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TREATMENT OF THE HOSPITALIZED MENTALLY ILL

By HARRY C. SOLOMON, M.D.

THIS is an exhilarating and exciting period for those of us who are concerned with treating the overtly ill mental patient, especially those afflicted with major psychoses. The reason for the exhilaration arises out of the fact that our efforts are meeting with a degree of success which could hardly have been contemplated two decades ago. To those of us who have been in the work for two or more decades the change in the results obtained with patients in this category is only equalled by the change in attitude of the younger physicians entering into the treatment of the mentally ill. In our institution, if a patient, no matter what his diagnosis, does not show distinct improvement in the course of days or a few weeks, the physician in charge of the case is disturbed and distressed and feels that he has somehow failed to offer the proper treatment. It is refreshing to find that the physician's questions are concentrated on the treatment. Diagnosis to be sure is important, not as the end of the road but rather as an indication of whether the treatment has been the proper one for a patient with a certain constellation of symptoms. This change in the medical attitude is unquestionably brought about from the fact that patients are being helped, that in a large majority of severe acute mental illness the expectation is for improvement of a degree sufficient for the patient to leave the hospital within a relatively short time and to take up his activities in the community as effectively as, or better than, before the illness.

In order to substantiate the statements about the high improvement rate I would ask your forbearance while I present to you the results of treatment at the Boston Psychopathic Hospital for one year. The year chosen is our statistical period of July 1, 1946 to June 30, 1947. This year is picked because it represents pretty accurately the situation as it exists today and, a period of 18 months having expired since the end of this period, there has been an opportunity to learn something of what happened to the patients. The statistical findings for the previous year, 1945-46, are very nearly identical, supporting the significance of these results.

The Boston Psychopathic Hospital is a small psychiatric clinic maintained by the Commonwealth of Massachusetts as part of its state hospital

Dr. Solomon is professor of Psychiatry at Harvard Medical School and Director of the Boston Psychopathic Hospital. This paper was delivered at the 4th B. T. McGhie Memorial lectureship

system, with a licensed bed capacity for 117 patients. Patients are admitted to the institution from any portion of the Commonwealth, but chiefly from the Boston metropolitan district. Patients of the old age group are not admitted. Otherwise any mentally ill patient requiring hospitalization is welcomed. There is usually a greater demand for admissions than can readily be handled, so a waiting list is usually in existence. Acute emergencies are of course given precedence and almost always accepted if the need is sufficiently great. Patients are admitted from the community almost exclusively either on a temporary care paper from a practising physician or on a voluntary basis. Another group of patients are transferred from other state hospitals for special diagnostic procedures or special treatment, particularly psychosurgery and treatment of central nervous system syphilis. In addition, a considerable number of individuals are sent to the hospital for psychiatric survey and study by the courts in the district near the hospital. This group, which represents a high percentage of admissions, come in for short study and occupy about 10 percent of the bed capacity of the hospital, the other 90 percent being used more specifically for therapeutic purposes. During the year under consideration 440 patients were admitted from the community on a doctor's certificate, of whom 36 or 8 percent were committed elsewhere, and an additional 118 patients were admitted voluntarily, of whom 1 was committed to another hospital.

It therefore appears that of the acute problems which came to our doors, approximately 90 percent remained for treatment. Of these 558 patients, 79 percent were returned home from the hospital with an average stay of 45 days. The remaining 21 percent were sent to larger institutions of the state hospital system. The reason for the transfer in each instance was that it was concluded that further intensive treatment was not indicated and that either the patient was for the moment considered as heading toward chronicity, for which no immediately applicable therapy was advised, or that he needed a convalescent period rather than intensive and definitive treatment.

It is pleasing to report that of the group who were transferred to other institutions, 48 percent improved sufficiently to be returned home after some months of care.

The immediate outcome therefore indicates that 89 percent of the patients admitted to the hospital for treatment during the period under consideration improved sufficiently to return to their community activities. May I emphasize the 89 per cent figure? Of the remaining 11 percent of the total patients admitted for treatment, some go on to chronicity and some of them improve in the course of several years. Of course the number who will get well after two or more years of illness is very small. However, for the patients who fall into the chronic classification, some form of psychosurgery is still available and, as will be indicated shortly, with the expectation of some good results. It may be added at this point that there will certainly be some relapses among the 89 percent who have

done well. Among the cases that relapse, some will have brief illnesses with recovery, some occasional severe illnesses, and some others will fall into the chronic category, and again for them psychosurgery will be available to benefit a fair percentage.

It is on the basis of these results with the acutely ill patients that I believe enthusiasm for modern therapy can be justified.

It is now in order to attempt to describe what is meant by the present day psychiatric therapy. All therapy must of course stem from careful diagnostic study of the individual to be treated. Such study includes a good general physical and neurological examination of the patient, with all the aids that general medicine has at its command which, in certain cases, would include rather special neurological studies such as electroencephalography and airencephalography. It includes in addition a careful psychiatric analysis of the case, with the assistance of the available batteries of psychological tests, and interviews aided by such drugs as sodium amytal, sodium pentathol and pervitin.

From the therapeutic standpoint psychiatry has at its service today a number of procedures and aids which can be briefly summarized in two groups, the first of which I will call the definitive psychiatric therapies and the second the general and socializing therapies.

Definitive Psychiatric Therapies	*General and Socializing Therapies*
Psychotherapy	Psychiatric Nursing
(a) Individual	Occupational Therapy
(b) Group	Psychiatric Social Service
Convulsive Shock	Recreation
Insulin Shock	Physio and Hydrotherapy
Lobotomy	General Environment
Penicillin and Fever	

These are the therapeutic processes that are responsible for the beneficial results I have mentioned. Until some 15 years ago our treatment procedures were limited to individual psychotherapy and the general and socializing therapies. In recent years the addition of the other so-called somatic therapies has aided a great deal toward a favorable prognosis. At the same time psychotherapy has become more effective and our general therapeutic processes have been improved. It is not possible to give a clear depiction of what each of our treatment procedures has added to the general over-all recovery and improvement rate of patients because each has unquestionably added its share, but some general ideas of values of some of the procedures may be considered.

Convulsive shock therapy has been a very effective therapeutic tool for a great many patients. Approximately 90 percent of the patients in the manic-depressive group treated by convulsive therapy are returned to a good mental status in a matter of days or weeks. The course of an attack is telescoped. Many patients in the schizophrenic groups are also improved sufficiently to lead comfortable community lives in relatively

short period. Of 157 patients at the Boston Psychopathic Hospital whose only specific therapy was electric convulsive, 83 percent recovered sufficiently to return to their homes. This included patients whose symptom constellation placed them in several diagnostic groups.

At the Westchester Division of the New York Hospital Drs. Hamilton and Wall made a very careful study of 100 consecutive female admissions with a diagrosis of schizophrenia who were treated by short courses of convulsive shock, and reported that 67 percent made a reasonably prompt recovery. This was approximately twice as great a recovery rate as had been obtained in a previous period at the same hospital with essentially similar treatment aside from the convulsive therapy.

