Nord cependant, un groupe de psychiatres utilise les actions tranquilisante et antipsychotique de ces drogues comme guide pour la dosification. Indépendamment de la méthode employée, le progrès général obtenu par l'usage correct des neuroleptiques au traitement et à la prognose des perturbations schizophréniques est surprenant. Ces neuroleptiques n'apportent pas la guérison de la maladie mais leurs résultats satisfaisants, au moyen d'un traitement plus prolongé dans le temps, facilitent la réadaptation sociale, justifiant par conséquent leur application.

En plus ces drogues permettent un meilleur rapport entre le médecin et le patient et aussi leur emploi se traduit par une amélioration du milieu thérapeutique à l'hôpital. L'usage clinique des neuroleptiques est altéré par notre ignorance actuelle quant à la pathogénèse des perturbations schizophreniques. Mais comme le signalent Delay et coll. [14] on se trouve devant maintes difficultés pour l'évaluation correcte de leurs effets cliniques dans la schizophrénie — les bornes imprécis de la diagnose de la schizophrénie, les critères employées pour établir le pourcentage de guérison et l'évolution clinique prolongée des perturbations schizophreniques dans certains cas.

Il n'est pas impossible que la compréhension des mécanismes d'action des neuroleptiques aident dans l'élucidation de la pathogénèse schizophrenique. D'autre part les recherches biochimiques, electrophysiologiques et de comportement ont fourni d'importantes correlations basiques qui n'empêchent pas cependant la necessité d'approfondir ces études. Afin d'évaluer les mécanismes d'action de ces drogues et d'autres similaires on doit tenir compte que le système nerveux central agit comme une unité, tandis que la recherche a été orientée jusqu'à présent vers le particulier. Il est possible qu'un concept unitaire et clair surgisse du particulier.

Nous croyons que les neuroleptiques constituent un groupe de drogues hautement specifiques qui exercent une action non seulement tranquilisante mais antipsychotique. Elles doivent être prises sous l'étroite vigilance du médecin ce qui lui rend nécessaire l'acquisition d'une profonde connaissance de la psychopharmacologie de ces drogues et de leurs potentialités ainsi que de leurs propriétés ayant tendance à provoquer des effets secondaires. Un nombre élevé de patients traités suggère que ces effets secondaires sont généralement reversibles et d'une importance réduite par rapport aux effets invalidants de la schizophrenie. Beaucoup de femmes enceintes ont été soumises à une thérapeutique neuroleptique et on n'a pas observé des effets thératogènes jusqu'à présent.

Les propriétés tranquilisantes et antianxieuses des drogues neuroleptiques ne peuvent pas être mises en question, mais depuis l'introduction des drogues plus faibles aux effets secondaires moins forts telles que la chlordiazepoxide et le meprobamate, et dont la specificité dans l'action antianxieuse est relative, l'usage des neuroleptiques doit être restreint aux psychoses où leur puissante action est nécessaire. En etablissant cette distinction on évitera la fausse application de drogues puissantes aux effets secondaires considérables dans des patients qui ne tolèrent pas la thérapeutique neuroleptique. Il serait convenable de rappeler aux médecins que les neuroleptiques se prennent avec de l'eau, mais pas comme s'ils étaient de l'eau.

Et quant au futur? L'histoire de la psychopharmacologie en commençant par l'usage des phénotiacines et de la réserpine dans le traitement de la schizophrénie fut suivie par l'apparition des inhibiteurs de la monoaminoxidase et des dérivés de l'iminodibenzyl; les deux groupes se sont montrés précieux dans le traitement des depressions. Entre temps des tranquilisants plus légers tels que le chlordiazepoxide, le meprobamate et l'oxacepam furent introduits avec succès pour le traitement des neuroses. Les dernières à aparaître furent les butirophénones. Ce que le futur nous réserve est encore incertain mais sans doute le progrès au domaine de la psychopharmacologie continuera.

ZUSAMMENFASSUNG

Die drei Gruppen von psychotropen Drogen, die bei der Behandlung der schizophrenischen Stoerungen benutzt werden — Reserpin, Phenotiazin und Butyrophenone — sind einer Untersuchung unterzogen worden. Alle drei haben neurologische Wirkungen gemein: die Aktivierung des extrapyramidalen Systemes, aber in verschiedenem Grade. Die Diaethylamino phenotiazine sind schwaecher als die Piperazinverbindungen dieser Gruppe, welche ihrerseits von diesem Standpunkt aus weniger stark sind als die Reserpine. Die Butyrophenone ueben die staerksten extrapyramidalen Wirkungen aus. Diese sekundaeren Nebenwirkungen haben eine Beziehung zwischen Dosis und Effekt und sind gewoehnlich reversibel. Sie scheinen das Ergebnis der Blockade durch Neuroleptica der Dopamine modulierenden Aktion auf das extrapyramidale System zu sein.

Einige psychiatrischen Schulen (wesentlich die europaeischen und suedamerikanischen) benutzen diese Aktivierung des extrapyramidalen Systems als Indikator, dass die Droge auf die maximalen Niveaus im zentralen Nervensystem wirkt und die Benennung dieser Droge als "neuroleptisch" kommt von dieser extrapyramidalen Wirkung her. Es ist interessant, dass waehrend dieses Saturations-Syndroms (medikamenteuse Impregnation), der Patient einen hoeheren Grad von suggestibilitaet entwickelt und oft Symptome imitiert, die bei der Hysterie beobachtet werden. Jedoch in Nordamerika gebraucht eine Gruppe von Psychiatern die tranquilisierende und anti-psychotische Wirkung dieser Drogen als Anzeiger fuer die Dosierung.

Ohne Ruecksicht auf die angewandte Methode, ist die allgemeine Besserung durch die geeignete Anwendung der Neuroleptica, in der Behandlung und Prognose der schizophrenen Stoerungen hoechst auffallend. Die Neuroleptica verursachen keine Heilung der Krankheit, aber die guten Ergebnisse bei laenger dauernder Behandlung erleichtern die soziale Wiederangleichung und rechtfertigen schon dadurch ihre Anwendung. Ausserdem vermitteln diese Drogen bessere Beziehungen zwischen Arzt und Patient, auch ohne die Besserung der therapeutischen Atmosphaere im Hospital zu erwaehnen. Der klinische Gebrauch der Neuroleptica ist gehemmt durch unsere augenblickliche Ignoranz ueber die pathogenese der schizophrenischen Stoerungen. Aber wie Delay und seine Mitarbeiter [14] hervorgehoben haben, sind verschiedene Schwierigkeiten bei der genauen Bewertung ihrer klinischen Wirkungen bei der Schizophrenie vorhanden — die unbestimmte Grenzen der Diagnose einer Schizophrenie, die verschiedenen Kriterien bei der Beurteilung des Grades der Besserung, und des ausgedehnten klinischen Verlaufes einiger Faelle von schizophrenischen Stoerungen.

Es ist nicht unmoeglich dass das Verstaendnis des Aktionmechanismus der Neuroleptica von grossem Nutzen bei der Aufklaerung der schizophrenen Pathogenese sein wird. Andererseits, die biochemischen, verhaltungspsychologischen und elektrophysiologischen Untersuchungen haben wichtige basische Korrelationen aufgedeckt, aber es sind noch weitere Untersuchungen noetig. Um die Aktionsmechanismen dieser und aehnlicher Drogen bewerten zu koennen, muss man sich stets vorstellen, dass das zentrale Nervensystem als eine Einheit arbeitet, waehrend viele der bisherigen Untersuchungen sich mit Einzelheiten beschaeftigen... Es ist nicht unmoeglich, dass vom Einzelnen sich ein unitarisches Konzept mit aufklaerenden Auslegungen entwickeln kann.

Wir sind der Meinung, dass die Neuroleptica eine hochzpezifische Gruppe von Drogen darstellen, die nicht nur eine tranquilisierende sondern auch noch eine antipsychotische Aktion ausueben. Sie sollten unter strenger aerztlicher Ueberwachung angewandt werden und aus diesem Grunde sollte der Arzt eine eingehende Kenntnis ueber ihre psychophar-

makologischen und klinischen Moeglichkeiten einschliesslich der Moeglichkeit Nebenwirkungen zu erzeugen, erwerben. Die grosse Anzahl von behandelten Patienten laesst annehmen, dass diese Nebenwirkungen gewoehnlich reversibel sind und keine Wichtigkeit haben gegenueber den invalidierenden Wirkungen der Schizophrenie. Viele schwangere Frauen haben unter der neuroleptischen Therapie gestanden und es sind keine teratogenen Wirkungen bis jetzt veroeffentlicht worden.

Die tranquilisierenden und anti-Angst Eigenschaft der neuroleptischen Drogen sind ueber allen Zweifel erhaben aber seit der Einfuehrung schwaecherer Drogen mit weniger potenten Seiteneffekten, wie chlordiazepoxide und meprobamate und mit der relativen Spezifizitaet ihrer anti-Angst Wirkungen, sollte der Gebrauch von Neuroleptica eingeschraenkt werden fuer solche Psychosen bei denen ihre wichtige Aktion notwendig ist. Indem man dieser einfachen Untrescheidung folgt wird man den Missbrauch der mehr potenten Drogen mit ihren starken Nebenwirkungen bei Patienten, die sich fuer die neuroleptische Therapie nicht eignen, vermeiden. Es waere Klug, wenn der Arzt bedaechte, dass die Neuroleptica mit Wasser und nicht wie Wasser eingenommen werden sollten.

Und was ueber die Zukunft? Die Geschichte der Psychopharmakologie, die mit dem Gebrauch des Phenotiazin und dem Reserpin in der Behandlung der Schizophrenie anfing, war gefolgt mit der Erscheinung der MAO Inhibitoren und den Iminodibenzilderivaten, und diese beiden Gruppen von Drogen haben sich als wertvoll bei der Behandlung der Depression bewiesen. Inzwischen wurden die weniger starken Tranquilisatoren wie Chlordiazepoxide, Meprobamate und Oxazepam mit Erfolg fuer die Behandlung der Neurosen eingefuehrt. Schliesslich sind die Butyrophenonen auf der Szene erschienen. Man weiss nicht was sie versprechen, aber es scheint, dass der Fortschritt auf dem Gebiete der Psychopharmakologie ohne Zweifel weitergehen wird.

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Repos Ailleurs[1]

par G. C. GUAZZI* et J. RADERMECKER**

Nulle devise ne fut jamais aussi prestigieusement personnifiée que celle de la famille van Bogaert ne l'est par le Docteur Ludo van Bogaert. Poursuivant sans répit sa course inlassable contre le temps, van Bogaert est d'une activité perpétuellement débordante et le personnage paraît se renouveler continuellement, déroutant l'observateur qui voudrait le figer dans un cliché. Il est pourtant tel qu'il était en 1923 à la Salpêtrière: une mèche coquette couvrant très discrètement le coin droit d'un visage flamand aux yeux doux, charmeurs, subtilement ironiques, comme s'ils avaient la tâche d'effacer le mythe du personnage.

Son costume, ses chaussures, sa cravate (le temps des foulards de jeune garçon est passé), la décoration à la boutonnière, l'argenterie, la place à table, sa perle fine, la robe de sa femme, la distinction de sa conversation, les blagueuses imitations des grands hommes mordus par le venin du succès sont uniques, comme s'il avait aimé être acteur au Théâtre de 10 Heures[2].