This type of therapy also has an amazing therapeutic value in cases of the involutional psychoses in which group the psychoses may be shortened by months or years, in contrast to cases that do not receive this type of treatment.

Probably the most spectacular effect of this type of treatment is obtained in cases of acute confusion and excitement. Such cases which in a few instances without this treatment go on to death, the so-called Bell's Mania, can be brought to a state of reasonable social behavior in a matter of days, and the jeopardy of death in the excitement is eliminated. The alleviation of excitements of almost all varieties, even when due to organic disease of the brain, can be usually accomplished very quickly. This obviates many grave dangers to the welfare of the patient and at the same time produces a condition in the wards that allows for better treatment of all the patients.

Perhaps a brief account from a nurse's report of the care of one patient will illustrate these latter points.

A 23-year-old woman was admitted to the hospital nine days after delivery of a daughter. She was tense, apprehensive and irritable. She was disoriented and misidentified people. She was in a state of great turmoil, was impulsive and was responding to auditory and visual hallucinations. She believed that someone had taken her baby from her and that her husband was unfaithful to her. She responded in an aggressive manner to the voice of a doctor by whom she had previously been treated. At times she was combative, assaultive and would explain her violence by saying "Dr. C. told me to do it." She would not keep any clothes on and any attempt made by the nurses to keep her clothed was met by aggressive action on her part.

On admission she showed signs of sepsis; her temperature reached 102°; she became jaundiced, her breasts were engorged, she was dehydrated and, because of her restiveness, it was difficult to maintain an adequate fluid level.

After three electric shock treatments a remarkable change in her mental state became apparent. She became co-operative, well oriented and free of hallucinosis. Her general physical condition improved

markedly; she ate normally. In less than three weeks she was relatively well and able to go home for a week-end visit. The nursing problem, which for the first three days before shock was administered was extremely dificult and far from adequate in its results, became simple and effective.

Convulsive shock treatment offers an opportunity for the alleviation of distressing symptoms, following which a better relationship may be established between patient and staff than can be obtained without this means. Regulation of a patient's sleep is part of the effects as is the lack of feeding difficulties. With proper sleep and nourishment, with reasonably good social contacts, treatment procedures may be carried out which under other circumstances would be quite impossible. Undoubtedly this whole group of circumstances affords a better opportunity for the recovery potentials of the individual to make themselves felt.

Insulin shock therapy in our hands has been reserved largely for those patients who have failed to respond to general care and convulsive therapy and for whom it is believed that psychotherapy alone is not adequate. In the case of certain schizophrenics insulin therapy is introduced early in the treatment program without the use of convulsive shock, but by and large in our cases convulsive therapy is first tried and if found ineffective insulin is given.

In the year under consideration 51 cases were given insulin coma therapy; 37, or 73 percent, improved sufficiently to be discharged home. When it is recalled that most of these patients were unsuccessfully treated before they were given isulin, the value of this treatment is apparent. There are relatively few well controlled series of patients treated with insulin in comparison with untreated cases. However, where it has been done, notably the Brooklyn State Hospital group, the evidence was strong on the point of the value of this type of treatment.

During the course of insulin coma treatment one is impressed by several observations. The patients in general thrive physically, they put on weight, they look well and they sleep well. Perhaps even more important, most of the patients become friendly and readily develop a warm relationship with the staff. Personally, I am continuously amazed that most patients receiving insulin coma treatment put up no resistance thereto but,on the contrary, seem to take pride in being a member of the treatment group. They feel, apparently, that they are especially distinguished thereby. All of this is important and helpful to the patient and probably in itself plays a role in the road toward improvement.

Psychotherapy in the general care of patients is of great importance. Psychotherapy in the course of the years has found itself in relation to the treatment of the psychoses. It is not the intent of this discourse to discuss the details of techniques. Suffice it to say that as our understanding of psychological dynamics has become greater, more definitive psychological treatment is available. In most cases the use of individual and group

psychotherapy is part of the total treatment program, and in a great many cases psychotherapy and general care represent the major if not the total program.

The decision as to what form of treatment to use and when to apply various methods is a matter that needs fine judgment. As in all treatment procedures, discrimination and judgment on the part of the physician directing the program is the first requisite. That judgment is not always perfect follows from the fact that medicine is still an art. The results of treatment of psychotic patients will vary according to the wisdom and ability of the physician as well as to the intrinsic capacity of the patient for recovery and the value of the therapeutic methods. Improperly chosen methods or the application of a method at the wrong period may be harmful rather than beneficial, and continuous study of our techniques is necessary. It will be long before we are able to offer a systematic formula which he who reads may utilize successfully.

It is my firm belief that the general and socializing therapies of the hospital should play a very heavy role in the total treatment program, and I have no doubt that the effectiveness of the treatments mentioned is dependent upon the skill and excellence of the 24-hour-a-day care of the patients. The conditions under which any individual lives greatly influence his reactions and behavior. If war experiences taught us anything, they taught us that emotional stress could cause grave damage to humans. They taught us that general morale was essential for adequate behavior. The same is true of the mentally ill patient in a hospital. If conditions are adverse it is hardly to be expected that the patient will flourish and improve. Catatonic syndrome is in many instances merely an expression of intense fear on the part of the patient who feels himself separated from human relationships and thus tries to hide within his own skin. If such an individual is met with aggressive behavior on the part of those who are looking after him, if he feels coldness in the emotional atmosphere, if his fear is increased by harsh words and restrictive and suppressive measures, he either retreats further into himself or becomes assaultive. Skillful treatment in the early period of hospitalization by the nursing staff is probably more important than the doctors' skills. It is our experience at the present time that the so-called catatonic retreat rarely lasts more than 24 to 48 hours; kindly understanding, sympathy and attention on the part of the nursing staff almost invariably lead to overcoming mutism and refusal of food. With good nursing and with the proper utilization of the specific psychiatric therapies, the acute wards of the hospital become not unpleasant places in which to be. Where aggressive and assaultive behavior is at a minimum, where the ward is quiet and the patients not too disturbing to others, a better chance for recovery exists than where tempestuous and distressing behavior predominate. In the ward where the patients are well behaved attention can be given to esthetics and this I believe has a very beneficent effect. The use of pleasing colors on the wards, an occasional picture, attractive bed-

spreads, drapes on the windows, comfortable chairs and a spirit of friendliness in the ward are extremely important details in the care of the patients.

The hospital allows no form of restraint except post-operatively when a patient's hands may of necessity be restrained to keep him from removing bandages and infecting a wound. No "legitimatized" restraint such as packs or prolonged baths are used nor is chemical restraint, in the form of sedative drugs to quiet a patient, permitted.

With the elimination of restrictive methods, the need of seclusion drops to a minimum. To be sure, occasionally a patient who becomes a little disturbing to others may have to be temporarily isolated, but this is rarely for more than an hour or two at a time.

The nurses and attendants in this circumstance become important members of the therapeutic team. Upon their shoulders rests the responsibility of seeing that the patient has the proper environment in which to live a somewhat reasonable existence. The nurses and attendants are challenged to use no force, to win the confidence of the patients through understanding their behavior and the factors that motivate them. This requires not only extreme skill but much understanding forbearance.