Deux signes peuvent vous donner le "la" de son esprit. S'il vous reçoit avec un ah! très court, le temps de remettre son armure, le même ah! qui lui échappe dans la chambre d'un malade ingrat ou difficile ou s'il a une mèche rebelle sur l'occiput, soyez bref, le moment est mal choisi. Ces deux signes les seuls à échapper à son contrôle. Tout le reste est lucide, réfléchi, conscient. Ils

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(1) Devise due à l'amitié de Marnix de Sainte Alegonde au XVIe siècle.
(2) Minuscule théâtre de chansonniers à Pigalle.

n'apparaitront d'ailleurs qu'à l'Institut Bunge et jamais chez lui, dans sa demeure ornée de tapisseries, de tableaux, de terres cuites chinoises, de bois romans, de verreries de haute époque et de combien d'autres pièces rares.

"C'est un homme admirablement armé. Il dégage intelligence et ruse comme le radium dégage de l'énergie. Avec la même silencieuse et pénétrante continuité, sans effort, sans arrêt, sans signes d'épuisement, dans toutes les directions en même temps. Qu'il est un savant habile c'est net au premier contact. Que cette grandeur professionnelle soit seulement un trait, une facette de la hauteur de son génie ou qu'elle soit justement son instrument de pénétration, son arme secrète pour rendre vaines les défenses, pour changer les non en oui, je ne pourrai jamais le dire. Ceci également fait partie du nuage qui l'entoure. C'est un nuage quasi-visible, une présence qui fait soupçonner sous chacune de ses actions, de ses phrases, de ses silences une tactique et une technique, la poursuite de finalités imperceptibles, un continuel travail d'exploration, d'insertion, de possession".

Le Bon Dieu, quoiqu'en pense Voltaire, confie chaque homme à un ange et à un démon. L'ange gardien du Dr. van Bogaert s'est transhumanisé dans l'image de sa mère. Le sens du devoir, l'abnégation silencieuse à la famille au sens patriarcal du mot, la compréhension des hommes, la hiérarchie et la forme, le maintien de soi, la religion catholique tout cela vient de sa mère, cette mère vénérée dont l'image n'a jamais quitté la table de travail de son fils.

Et son démon? Le travail. Selon certains théologiens, l'enfer consisterait pour le damné à obtenir pour l'éternité ce qu'il a désiré durant toute sa vie. Obliger cet homme au repos ne fut-ce que pendant dix jours, cet homme vivant et plein de jeunesse, ce serait à la réflexion le pire tourment. Car bien sûr ir voudrait se donner des vacances, courir en Provence, lire dans les Jardins du Luxembourg, flâner le long de la Seine, s'exposer aux vents de Bretagne, se relaxer dans les hôtels vieillots d'Angleterre, mais il ne le peut pas. Son démon le pousse à courir, à courir dans sa maison, à l'hôpital, dans ses voyages, dans son jardin, toujours avec une mince malette de cuir raccomodée dans les coins comme une vieille ferme flamande.

Si sa mère est son ange gardien, son père fut, d'après le propres paroles de van Bogaert "Un homme sévère mais juste". Grand médecin anversois, le Dr. Louis van Bogaert fut le premier à recevoir sur rendez vous et à faire ses visites avec son landau particulier. D'aucuns se souviennent de cette altière silhouette à côté de laquelle était bien souvent assis un petit garçon en culottes courtes qui à ce moment ne se doutait pas de son destin.

De son père, le Docteur Ludo van Bogaert apprendra à mener les hommes, à n'importe quel titre. Même assistant, il s'impose comme chef d'équipe. S'il n'est pas Directeur de l'Institut Bunge, l'Institut Bunge c'est lui. Cependant il n'oublie jamais les formes et chaque Noël il va présenter ses voeux de Nouvel An au Directeur. Durant la première guerre mondiale, chef d'un groupe de commandos, il obtiendra de ses hommes ce qu'il désire. Ses laborantines l'adorent, épient ses désirs. Elles savent qu'en plus de 30 ans passés avec lui elles n'ont jamais reçu d'ordres. Le tableau noir avec l'annotation des choses à faire, qu'il avait vu à Bruxelles chez le Prof. Dustin père, n'entra jamais dans son laboratoire. Il n'en a jamais eu besoin.

A la mort de son père c'est lui le chef de famille. Mais les formes, toujours, seront sauvegardées. L'argent qu'il gagne va à sa mère. Partant pour Paris pour faire une communication à la Salpêtrière il demande l'argent à sa mère. A la veille d'un évènement important, lorsque son coeur hésite, il suivra docilement le conseil de sa mère: "Un van Bogaert, dit-elle, ne recule pas". Le conseil reste actuel.

Fils de médecin, il choisit très jeune la carrière médicale. Il l'interrompt pour partir comme volontaire au front et choisit l'infanterie, puis plus tard les commandos. A sa seconde blessure, en 1918, abandonné sur le champ de bataille des Flandres, il encourage le camarade qui perd son sang, lui indique comment mettre un garrot pendant que lui même suit minutieusement ses jambes qui refroidissent et son hémorragie pulmonaire. A l'hôpital de campagne où il est transporté (fracture d'une vertèbre, commotion spinale, une balle de mitrailleuse intrapulmonaire) il regarde avec étonnement les médecins qui pratiquent chez lui une ponction lombaire tous les trois jours avec un gros troquart de Quincke tout en ne sachant qu'attendre de cet exercice. Sa curiosité pour les mystères du système nerveux s'éveille.

Terminée sa convalescence, en 1919, avec le prestige de l'uniforme, il termine brillamment, dans un temps très court, ses études de médecine. Quatre ans plus tard il se présente à l'agrégation de l'Université Libre de Bruxelles. Son père, catholique, l'y avait fait entrer dans le souci de ne pas mêler science et religion. L'agrégation lui est décernée mais il refuse de renier sa religion et de ce fait sait qu'il ne sera jamais chargé d'un enseignement ordinaire. C'est ainsi qu'à 28 ans il préfère s'écarter de toute carrière universitaire que d'être parjure à sa Foi.