Perhaps a picture of the nursing problem can be best presented by a quotation from the nurses' notes concerning the patient briefly mentioned above.

Feeding problem: On admission Phyllis had many paranoid tendencies, so therefore she refused food, accusing us of putting something in it. With much patient persuasion she would drink a glass of milk, eggnog or eat some food. However, she was very unpredictable and just when we had become quite confident in her she would throw the milk at us or pour it on the floor and play with it.

"Under the influence of sodium amytal she was fed, bathed, clothed, mouth care was given and blood was taken for examination.

"Elimination: She defecated and urinated on the floor several times a day. More frequent toileting helped this somewhat. She was changed from one seclusion room to another to keep her as clean as possible. Probably due to her overactivity, there was still more lochial discharge. She masturbated at times and when spoken to would say, 'I shouldn't do that, should I?'

"Personal hygiene: Her lips were cracked and dry due to her overactivity, refusal of fluids and elevated temperature. Her teeth became coated and her tongue parched and dry. Ointments were applied to her lips and, under sodium amytal, mouth care given. This didn't seem to have too much effect on her broken, bleeding mucous membranes.

"As she was denudative it was difficult to attain bodily cleanliness as she would lie on the bare floor, ignoring the mattress, refusing any type of clothing, even slippers on her feet. She also played in feces, covering

the walls with it. When placed in the bathtub, Phyllis seemed to have no regard for her surroundings and splashed freely, succeeding in getting the floor and screens all wet.

"Her body was badly bruised, especially her legs, arms and the back of her neck. Her bed had been removed from the room to prevent any further injury to herself so that only the mattress and blanket remained, as she destroyed sheets, etc., if given to her.

"Her door was locked to prevent disturbing the other patients. She was unpredictable and became assaultive to nurses who would try to feed her or care for her in any way. At times she would hug another nurse and express homosexual desires. Being denudative was also an important reason for placing her in seclusion.

"As far as relationship with patients and personnel was concerned. Phyllis had her own companions with her visual and auditory hallucinations. She would stand in a catatonic-like position, look at the light, seeing the 'twinkle' in Mac's left eye, also saw this in other people's eyes. She would wink and laugh inappropriately in response to many things said to her.

"There was a definite problem in keeping the breast binder on, prescribed because of engorged breasts, although she said they didn't pain her. Pins, of course, couldn't be used, therefore wide tape was substituted. She would only keep this on for a short period of time.

"Now that most of these previous problems have subsided, the present problem is that of keeping her active."

Now that Phyllis is well she is most grateful to the nurses whom she so badly tormented, and they are more than pleased with the effectiveness of their contribution to her recovery. The last sentence of the notes above quoted states that the present problem is to keep her active and here is where the matter of occupational therapy and recreational facilities come in. It is with the acutely ill patient that occupation and recreation are most needed. I fear that too frequently these procedures are afforded patients who are already well enough to take advantage of them. Our efforts are now directed toward giving the maximum in occupation and recreation to the patients who are too ill and too poorly socialized to go to an occupational therapy room. It is in the acute ward that the occupational therapist and the recreationalist can perhaps offer the greatest benefit. As the patient improves in his general behavior and socializing possibilities he can gain more freedom of action and have perhaps a greater scope for his abilities, but it is in the early and acute stage of his illness that special study by the occupational therapist probably pays the greatest dividends.

As one learns more and more of the internal mechanisms of the patient one learns more concerning fear and apprehension and anxiety on the one hand and resentment, sense of frustration and objection to being bossed. The elimination of factors leading to such viewpoints is an

essential feature of general psychiatric treatment. As far as is consistent with the welfare of others, the patients are allowed to express themselves.

The patients on our more convalescent wards have a self-governing committee composed of men and women patients who make their own rules and regulations, assign tasks and police the wards. If 9 hours are given over to sleep, there remain 15 hours to be occupied in some fashion by the patient. If left to themselves they soon slump into a state of inertia or destructive activity or retreat into ruminating and hallucinating phantasies.

It is rarely possible for a hospital to have a staff sufficiently large to give the necessary individual and group attention to patients. Therefore assistance must be obtained from various sources. The development of initiative and responsibility on the part of the patient is important. Students working and learning at the hospital add a good deal to the interest and color of the daily life of the patient. Volunteers of many varieties can add greatly to the interest of a patient's day. Many, if not most mentally ill patients have great difficulty in inter-personal relations. Many are shy, most feel out of touch with other persons. The socializing efforts which can be applied become valuable therapies. In our hospital, in addition to the attention given patients by students of several disciplines such as psychologists, sociologists, psychiatric social workers, nurses and clerics, much satisfactory work is done by volunteers.

Perhaps a good viewpoint to hold is that if a patient is unfortunate enough to be so ill as to need treatment in a mental hospital, his stay should be utilized to give him new outlets, new interests and perhaps new skills. He should have some things in his repertory of capacities over and above what he had when he entered the hospital. A dancing class has been found to afford the patient great interest; similarly cooking and candy-making, hat-making and dress-making offer the development of skills that have value to the patient on leaving the hospital.

During the year under consideration 166 patients were subjected to the lobotomy operation. The patients who received this type of treatment were selected on the basis of a long period of mental illness with the conclusion having been reached that the probability of recovery through any other form of treatment was extremely small. Of this group of 166 patients, 75 (45%) returned to their homes with some degree of improvement. The majority of these patients were in the chronic stage of schizophrenic psychosis, namely 123 out of the 166. The results in these patients were approximately the same from a percentage standpoint as for the total group.

The greater majority of the patients who were subjected to the operative procedure were sent to the Boston Psychopathic Hospital from the larger hospitals of the state hospital system. The group was made up of patients many of whom had been in hospital for a great number of years and who were extremely disturbed, distressed and distraught. A smaller

portion of the patients had been ill or hospitalized a much shorter period of time, in the neighborhood of two years, and had very intensive treatment in the present mode but had failed to respond satisfactorily. There were 47 such patients operated upon of whom 37 or 97 percent were able to return to community living. This is in considerable contrast to the group that have been sent to us after a long hospital stay, of whom only 26 or 24 percent of 105 patients were sufficiently improved to allow them to go home. This result is consistent with the experience of others as well as ourselves, namely that a greater degree of success from psychosurgery is to be expected in patients who have not been ill too long.

I would emphasize that of the type of patients who seek service in an acute hospital installation such as ours and who come to psychosurgery because of failure of our other forms of treatment, a distinct improvement can be expected in well over 50 percent. It is our procedure in many cases to give the patient the treatment which we are able to offer at the time of admission and, if improvement does not occur, the patient, unless he has been ill for a considerable period of time before admission, is sent to a larger hospital with chronic facilities with the idea that if, in the course of a year or 18 months, improvement has not resulted, he will be returned to us for psychosurgery.