D'ailleurs, sa conception de la neurologie s'accordait mal avec les structures préétablies. Le souffle et le développement qu'il allait apporter à cette branche de la médecine avaient besoin de trop de champs pour être acceptés sans aigreurs et jalousies par les maîtres de la pathologie interne. Sans vains regrets, il développe une neurologie clinique qui englobe les sciences connexes. La vie de son institut, quel que soit le nombre de ses collaborateurs, suit quelques grandes règles qu'il s'est lui même imposées.

"Notre Institut —et c'est là sa fierté, sa raison d'être et on peut dire sa devise— se situe en dehors de toute constellation politique ou religieuse". "Nous n'exigeons de ceux qui entrent dans notre ordre qu'un seul voeu: celui du travail et si possible du travail d'équipe... Tous ceux qui chez nous ne l'ont pas accepté ou qui n'ont pas contribué à la maintenir ont été ou se sont éliminés d'eux mêmes comme des corps étrangers à notre organisation".

L'homme est tout entier, quoi qu'il fasse et où qu'il soit. Devant un patient, chez un marchand d'art ou un grand libraire, à son microscope. C'est sa nature flamande qui se révèle. Son analyse est vite familière avec l'objet. Son contact est immédiat tout en étant électif. Les conclusions qu'il tire, qu'elles restent simplement gravées dans sa mémoire, écrites ou dites dans un commentaire isolent et valorisent les traits essentiels de la question.

Ecrivant ses impressions personnelles au retour d'un voyage en Russie, les détails donnés en 15 pages se résument en dix lignes de conclusion d'où ressortent toutes les analogies entre le comportement des Soviétiques et celui des Américains.

Racontant son voyage aux Etats Unis, il se compare à un Grec arrivant à Rome: le poids d'une culture scientifique née de Pierre Marie et de Spielmeyer face à une technique. Il se sent un poisson hors de l'eau, un homme du XVIIIe siècle dans une usine à la chaîne. Il sait cependant la valeur de cette hyperspécialisation et dans une lettre il admet que s'il était jeune c'est là qu'il irait travailler pendant quelque temps.

Comment marquer chronologiquement l'évolution de sa carrière?

Nous commencerons en 1922-23 par sa rencontre avec Oscar et Cécile Vogt, étudiant l'architectonie dans la sclérose latérale amyotrophique. C'est le même travail qui le conduit chez von Economo.

Malgré l'antagonisme des Vogt et d'Economo dans le domaine de l'architectonie, malgré les difficultés pour faire reconnaitre à Economo la priorité de l'encéphalite léthargique, il réussit à rester l'ami des Vogt et d'Economo jusqu'à leur mort.

A la même époque, il a pris le chemin de Paris pour se spécialiser en neurologie chez Pierre Marie. Des liens d'amitié s'établissent aussitôt avec Tournay, Alajouanine, Pierre Mathieu, Thévenard, Péron, Christophe, Garcin, Dereux et tant d'autres[3].

Ivan Bertrand lui donne les bases de sa neuropathologie. Van Bogaert le considérera toujours comme son premier maître. Leur collaboration s'étendra sur toute la vie de Bertrand. Leur dernière oeuvre est, pour Bertrand, posthume.

Au moment où Bogaert est accueilli par Pierre Marie, Ivan Bertrand venait de terminer une thèse sur les "Processus de désintégration du système nerveux". Pour la première fois en langue française se trouvaient explicitement exposées dans leur ensemble les descriptions des attritions et des organisations tissulaires à la lumière des données cytologiques qu'on devait à Nissl, Alzheimer, Achucarro, Alfons Jakob, etc. A cette époque, ces noms n'avaient pas beaucoup pénétré encore dans les milieux de la recherche française, sauf dans les travaux de quelques chercheurs exceptionnels comme Jean Lhermitte, Dide, Anglade, etc.... Cette méthodologie cyto-pathologique apportait un enrichissement considérable à la méthode anatomoclinique dont les neurologues s'étaient nourris jusqu'alors.

Un jour un jeune Estonien, le Dr. Rives, qui travaillait à ce moment chez Ivan Bertrand, offrit à van Bogaert, en souvenir, l'Histopathologie des Nervensystems de W. Spielmeyer en langue allemande, édition princeps et presque personne alors ne connaissait dans nos pays, van Bogaert s'est nourri de cet ouvrage comme de l'Evangile. Il l'a annoté, mis à jour et d'innombrables travailleurs dans son laboratoire ont recopié le vieil exemplaire dactylographié de sa traduction. Il n'a été content que du jour où il a pu connaître et travailler personnellement avec Spielmeyer à Munich et où il a rencontré Scholz, Hallervorden et Spatz. C'est grâce à cela qu'il a pu servir de liaison entre l'Ecole Allemande qui est vraiment la créatrice de la neuropathologie et l'Ecole Française qui est la fondatrice des sciences anatomocliniques et hodographiques. Il est resté fidèle à cette double tradition et sa vie a été nourrie à cette double initiation.

A son retour à Anvers, il est nommé à Hôpital Stuyvenberg où il franchira les différents échelons pour y terminer sa carrière comme chef du Service de Médecine Interne. Ceci ne l'a pas empêché de monter dans les caves de cet hôpital un laboratoire de neuropathologie qui y fonctionne de 1925 à 1934, dans une ancienne chambre de stérilisation. Il a souvent évoqué devant les jeunes les difficultés inouïes dans lesquelles il s'est trouvé pour faire de la technique dans cette cave surchauffée en été, glaciale en hiver. Il faisait lui même ses autopsies avec l'aide de son dévoué mécanicien-chauffeur M. Paul Gaethofs que tant d'entre nous ont connu. Ce n'est que beaucoup plus tard, vers 1933, qu'il envoya sa première technicienne qui restera le pilier de son laboratoire, Melle Snieders, se former chez les Prof. Spielmeyer à Munich et Brouwer à Amsterdam. Paul Gaethofs, plus connu sous le nom de Paul, devient son prosecteur: il lui fait suivre des cours d'anatomie et de dissection. Pendant longtemps le chauffeur-prosecteur apprendra aux jeunes stagiaires du département de neuropathologie l'art de faire proprement tous les prélèvements et de remettre le corps dans un état présentable à la famille.

(3) A Paris son humanisme s'affirme au contact personnel de Baillon, d'Adrienne Monnier, plus tard de Valéry Larbaud, Léon Paul Fargue, Paul Valéry, Henri Bosco, La Varende et Simon Lévy.

En 1925, avec Paul Martin et Rodolphe Ley, il fonde le Groupe Belge d'Etudes Oto-Neuro-Ophtalmologiques et Neurochirurgicales, un an après que le Prof. Barré eut fondé à Strasbourg la Société Française d'Oto-Neuro-Oculistique: le but poursuivi était le même mais les Belges y associaient en outre directement la Neurochirurgie de façon à la rapprocher elle aussi des sciences ophtalmologiques, otologiques et neurologiques. En ce qui concerne la Neurologie Belge, rappelons ici que van Bogaert, Ley et Martin ont tout fait pour garder en neurologie une unité nationale et une unité scientifique et cela à travers toutes les mesquineries académiques et linguistiques qu'ils n'ont pas manqué de subir. Van Bogaert n'oubliera jamais ce que la Société Belge de Neurologie doit à son ami Rodolphe Ley qui non seulement l'anima pendant 40 ans, mais qui dirigea de main de maître pendant toutes ces années le Journal Belge de Neurologie, devenu ultérieurement les Acta Neurologica et Psychiatrica Belgica.

Vers 1930, un puissant homme d'affaires sur le plan international et mécène anversois, Monsieur Edouard Bunge, confia une somme importante à son chirurgien et médecin, le Dr. Nestor Vanderstricht pour édifier à Anvers, ville alors non universitaire, un centre d'études et de recherches médico-chirurgicales. Van Bogaert accepta aussitôt d'y participer et c'est ainsi qu'en 1934 l'Institut Bunge ouvrait ses portes avec une capacité de 27 lits et quelques laboratoires.

A la fin de la seconde guerre mondiale, après sa reconstruction, l'Institut Bunge se développa.

En 1966, la Reine Fabiola inaugura la nouvelle Fondation Born-Bunge qui, bien que distincte, complète la clinique. L'Institut Bunge et la Fondation Born-Bunge virent dès leur naissance arriver dans leurs murs une foule de jeunes gens qui devinrent d'abord les élèves et les collaborateurs du Maître et qui se sentent parfois plus près de lui que la soi-disant deuxième génération.

Ce sanctuaire des sciences neurologiques s'est fait à l'image d'une cour de la renaissance italienne ou de l'atelier d'un grand peintre. Les uns y broient les couleurs, les autres peignent les figures ou les motifs qu'il retouche et complète. Et le travail, auquel chacun concoure, porte la marque de l'oeuvre toute entière. Tout le monde ramasse ce dont ses bras débordent: chacun y trouve qui son syndrome, qui les idées qui feront sa réputation. Dans ce concert, tous trouvent, dans la recherche scientifique, la même maîtresse exigeante.

Ses élèves viennent d'au delà des frontières. Le "Patron", conseiller occulte et parfois pélerin infatigable, ne les oublie pas. Chez eux ils gardent les volumes de l'Institut Bunge et de la Fondation Born-Bunge. Ils y retrouvent le style de van Bogaert écrivain. C'est un langage parlé. La description d'une histoire clinique ou d'une coupe s'éclaire de la touche d'un Rubens, de la mesure bien française de Cézanne, du ciel bleu d'Ingres. Ses phrases en italique sont dépouillées comme le trait chez Rik Wouters.

Parmi les activités du Docteur van Bogaert une place considérable revient, ces dernières années, à la Fédération Mondiale de Neurologie.

L'histoire de cette fédération nous semble fort instructive pour connaître ce fier Flamand et elle doit être évoquée.

En 1949, après le Congrès International de Neurologie tenu à Paris, le Prof. Brouwer insista auprès de lui pour que le prochain congrès c.à.d. celui de 1953 ait lieu à Bruxelles ou à Louvain. Comme la clinique du Prof. van Gehuchten était à ce moment en pleine transformation et qu'il avait l'intention de demander à van Gehuchten —nom historique dans la neurologie

et l'anatomie belges— de présider ce congrès on décidé de réunir le congrès de 1953 à Lisbonne.

En 1953, quand après Lisbonne on demanda au Dr. Ludo van Bogaert d'entrer dans un groupe de neurologistes constituant une Commission ayant pour objet de rallier à la neurologie l'électroencéphalographie et la neurochirurgie, il comprit que le but à poursuivre à ce moment pour les congrès internationaux était de grouper toutes ces disciplines.

En 1953, on proposa de tenir le congrès suivant en Belgique. Le Dr. van Bogaert avait d'abord refusé étant donné qu'il trouvait la charge trop lourde. C'est le Dr. Radermecker qui l'a convaincu d'accepter le secrétariat général à condition que le Prof. van Gehuchten acceptât la présidence. C'est ainsi qu'en 1955 on s'est réuni à Bruxelles pour la première fois à l'occasion de la constitution du comité préparatoire du Congrès de 1957. Se souvenant de ce qui lui avait été demandé en 1953, van Bogaert a alors tenté de réunir toutes les disciplines en un Congrès Unique Interdisciplinaire.