Let us review then what our experience indicates as the fate of the type of patient who enters our hospital as a more or less acute mentally ill individual. On the basis of treatment which we have availaible and which we have already discussed, it is seen that nearly 80 percent will be returned home in an improved state directly from our institution, that some 20 percent will be sent to other mental hospitals for more prolonged care and that of these approximately one-half will make a sufficient improvement to return to their homes within 18 months. This accounts for almost 90 percent of the patients. Of the remaining 10 or 11 percent who have failed to recover and may be considered as chronically ill, a considerable number will be good subjects for psychosurgical intervention, and of those who receive such treatment more than 50 percent will be benefitted sufficiently to be out of the hospital. One arrives at the astounding if not phantastic figure of well over 90 percent of the patients entering a hospital such as ours being returned to the community.

I have carefully avoided the use of the word "cured" or "recovered," not because I think that the term is not applicable but because there is such a strong sentiment or prejudice in the minds of most people, psychiatrists, psychologists and nurses, as well as the layman, to talking about recovery of the mentally ill. The question always is asked, "But do the patients remain well? Don't they relapse?" Indeed this is a proper question as it is in the case of cancer or heart disease or perhaps pneumonia.

Some of the patients about whom I have given these statistics relapse or have another attack of mental illness. Indeed this is characteristic of patients who have a manic-depressive psychosis and it is true for a con-

siderable number who are diagnosed as having schizophrenia. Unfortunately I am not able at this moment to furnish accurate statistics about recurrence of mental illness in the patients of our group. Such a study is being conducted but is not far enough advanced to be discussed. The number who break down within a one, two or three year period, however, is not great. Those who do have a recurrence or a new attack are usually treatable again and the results of the treatment of the new attack are on the whole rather similar to what has been described above. A certain percentage do fail to recover from a second, third or subsequent attack of mental illness and become chronic. These patients again form a group for whom psychosurgery offers great advantage. It is from this group that perhaps the best results of operative intervention are to be expected.

I would belabor the point that too much pessimism exists about recurrence of mental disorders in individuals who have once been afflicted and would emphasize the point that there is not as great a danger as is often believed, but I would emphasize more especially that recurrence may be of very short duration and the outcome excellent. I would point out that the period of disability in many of the patients in our group is relatively short—ten, twenty, thirty, forty or fifty days.

Another tendency in thinking of mental disorder which has had a deleterious, almost paralyzing effect, is to be overly concerned as to whether recovery occurs without any defect. In hardly any other field of medicine does one expect complete restoration.

It has been stated in the course of these remarks that general care and psychotherapy are utilized and relied upon either as a total or certainly as an associated treatment procedure in most cases. Treatment does not necessarily cease when the patient leaves the hospital—on the contrary it is after returning home that most intensive work is often necessary. Many of our patients continue treatment for weeks or months as out-patients. Prior to as well as after the return home it is often important that much work be accomplished with the families of patients, and in this sphere of endeavor the psychiatric social workers have a big stake.

As we scrutinize the results of our experience in the treatment of patients with acute mental illness we come to the conclusion that the opening statement of these remarks is correct, that it is indeed a period in which we have reason for hope and a considerable amount of satisfaction. There are many, many things still to be accomplished. However, with the methodology at hand, it would appear that a concentrated therapeutic attack upon the early stages of a patient's illness brings worthwhile results. General Eisenhower in his book "Crusade in Europe" stressed that in the campaign it would have been more costly to set up a perfect line of defense and sit tight than to continue a vigorous offensive. Similarly an intensified offense toward early treatment of the mentally ill would seem to be infinitely more effective than preparations for prolonged care of patients who have not been given the utmost at the period of onset of the illness.

ADVANCES IN GASTRIC SURGERY

By RAYMOND W. MCNEALY, M.D.

THE advances in gastric surgery have been of an evolutionary type. On the whole, they have developed along lines which have had their foundations in mechanical rearrangements of the viscera with a view of eliminating the pathology, at the same time preserving a gastro-intestinal continuity.

Gastric resections were performed successfully as early as 1879. The first resection was done for carcinoma involving the pyloric end of the stomach. It is very interesting that gastric resections were done before the technique of gastro-enterostomy was developed. The first gastro-enterostomy was done by Wolfler in 1881. It was performed for an unresectable carcinoma of the pyloric end of the stomach. The first gastro-enterostomy for a benign ulcer of the duodenum with pyloric stenosis was done in 1884.

The operation of gastro-enterostomy was popularized in the United States following a visit in 1902 of Sir Berkley Moynihan. This operation gained great favor in the treatment of peptic ulcer and its complications. It was revealed by careful follow-up of these gastro-enterostomy patients that stomal and jejunal ulcers were serious complications in more than 25 per cent. About 1927 Finsterer and other continental European surgeons stressed the value of partial gastric resection for peptic ulcers that were unsuited to medical management.

Even partial gastrectomy left much to be desired, for some of these patients developed stomal and jejunal ulcers.

Vagotomy has been suggested as a means of lowering the acid-pepsin factor which is generally conceded to be the perpetuating influence of ulcers in the upper gastro-intestinal tract. The thoracic approach to the vagus nerves afforded the most reliable method for exposure and complete division of these structures. This exposure, however, had the disadvantage of allowing no exploration of the stomach and duodenum or of the other viscera in the abdominal cavity. The abdominal approach had the advantage of permitting exposure and examination of the viscera but the dissection and complete division of both vagi and all their branches were far more difficult. There was a further complication that developed in those whose nerves were severed. They developed motor deficiencies which were followed by poor emptying and gastric dilatation. Gastro-enterostomy or partial resection seemed necessary as a supplementary measure to vagotomy.

There have been several very dependable studies made on these patients with vagotomy. The final evaluation of this procedure cannot

Dr. McNealy is professor of surgery at Cook County Graduate School of Medicine and president of the staff of Cook County Hospital. This paper was delivered at the annual Academy Day Program of the London Academy of Medicine.

be made at this time. The operations have not been of one type in enough cases to permit one to draw conclusions as to the merit of this type of surgery.

We have had very few successes in surgery which were the result of mechanical interventions in physiological activities of the body. Our resection of the major portion of hypersecreting goiters has been the most outstanding. Resections of other hypersecreting endocrines have also been successful but they are not so numerous as to give great encouragement to less direct invasions of the field of unbalanced physiology.

Our advances in gastric surgery in 70 years leaves much to be desired. There is much to be done.

NEW DRUG ON PRESCRIPTION ONLY

Ottawa, Feb. 28.—Hon. Paul Martin, Minister of National Health and Welfare, announced to day that it had been found necessary to add to the list of drugs to be sold only on prescription, Tetraethylthiuram disulphide, commonly known as Antabuse or Abstinyl.

He pointed out that this drug, which is very potent, will be available on the Canadian market almost at once, and that, in view of its effects, had to be restricted as to sale.

A STUDY OF THE ADRENERGIC BLOCKING AGENT, DIBENAMINE

(N,N-dibenzyl-beta-chloroethylamine)

By MARION G. MARSHALL

History

THIS chemical is a member of a series of tertiary amines which have recently been found to possess considerable power and specificity as adrenergic blocking agents, both in animals and in man (9, 10, 13, 23). First of the series to be discovered, and described by O. Eisleb in 1930, was Dibenamine. The original synthesis of this drug in North America was by Dr. W. Gump of Givaudan-Delawanna, Inc. of New York. This chemist has subsequently prepared a number of the congeners and related compounds of Dibenamine.