Ce Congrès de 1957 a été un grand succès au point de vue organisation grâce à l'équipe du Dr. Radermecker et à tous ceux qui s'y sont associés en un effort inoui. On peut dire que ce congrès a été réellement l'oeuvre de l'Institut Bunge et de son staff à cette époque.

C'est devant le succès de ce Congrès de 1957 que les Américains, et en particulier les Drs. Pearce Bailey et Houston Merritt, ont décidé de brusquer la naissance de la Fédération Mondiale de Neurologie. De longs échanges écrits avaient déjà eu lieu entre le Dr. P. Bailey et le Dr. van Bogaert depuis 1953 sur la manière dont on pourrait envisager la création d'une telle fédération.

C'est grâce à l'énergie de Houston Merritt et de Pearce Bailey que pendant la durée même du congrès ont été jetées les bases de la Fédération Mondiale.

Dans l'idée des Américains, cette Fédération devait constituer un organisme permanent d'organisation des congrès. Ce n'est que quand ils ont vu le succès des échanges interdisciplinaires qu'ils ont demandé d'envisager une méthode qui permettrait d'intéresser d'une façon régulière les disciplines ancillaires comme la neuropathologie, l'EEG, la neurochimie, etc... à la neurologie elle-même. C'est ainsi que dans le courant des années 58 et 59 avec le Dr. Charles Poser, van Bogaert a mis sur pied les différents groupes de travail qui sont restés un des organismes les plus effectifs de la F.M.N. La constitution des groupes de travail a d'ailleurs été à l'origine de toutes sortes de difficultés, étant donné que van Bogaert avait, d'une façon très démocratique, constitué les groupes en prenant à travers le monde les gens les plus qualifiés pour y siéger. Van Bogaert a su garder la plus grande liberté d'action en ce qui concerne surtout nos vieilles nations européennes et les pays en voie de développement. Il voulait que tous ceux que travaillent aient leur place, pauvres ou riches, amis ou ennemis, la science ne connaissant pas de frontières ni de rideaux.

Dans cette perspective de neurologie dont le rayonnement dépasse les frontières, un mot sur ses rapports avec les Allemands.

Nous avons déjà parlé de sa filiation directe vis à vis de l'Ecole de Munich. Malgré les évènements des deux guerres qui ont fait des Belges et des Allemands des ennemis, il sut garder avec ces derniers les meilleurs rapports au point de vue scientifique, même pendant la guerre. Il ne pouvait recevoir chez lui Spatz dans son uniforme militaire, mais il lui ouvrit sans arrière pensée son laboratoire. Spatz intervint de son côté lors de la menace de réqui-

sition de l'Institut Bunge par l'aviation allemande et il fit afficher sur les murs de l'hôpital qu'il s'agissait d'un centre de recherche qui ne pouvait pas être requisitionné. La maison sauvée, le Prof. Spatz assista également la laborantine en chef, Mademoiselle Snieders, qui faisait de la propagande anti-allemande et qui avait été incarcérée bien qu'impotente.

La guerre terminée, van Bogaert, Haymaker et Radermecker ont aidé comme ils ont pu le Prof. Spatz et d'autres neurologistes allemands en difficulté. Les invités de van Bogaert ont écouté à mainte reprise, pendant les dîners d'amis, le récit de cette visite et chaque fois il semblait ému, tout comme quand il parlait des misères subies par son ami Greenfield pendant les bombardements de Londres.

La guerre terminée, quand le Dr. van Bogaert fit nommer Hallervorden rapporteur à Lisbonne sur les idioties amaurotiques, quelques grands neurologistes anti-allemands déclenchèrent contre Hallervorden, à cette occasion, une violente campagne. Van Bogaert fit alors lui même une enquête à Bonn: il put consulter les pièces originales du Procès de Nurenberg. On accusait Hallervorden d'avoir dirigé la liquidation d'idiots pour obtenir leur cerveau. La plupart des neurologistes qu'il consulta à cette époque pour leur demander leur opinion dans ce cas délicat, où on le priait d'exclure officiellement Hallevorden comme rapporteur, n'eurent pas le courage de se prononcer ni de le soutenir dans son effort de réhabilitation.

A la demande du Président du Congrès de Lisbonne qui craignait de voir ces disputes retentir sur le succès de son congrès, il renonça à faire parler Hallervorden comme rapporteur mais il fit lui même l'exposé à sa place pour bien montrer qu'il n'avait pas peur de perdre quelques amis mais qu'il refusait de désavouer une personne qu'il jugeait innocente. Son enquête à Bonn avait d'ailleurs montré qu'il y avait eu en faveur du Prof. Hallervorden un non lieu au procès de Nurenberg.

Ce besoin de loyauté et de justice vis à vis de tout le monde et vis à vis de lui même ses élèves le connaissent. Nous l'avons toujours vu prêt à se corriger, à se démentir si on démontre qu'il s'est trompé mais il va jusqu'au bout, sans craindre les conséquences, lorsqu'il croit que son jugement est juste.

Book Reviews

RECOLLECTIONS OF MY LIFE by Ramon y Cajal. — Translated by E. Horne Craigie with the asisstance of Juan Cano. The M.I.T. Press, Cambridge, Mass., 1966. 638 pp. Illustrated.