The pharmacology of Dibenamine was first studied by Nickerson and Goodman of the University of Utah School of Medicine. They reported at a meeting of the American Federation for Clinical Research in March, 1946 (15), and later in the literature (14), a large number of experiments on animals and a more limited number on man. The detailed pharmacology with regard to man was studied by Hecht and Anderson in the Department of Medicine of the University of Utah. Since that time Givaudan-Delawanna has supplied the drug to a number of other laboratory and clinical workers for investigational use. The distribution for clinical studies is now in the hands of Smith, Kline, and French laboratories, Philadelphia.

Chemistry

The chemicals of the series of which Dibenamine is at present of greatest interest, and thus here considered as the prototype, are beta-chloroethylamines. At least one chlorine and one benzyl group was found to be necessary for activity of the series (7). The series is chemically related to the nitrogen mustards (bis- and tris-chloroethylamines).

Although Dibenamine does not have the second beta-chloroethyl grouping of the nitrogen mustards, it exhibits many of their characteristic chemical reactions. This fact affords a clue to the possible type of chemical union between Dibenamine and the adrenergic receptor substance. Nickerson believes that such a chemical union does take place (16) and is responsible for the action of the drug; at present further investigations along this line are being carried out (13). Since it is known that nitrogen mustards owe their pharmacological activity to an intra-molecular ring formation with liberation of chlorine, a similar mode of action has been proposed for Dibenamine (7).

It is believed by Nickerson (13) that Dibenamine in aqueous solution may undergo intramolecular rearrangement to form a cyclic ethylenimonium cation. Dibenamine presumably exerts its pharmacodynamic effects through this intermediate product, for ethylenimonium cations are known to have great chemical activity.

In aqueous solutions at normal body pH, Dibenamine after cyclizing reacts with water to form the alcohol, N - N - dibenzyl ethanolamine which is inactive as an adrenergic blocking agent.

Physical Properties and Administration

Most of the investigators of Dibenamine have made use of the hydrochloride salt, because it is more easily handled than the free base which is an oily liquid. There is, however, no real difference in the activity of the compound or any of its salts with organic or inorganic acids (13).

The hydrochloride is a white crystalline substance almost insoluble in water near neutrality but soluble in aqueous acid solution of 95% ethanol, and in propylene glycol. The present distributors of the drug supply ampules for intravenous administration as a 5% solution in alcohol-propylene glycol, acidified for stability.

Dibenamine produces its systemic effects when given orally, intravenously, subcutaneously, or intraperitoneally. However, it can be administered in man only by the first two routes.

Pharmacodynamics

The systemic effects of Dibenamine, when administered in the proper manner and in physiological dosage, are of a single type: blockage of all excitatory adrenergic functions. Not only are epinephrine and circulating sympathin rendered ineffective but also, by a slightly larger dosage of the drug, direct or reflex stimulation of the sympathetic nerves.

Dibenamine does not affect inhibitory adrenergic functions, in fact it often unmasks these, by removal of the excitatory elements of response, to produce rather remarkable effects.

I. Actions on the Cardiovascular System

1. (a) *Normal Laboratory Animals*

Dibenamine administered slowly in full blocking doses produces no significant changes in blood pressure, basal heart rate, cardiac output, or electrocardiogram (13).

(b) *Resting, Non-hypertensive Human Subjects*

The effects of Dibenamine are similar to those in laboratory animals. However, when these human subjects rise from a supine position there occurs a marked orthostatic hypotension, which is maximal in 6 hours and lasts 1 to 2 days or longer (7). This temporary hypotension is apparently due to the pooling of venous blood in the extremities because Dibenamine abolishes reflex postural sympathetic vasoconstriction. The recovery then is seemingly due to the adjustment of vascular muscle to maintain blood pressure in the absence of sympathetic nerve impulses as after sympathectomy.

2. *Adrenolytic Action*

(a) *In Animals*

In epinephrine-treated animals, Dibenamine not only blocks, but actually reverses the pressor response. This response is true for all doses of epinephrine investigated (0.1 microgram to 10

mg./kg.) (14). Only the excitatory (vaso-constricting) activity of epinephrine is blocked and the fall in blood pressure is therefore due to the unrestrained effect of the concurrent inhibitory (vasodilating) activity of epinephrine. This is illustrated by the fact that the fall in blood pressure with a massive dose of epinephrine lasts only until the concentration of circulating epinephrine has fallen below the value necessary to produce vasodilation. Another proof of this strange fact is that in the rabbit which, unlike most laboratory animals, does not have an adrenergic vasodilating system, Dibenamine prevents an epinephrine-induced pressor effect but does not reverse it (13).

The chronotropic and positive inotropic effects of epinephrine on the heart are not, in animals, changed by Dibenamine (1, 13), and sinus rate, stroke volume, and cardiac output are increased as usual. Nickerson believes the explanation for this seeming contradiction to the adrenolytic action of Dibenamine to be the existence of a basic difference in the effect of epinephrine on the sino-auricular node and on the force of myocardial contraction from its effect on vascular smooth muscle.

The ability of epinephrine to evoke ventricular arrythmias in animals under cyclopropane anesthesia is prevented almost absolutely by Dibenamine, although in Nickerson's study (13, 14) by a larger dose than is required to reverse the pressor effect of the same dose of epinephrine. Nickerson reports an experiment with dogs in which the controls, unprotected by Dibenamine, developed ventricular extrasystoles multiple focus tachycardia, and/or ventricular fibrillation. Those receiving Dibenamine 30 minutes previously developed only sinus tachycardia with the very occasional extrasystole. In other experiments up to 500 times the 10 microgram dose of epinephrine was administered after Dibenamine injection without the development of any serious ventricular arrhythmias. Since sinus tachycardia always appears in spite of Dibenamine, this is probably produced by a different action of epinephrine than that which provokes arrhythmia.

Garb and Chenoweth (3) report slightly different findings from those reported by Nickerson. They note that ventricular fibrillation can be caused by the interaction of any hydrocarbon and any sympathomimetic amine and that Dibenamine is as effective against this arrhythmia as that caused by the combination of cyclopropane and epinephrine. Their experiments also demonstrated the fact that Dibenamine is an efficient protecting agent against ventricular fibrillation even in very small doses (3 mgm/kgm) which do not reverse the hemodynamic effects of epinephrine. This is seemingly contrary to the opinion of Moe et al. (12) who state Dibenamine "prevents ventricular rhythms *because it prevents the pressor response to epinephrine.*" However.

Garb and Chenoweth found that, although ventricular fibrillation was prevented by these very small doses of Dibenamine, heterotopic rhythms developed as frequently as in experiments without Dibenamine. They believe, therefore, that the antifibrillatory effectiveness of Dibenamine in doses too small to reverse the pressor effects of epinephrine is related to the quinidine-like action of Dibenamine described by Acheson (1) in experiments on a heart-lung preparation of a dog and an isolated rabbit auricle.

(b) *In Man*

In epinephrine-treated human subjects, Hecht et al. (7) found that Dibenamine did not reverse the pressor effect, except in one of ten subjects, this being an individual with arteriosclerotic heart disease. Dibenamine, however, caused the systolic blood pressure to rise only slightly while the diastolic fell strikingly. The increase in pulse pressure was thus rather marked.

Nickerson (13) states that in some experiments in man. Dibenamine not only greatly reduced pressor response to epinephrine, but actually reversed it, as is seen regularly in animals.

The chronotropic and positive inotropic effects of epinephrine on the heart in man are not affected by Dibenamine, exactly as is the case in laboratory animals. Sinus tachycardia, increased cardiac output, greater peripheral blood flow, and T-wave changes in the electrocardiagram which epinephrine ordinarily produces are still seen after Dibenamine administration. However, epinephrine-induced ectopic ventricular beats are decreased markedly.

Ominous types of ventricular rhythms occurring in surgical patients under cyclopropane anesthesia can be reduced in number, shortened in duration, or even abolished by the use of Dibenamine as shown by the experience of the Department of Anesthesia of the University of Utah (13). As was noted in animals by Nickerson, larger doses of Dibenamine are needed than those which block or reverse the excitatory responses to stimulation of the adrenergic system.

3. *Sympatholytic Action*

(b) *In Animals*

The response to both direct and reflex sympathetic nerve stimulation after Dibenamine administration has been studied in animals in a variety of experiments. Nickerson (13, 14) demonstrated the reversal by this drug of the vasopressor response to electrical stimulation of splanchnic nerves. This is seen both in the intact animal and after bilateral adrenalectomy. This latter operation ensures the demonstration of the effect of Dibenamine on the splanchic nerves alone since it makes impossible the release of adrenalin or any sympathin into the systemic circulation. Somewhat larger doses of the drug than those which blockade epine-

phrine and circulating sympathin are required to be effective against adrenergic nerve stimulation.

In addition to blocking of this regional sympathetic nerve discharge, Dibenamine has been shown (13, 14) to reverse the pressor response to generalized sympatho-adrenal discharge. Atropinized cats were injected with a large dose of carbaminoylcholine. Atropine prevents the vasodilator and cardiodecelerator effect of this choline ester leaving intact one element only of its nicotinic properties: the ability to stimulate the sympathetic ganglia and the adrenal medulla. Dibenamine is able to reverse both components of the rise in blood pressure; and, after bilateral adrenalectomy, to reverse the single rise due to sympathetic ganglionic discharge alone.

Reflexly-elicited generalized adrenergic discharge is also blocked by Dibenamine. Nickerson (13, 14) reported experiments on cats subjected to periods of anoxia after Dibenamine. The expected rise in blood pressure is converted by this chemical to a fall.

(b) *In Man*

The response to reflexly-elicited sympathetic nerve stimulation in human subjects after Dibenamine administration was reported by Hecht (7). Studies were made with the cold pressor, breath-holding and Flack tests. In each of these Dibenamine either markedly diminished, abolished, or reversed the expected vasopressor response. The orthostatic hypotension developing after Dibenamne, referred to above, also illustrates the blocking of reflexly-elicited sympathetic nerve stimulation so that postural vasoconstriction does not occur.

4. *Action on Sympathomimetic Amines Other Than Epinephrine*

(a) *In Animals*

The effect of previous Dibenamine administration on the responses to some 25 sympathomimetic amines has been tested. With all of these the customary pressor response is markely decreased although it is reversed in only certain cases (13). Complete blocking and reversal is seen with amines having the 3-4-catechol nucleus and an aliphatic substitution on either the nitrogen or the beta carbon. Reversal is more difficult with amines which have a single hydroxyl group on the aromatic nucleus. Special conditions are required to reverse straight chain amines, those with an unsubstantial aromatic ring, and those with an aliphatic substitution on either the nitrogen or the beta carbon.

To give specific instances, it has been found that Dibenamine in its usual dosage does not completely block the effects of tuamine or of benzedrine. This will mean, in a practical way, that these drugs could be used to elevate Dibenamine-depressed blood pressures in cases where this should prove necessary.

Nor-epinephrine, according to several investigators as, for instance, Goldenberg et al (4), is actually Sympathin E, one of the two sympathins whose existence was first proposed by Cannon and Rosenbleuth in 1933.

If this is true, Dibenamine, which has been shown to block the excitatory effects of epinephrine but not its inhibitory effects, might be expected to block but not reverse the vasopressor effect of nor-epinephrine. This has been shown to be the case (13).

(b) *In Man*

One of Hecht's experiments (7) tested the effects of Dibenamine on neosynephrin when both drugs were given intravenously to 22 patients. This sympathomimetic compound is one of the type which appears to possess a predominant peripheral action in most individuals and to have few of the excitatory effects on the heart of epinephrine. It is noted that the bradycardia caused by reflex vagal slowing secondary to the usual rise in blood pressure does not occur when Dibenamine has been administered previously. This is apparently due to the prevention of a vasopressor response to the amine. As with epinephrine, Dibenamine prevents abnormal cardiac rhythms, here those of the type which result from "sinus default" or "vagus escape".

The fact that Dibenamine's main action on sympathomimetic amines is a blocking of their excitatory powers, especially with regard to the cardiovascular system, lends weight to the conception of Gaddum and Kwiatkowski, 1938, that these drugs exert their sympathomimetic effect on the body by preventing the destruction by oxidation of epinephrin and sympathin.

5. *Action on Certain Non-adrenergic Substances Which Affect the Cardiovascular System*

Dibenamine has been found to have a very slight effect against histamine, the physiological opposite of epinephrine. However, many of its congeners (9) synthesized recently appear to possess much greater potency in this respect than the antihistamines now in current clinical use (13). Since these substances also possess adrenergic blocking powers, an interesting field of speculation is opened up regarding the mechanism of action of this whole series which can allow this dual property of opposition to certain effects of both histamine and epinephrine.

The effect of Dibenamine on the pressor response to angiotonin has been found to be negligible (13). Specificity of action as an adrenergic blocking agent appears to be one of the main characteristics of Dibenamine.

6. *Action on Hypertension*

The experiments with Dibenamine referred to above were made mainly on normotensive animals and human subjects. Of great interest

are several other investigations on experimentally-produced hypertension in dogs and on patients with various types of hypertension.

(a) *In Animals*

Nickerson (14) produced renal hypertension in rats by compressing the kidneys according to the technique of Grollman. Dibenamine was administered orally and resulted in a marked decline in the hypertenisve level of the blood pressure. This persisted for several days after the last dose of the drug. Nickerson believed at the time that this experiment might afford a ray of hope for the use of Dibenamine in lowering chronic renal hypertension in man. However, in a later article (13), he admits that evidence for the value of Dibenamine (as for the value of other adrenergic blocking drugs) for this purpose is still inconclusive.