The late professor Craigie's translation of the autobiography of Ramon y Cajal was first published in 1937, as volume VIII of the Memoirs of the American Philosophical Society. In retrospect of the past 30 years, the significance of Cajal's contribution to the knowledge of structure and neuronal organization of the nervous system, and his figure as a man of science have continued to grow. His fundamental discoveries laid the foundation for the physiology of the spinal cord and cerebellum, and for the application of the mathematical and biophysical principles of electrophysiology in brain research. The reprinting by the M.I.T. Press of Craigie's translation of Cajal's autobiography answers now a need of a much wider audience of readers. Cajal's "Records of My Life," as he called his recollections, were written in 1917-21 when he was in his late sixties and about to retire from the active directorship of the "Instituto Cajal" for Biological Research in Madrid. He died October 10, 1934. His major works were published before 1914. He received the Nobel Prize, shared with Camillo Golgi, in 1906. The autobiography is composed in two parts: Reminiscences of childhood and youth, and the account of his life as investigator from the time he was appointed professor of anatomy at the University of Valencia in 1884, at 32 years of age.

In the first part, he recounts the years of his boyhood and youth in the craggy foothills of the Pyrenees deep in the heart of Arragonese Spain. The ruins of a glorious past clashed, it seems, in particularly sharp contrasts with the rapidly changing world beyond the horizons of the small villages of Ayerbe where he has grown, of Larres, where his parents were born, and of Petilla where he was born on May 1, 1852. He was christened Santiago in dedication to "the apostle, the patron of Spain and the Terror of the Moor." With candor and the detached and lonely wisdom of an aging man, Cajal recounts the episodes (he calls them "escapades") of the childhood and youth of a congenital rebel: Protest against the single-minded, domineering father, boredom and conflicts with the teachers in school, recurrent boyish pranks and punishments, and constant "scrapes" with the stronger "bullys", — each defeat feeding the indomitable will to get the better of adversities. As would any youngster, but in Cajal's case with the right of primogeniture, as it were, he identified himself with the positive and literal, rather than metaphoric side of the character of Miguel Cervantes' Knight of La Mancha: "I took the figure of Don Quixote seriously and so felt keenly the damaged state in which the valiant knight emerged from nearly all his quarrels and adventures."

The second part is a record of Cajal's discoveries in the histology of the nervous system, of reverses and grievances of "academic scrapes" for priorities, and of his major battle and greatest victory in proving that the neuron is a structural and functional unit, against a formidable array of contemporary authorities (Golgi, Bethe, Marchand, Monckeberg, O. Schultze) who held to the then prevalent theory of the protoplasmic continuity of the neuronal reticulum. This part of the autobiography gives an interesting historical material and insight into the intellectual climate which prevailed in the academic world in Europe between the Franco-Prussian war of 1870 and the War of 1914-18. In that period of some 40 years, the center of politico-economic gravity, and with it of the scientific authority and prestige, was shifting from the Latin to the Germanic Europe. The technological revolution in scientific methods and instrumentation, which followed the industrial revolution, has its beginning in those decades. Technical armamentarium with which Cajal made his major discoveries in histology of the nervous system, was based largely on the method of silver impregnation of tissues discovered by Camillo Golgi in 1880. Cajal was not a technological inventor. It was Luis Simarro, faculty colleague of Cajal, who acquainted him with the Golgi method and introduced the use of photographic reducing agents in its later and numerous modifications by Cajal and his pupils. However, he was his own and unexcelled technician. The first opportunity to present his discoveries to the scientific world came in 1889 on the occasion of the meeting of the German Anatomical Society in Berlin. He describes the event (pp. 355-358) with undisguised emotion:

> "Among those who showed most interest in my demonstrations I should mention His, Schwalbe, Retzius, Waldeyer, and especially Kölliker..... these savants, then world celebrities, began their examination (of Cajal's preparations, Rev.) with more scepticism than curiosity .....However, when there had been paraded before their eyes in a procession of irreproachable images of the utmost clearness, the axons of the granules of the cerebellum, the pericellular basket-endings, the mossy and climbing fibers, the bifurcations and ascending and descending branches of the columns of white matter, the terminations of the retinal fibres in the optic lobes, etc., the supercilius frowns disappeared. Finally

the prejudice against the humble Spanish anatomist vanished, and warm and sincere congratulations burst forth."

In his own appraisal of himself, Cajal was an artist and would have become one, if the paternal intransigence and his own unsatiable curiosity about nature had not deflected him from his ambitions to become a painter. After a stint as a cobbler's apprentice and again as a barber's assistant, he took up the study of medicine at Zaragossa. He defined his own cerebral constitution in William James' term as "visual," and points out that in school he was a poor listener and exulted in visual demonstrations. In his work as a scientific observer he was a poet of pattern and form as an idea in the Platonic sense. He describes the delight and elation he experienced when after many failures he obtained at last the preparations in which he saw the nerve cell and fibres with all their ramifications. The image which he sought and saw under a microscope in a section of brain tissue provided him with an aesthetic pleasure. He went after this inchoate "constellation of the unknowns" with the obsession of an artist seeking a perfect image of the reality which can be visualized. In his scientific writings he described the image in a meticulously, yet often laboriously worded text, and was most eloquent and explicit in his exquisite drawings with which he illustrated the text. His startling conclusions followed inexorably from what he saw. These conclusions were statements of a new empirical reality which contradicted the accepted notions, i.e., the prevalent theory, of reality. Such is the essence of a true discovery. Hence the incredulity with which his conclusions were met in the scientific world of his time. Aloof and chary of his private life, reminiscing of a particularly difficult period of his life in 1891, when his child was dying, Cajal allows in his biography an intimate and revealing paragraph:

> "Perchance in such distressing circumstances, anguish was the sovereign sharpener of my wits. Continuously awake, exhausted with fatigue and distress, I developed the habit of drowning sorrows during small hours of the night in the light of the microscope, so as to lull my cruel tortures. And one bitterly fateful night, when the shadows were beginning to fall on an innocent being, there suddenly blazed forth on my mind the splendor of a new truth."

The stories of Cajal's adventures in childhood and youth and the episodes of his scientific life are interspersed with frequent allusions and references to the ancient lore of Spain. These "digressions," as he calls them, reveal Cajal as a Spanish patriot, keenly aware of the gentle graces and manly virtues of his people, proud of the great past of his country and saddened by its socio-economic and political shortcomings and by the ignorance and "neglect" of Spain in foreign lands. To the reader inclined to extrapolations, Cajal's memoirs evoke naturally the hoary history of the Iberian peninsula. (In a broad context of the history of Greco-Roman, Judeo-Christian civilization, the vectorial forces of the migration of people and cultures southwestward, built up through the middle ages a tremendous pressure in the Iberian "cul-de-sac" of the continent, and burst forth there across the Atlantic five centuries ago. The forces of the migration were, spritual as well as ecological. Cajal's memoirs reveal the deeply seated consciousness of the historical debt the Western civilization owes to Spain for holding during nearly seven hundred years the right flank of the European defenses against a great and then powerful, but different civilization. The glories of the Renaissance in Italy and Western Europe would hardly be conceivable, had the Spaniards been absorbed by the Moors. (Even as on the northeastern extremity of this historical confrontation the left flank of Europe was held by the ancestors of another "congenital rebel" and Cajal's contemporary, Ivan Pavlov).

From the pages of this autobiography emerges the figure of a great man who incarnated all the strengths and weaknesses of his race — uncompromising dedication and fanatical loyalty to an ideal, frugality and an indomitable courage to endure adversities, and, in the guise of humility, an immense personal pride. This race produced great conquistadores, militant saints, and adventurous explorers of hitherto unknown lands, and great painters and poets. Cajal is almost unique as a great scientist, and his life as a scientist reveals the feature of a dedicated conquistador and poetic adventurer in the unknown. In some of the portraits of Cajal in his later years, the deep-set, somber eyes and the ascetic verticality of his angular face remind one of the saints in the paintings of El Greco.

Paul I. Yakovlev.

Feb. 14, 1967.

Henry Alsop Riley

(1887-1966)

Henry Alsop Riley was born in New York City on July 23, 1887. He received his academic education at Yale University where he was awarded the Bachelor of Arts in 1908. His entire career in medicine was associated with the College of Physicians and Surgeons of Columbia University. He manifested an interest in the nervous system from the start and received the Master of Arts degree for his studies in anatomy in 1912 and at the same time he was awarded the Doctorate of Medicine. He served as intern at the Presbyterian Hospital for 18 months in 1913 and 1914 and was Assistant Pathologist to the New York Nursery and Childrens Hospital in 1915 and 1916. He joined the Department of Neurology at the Medical School as Instructor in 1916 and advanced to the rank of Professor of Clinical Neurology in 1939 which post he held until his appointment as Professor Emeritus in July 1, 1953. He was associated with the Vanderbilt Clinic from 1924 and was Chief of Clinic from 1929 to 1934. He moved to the Neurological Institute in 1929 when this Institution became an integral part of the Medical Center and served for 24 years as Attending Neurologist and Chief of the West Service. At the same time he conducted a private practice of neurology in New York City and became one of the foremost consultants of the country.

He was closely associated with Dr. Frederick Tilney, Professor of Neurology and Director of the Neurological Institute in his clinical activities and in research investigations on the anatomy of the nervous system. Their monograph on Form and Function of the Nervous System first published in 1920 is still a classic on this subject.

He was especially gifted in the organization and direction of the special societies in the field of neurology, serving as President of the New York Neurological Society in 1932-1934, Secretary of the Section of Neurology of the New York Academy of Medicine in 1922-33 and Chairman in 1923-24. He was a dynamic figure in the American Neurological Association serving as Secretary from 1922 to 1946 and as President in 1946-1947. In conjunction with Dr. Bernard Sachs he was a leading figure in the formation of the International Neurological Congress, serving as Secretary General at their first meeting in Berne, Switzerland in 1931 as Vice-President of all of the congresses held since that date. He was one of the founding members of the Association for Research in Nervous and Mental Disease and served as a member of the Board of Trustees until his death. He was a member of many local and national medical societies and was President of the Society of Alumni of Presbyterian Hospital in 1935-36. He was honored by membership in many foreign medical societies and was made Chevalier of the Legion of Honor of France on the occasion of the meeting of the International Neurological Congress in Paris in 1939.

Dr. Riley served as First Lieutenant in the Medical Corps of the National Guard from 1909-1914 and as Captain in the Medical Corps, assigned to the 105th Machine Gun Battalion in 1917-18. He was Adjutant to the New York Neurosurgical School of the War Department in 1918. This School was stationed at the Neurological Institute. He was a member of the Medical Advisory Committee of the Selective Service System from 1941-45.

He was awarded the Distinguished Service Medal of the Columbia-Presbyterian Medical Center on the occasion of the Center's twenty-fifth anniversary in 1953, and the Honorary Degree of Doctor of Science by Columbia University on the occasion of the fiftieth anniversary of the founding of the New York Neurological Institute in 1959.

Dr. Riley was an Elder in the Brick Presbyterian Church. He was married to Mary Chapman Edgar on November 6, 1917 and after her death in 1948 to Mrs. Margaret Hamilton Henshaw in 1954.

He was a member of the Union and University Clubs in New York, and had many friends outside of the medical profession. He was noted for his honesty and frankness in all his relations with his students and colleagues. He was an excellent clinician and insisted on the importance of a thorough history and careful examination of the patient.

His death on November first, 1966 has deprived the medical profession of an astute clinician and a gifted neuroanatomist and those who knew him have lost a good friend who was always ready to help them with their problems.

It is moved that this memorial be spread on the minutes of the meeting of the Faculty of Medicine on December 19, 1966 and that a copy be sent to his widow, to his son, Dr. Edgar Alsop Riley of New York and his daughter, Mrs. Herbert Patton of St. Louis.

H. Houston Merritt.