(b) *In Man*

Hecht (7) found that in cases of hypertension in human subjects, Dibenamine occasionally lowered the blood pressure toward normal levels, but that this reduction was never striking. He attributes this failure of Dibenamine to the relatively small doses which can be safely administered in man, 6-7 mgm./kgm, as opposed to approximately 20 mgm./kgm. in animals.

Console (2) who investigated the effects of both tetraethylammonium and Dibenamine on 96 patients with peripheral vascular disease and hypertension found that neither of these drugs consistently reduced the blood pressure for a period long enough to be of value in the treatment of hypertension, nor even to aid in the selection of patients for sympathectomy.

Haimovici and Medinets (6) report results at variance with those of Hecht and Console. They found that Dibenamine was always able to lower blood pressure toward normal in patients with early or only moderately advanced essential hypertension. A single intravenous dose of Dibenamine caused a really significant lowering of the blood pressure, and one whose duration was many hours. This reduction could be maintained if the drug was administered at properly timed intervals. In patients with malignant hypertension no change resulted from the use of the drug.

Spear and Griswold (21) reported a case of intermittent hypertension, due to the presence of a pheochromocytoma, where the hypertension was definitely reduced to normal limits with every injection of Dibenamine. The drug here aided in proving the diagnosis of the tumor in a way less dangerous than the older method of using histamine to provoke an attack (20) and more definitely than by the more recent method of nullifying an attack for a very brief period by the use of a benzodioxane compound (5). Dibenamine, because of its prolonged effect in lowering the blood pressure, which remained within normal limits for 24

hours, and in allaying the symptoms, which did not recur for 72 hours, was very helpful in building up the health of the patient prior to surgery.

It would appear, therefore, that Dibenamine lowers hypertension in man: (1) by attacking the excessive sympathetic tone which, many investigators believe, plays the primary role in the genesis of at least essential hypertension; (2) by rendering ineffective any circulating sympathin or epinephrine, as shown most clearly when a pheochromocytoma is present. Thus both the sympatholytic and adrenolytic properties of Dibenamine are concerned in its action on hypertension. How useful this action is clinically is still a matter not finally elucidated.

7. *Action on Peripheral Blood Flow*

Hecht (7) found that visible peripheral vascular dilation was not observed in resting normal individuals after Dibenamine administration, but was seen in subjects with peripheral vascular disease, e.g., hypertension, thromboangitis, Raynaud's syndrome, etc. A marked rise in skin temperature was noted in these cases. Apparently Dibenamine is able to block the excessive sympathetic tone governing peripheral vessels in these conditions and thus permit more vasodilation.

Console's findings (2) were similar to those of Hecht. His investigations proved that peripheral blood flow in subjects with acute vascular occlusions could be effectively increased by the use Dibenamine, and that this action was much more prolonged than that of tetraethylammonium. In chronic vascular occlusions, temporary vasomotor paralysis can also be caused by Dibenamine, but its value here is more doubtful. However, Dibenamine may be useful in selecting certain of these patients for sympathectomy.

8. *Action Opposing Lethal Adrenergic Activity*

(a) *Administration of Fatal Doses of Epinephrine*

Raab and Humphreys (17) found that Dibenamine protects the heart of rats from normally fatal doses of epinephrine and permits their survival with normally fatal accumulations of epinephrine in the myocardium. Dibenamine is far more effective than Priscol, or 933 F in this respect.

Loew and Micetich (9) reported that Dibenamine protects mice against toxicity of epinephrine injected two hours later. However, they feel that the magnitude of the dose required and the slowness of onset of the protective action of the drug do not justify the designation of Dibenamine as the powerful adrenergic blocking agent Raab and Humphreys considered it to be. This is especially evident when Dibenamine is contrasted with other more active members of its own family, the beta chloroethylamines. However, Dibenamine is admittedly superior to Priscol, Yohimbine and the Fourneau compounds.

(b) *Excessive Sympathetic Activity Following Shock*

Ordinarily excessive compensatory vasoconstruction follows severe haemorrhage and this leads to the shock state. Wiggers et al. (22) found, in experimenting with dogs, that the administration of a very small dose of Dibenamine (2-4 mgm./kgm.) in the middle of the post-haemorrhagic hypotension period improved the blood flow to such organs as the kidneys, liver, and intestines even under the prevailing low blood pressure. Apparently the abolition of severe vasoconstriction delays the onset of irreversible shock, for 80% of the Dibenamine-treated group survived as compared with 30% of the controls.

Remington et al. (18) conducted somewhat similar experiments with dogs. However, Dibenamine was administered one hour before, rather than after, the haemorrhage was begun. In the treated dogs the survival rate was 90% after a haemorrhage of 30 c.c. among the controls only 7% survived. Pulse rate and blood flow per second were consistently greater in the treated group.

These investigators also tested the effect of Dibenamine on the shock following muscular trauma. Of the group of dogs treated with Dibenamine before the administration of multiple blows with a mallet on each hind-leg, 89% survived; of the controls 100% suffered fatal shock. Dibenamine's protective activity seems to be due to its prevention of the high degree of vasoconstriction which follows muscular trauma, apparently brought about by afferent nervous discharge from the traumatized limbs.

The largest part of this description of the pharmacodynamics of Dibenamine has been confined to the action of this chemical on the cardionvascular system. This has been deliberate since the action of autonomic drugs can usually best be studied with reference to this system. Workers have been able to perform clear-cut experiments and to record the changes in a system which is sensitive to small amounts of sympathin or epinephrine and also of their opponent, Dibenamine.

However, there are a number of other interesting actions of Dibenamine on the body which should also be mentioned.

II. Actions on the Eye

(a) *In Animals*

In intact animals Dibenamine causes miosis, ptosis of the eyelid, and marked extension of the nictitating membrane.

Dibenamine prevents or reduces the mydriasis, widening of the palpebral fissure, and retraction of the nictitating membrane usually induced by administration of epinephrine or by cervical sympathetic nerve stimulation (14).

(b) *In Man*

Miosis appears early and persists for the duration of action of

Dibenamine, and is the most sensitive indicator of the activity of the drug (7).

The effect of Dibenamine on the ciliary body and accommodation is not yet known; when the effect is discovered it may provide information as to the role of the sympathetic nerves in accommodation.

III. Other Actions of Dibenamine

(a) *In Animals*

1. Dibenamine abolishes the pilomotor response to sympathetic nerve stimulation (14).
2. It prevents the contraction of the spleen which is largely responsible for the erythremia and leukocytosis which normally occur during excitement (14).
3. It blocks the response of denervated effector cells to epinephrine so that when Dimenamine is previously administered they fail to respond to 100 or more times the effective dose (13).

(b) *In Man*

1. The nasal mucosa becomes congested after Dibenamine in many of the human subjects tested (7).
2. Spontaneous sweating in certain body areas is prevented by Dibenamine (7, 13). This is an interesting finding because, although the sweat glands are innervated by fibres from the sympathetic system, they are generally considered to function under the direction of the parasympathetic. However, some sympathomimetic amines cause sweating; epinephrine does not do so presumably because of its local vasoconstricting action. Nickerson (13) reports a study by Haimovici of palmar sweating and its inhibition to a marked degree by Dibenamine. Moreover, the sweating caused by neosynephrine is completely blocked by Dibenamine. It seems likely, therefore, that adrenergic sweating in certain cutaneous areas of man is a normal body process; Dibenamine may help to elucidate the complex mechanisms of sweating.

IV. Certain Responses Not Affected by Dibenamine

1. The respiratory effects of epinephrine are not altered, i.e. the transient "epinephrine apnea" is not blocked by doses of Dibenamine which readily reverse the blood pressure response; hyperventilation, elicited by large doses of epinephrine, still occurs; the bronchial musculature is believed to relax as usual (13).
2. The metabolic effects of epinephrine are not altered by Dibenamine. For instance, the rise in blood sugar is not prevented; in fact it occurs more quickly after Dibenamine for the epinephrine more readily enters the systemic circulation since it no longer limits its own absorption by local vasoconstriction (13).

3. Smooth muscles which are relaxed by epinephrine or sympathetic stimulation are uninfluenced by previous administration of Dibenamine, e.g. the intestine and the non-pregnant cat uterus still relax after this drug when stimulated adrenergically. However, in contrast, the rabbit uterus which is normally stimulated by epinephrine to contract, relaxes when Dibenamine is previously administered. This is further evidence that Dibenamine, which cannot block the inhibitory adrenergic functions, is fully able to block any excitatory ones (14).
4. The functions of the gastrointestinal, genitourinary and somatic neuromuscular systems are not apparently changed. Similarly body temperature and the blood picture are not altered. Not much is yet known of the action of Dibenamine on renal haemodynamics and renal function (13).

TOXICITY

I. Side-Effects

1. *Oral Administration*

Rockwell (19) found that the only reactions to enteric-coated capsules were nausea and vomiting in 5 of 50 patients with the first dose. However, Hecht (7) and other investigators found that nausea, vomiting, and burning in the epigastric area were frequent. Moreover, pharmacological effects in doses which could be tolerated were found to be unpredictable; accordingly oral administration has been abandoned by most workers in favor of the intravenous route.

2. *Parenteral Administration*

This route produces some unpleasant reactions, such as pain along the injected arm, in a majority of patients, according to Hecht (7). The only safe parenteral method is intravenous infusion in hospitalized patients. Extravasation may result in pain and local tissue damage. Direct intravenous injection sometimes causes venous thrombosis. Too rapid infusion may result in nausea, vomiting, central excitation, tremors, etc. at least 60 min;-utes should be taken for administration of the infusion.

II. Acute and Chronic Toxicity

1. *Local Tissue Damage*

As pointed out above, Dibenamine is chemically related to the nitrogen mustards, and this in all probability accounts for the tissue necrosis which it can inflict unless very carefully administered.

2. *Central Nervous System Excitation*

In both animals and man too rapid injection causes acute symptoms such as coordinated convulsions. The central effect is apparently independent of the adrenergic blocking action for it appears earlier and disappears earlier than the latter action. Moreover, the

congener of Dibenamine, N,N-bibenzyl animoethanol, possesses no adrenergic blocking power, but shows a similar convulsive action. An odd psychic feature of the central effect of Dibenamine was a disturbance of time sensations with some hallucinatory features and with repetitive perceptions of actual events so that an incident just occurring seemed to have been already experienced. This psychosis was noted in 15 of Hecht's 70 patients (7) and lasted for two to three hours. Consciousness usually was at its height. Psychiatrists may find Dibenamine useful for elucidating this phenomenon which occurs without known cause in certain of the mentally ill.

3. *Only Slight Cumulative Toxicity Has Been Noted*

Nickerson reports (14) that growing rats subjected to daily subcutaneous injections of 3 times the adrenergic blocking dose for a period of 4 months showed no permanent ill effects and only a slight decline in the growth rate during the period of treatment. Hecht reports (7) that human subjects treated with the average tolerated dose, 4-6 mg./kg., showed no striking alterations in blood counts, urinalyses, electrocardiograms, temperature, or body functions. Of great importance is the fact that Dibenamine does not possess the property so characteristic of the nitrogen mustards of producing a toxic effect on the bone marrow (13).

III. Therapeutic Ratio

The relationship between the effective and the toxic doses of Dibenamine is on the order of 10 - 100, a therapeutic ratio which, although not high, compares favorably with that of other adrenergic blocking agents. Slow intravenous administration appears to give the greatest margin of safety in animals (14).

Dosage

The manufacturers of the drug state that a "single dose for adults is 5 to 7 mgm. per kg. body weight, with the average dose 6 mgm. per kg. Regardless of weight, the single total dose should not exceed 500 mgm. (contents of one 10 c.c. ampule). The single dose may be repeated two or three times weekly." (Quoted from the circular which accompanies supplies of the ampules.)

Dibenamine is also available in enteric-coated tablets of 130 mgm. for oral administration.

Absorption, Onset and Duration of Action

No specific information on absorption by the oral or the various parenteral routes is apparently available in the literature at present, probably because the intravenous route has largely displaced other methods of administration by reason of its greater safety.

The onset of action is rather slow, especially in comparison with that of some of its congeners (9). Loew reports that it failed to decrease the toxicity of epinephrine until the third hour but protected the mice until

18 hours after treatment. Nickerson (14) states that the maximal blocking action is not observed until at least 30 minutes after administration of the drug but that the duration of effect from a single injection is from 36 hours to 5 days. Haimovici (6) found that the depressor effect started at the end of the (slow) infusion and lasted 24 - 72 hours.

Although Dibenamine may be considered slow in onset as compared to other recently synthesized beta-chloroethylamines (known in the literature as SY compounds and still very much in the investigational stage as far as present use is concerned), it is fairly rapid in its commencement of action compared to other clinically available adrenergic blocking agents. Its long duration of action is admitted by all investigators.

Mechanism of Action

It is considered likely (6, 15) that the site of action is the neuro-effector cells where Dimenamine blocks the sympathetic impulses or the action of sympathomimetic substances (sympathin E, epinephrine).

The prolonged blocking effect of a single dose of a drug which is known to become inactivated within a few minutes at the pH of the body, suggests, Nickerson feels, that there is "prolonged inhibition, or actual destruction, of some structure or substance involved in the excitatory responses to epinephrine and its slow reactivation, repair or replacement so that complete recovery occurs without residua" (15). In later articles (14, 16) Nickerson rules out, by a process of elimination, "any major effect of Dibenamine on (a) autonomic ganglia, (b) post-ganglionic neurones, or (c) on the release, alteration or destruction of epinephrine and sympathin", so that he feels Dibenamine's action must be exerted directly upon the effector cells (i.e. vascular smooth muscle).

The action on the effector cells could then be exerted in three ways: "(i) by preventing the penetration of sympathomimetic agents to their site of action, (ii) by blocking or destroying some receptor substance or mechanism necessary for excitation by these agents, (iii) or by attacking the contractile mechanism itself." Nickerson's experiments (16) upon the nictitating membrane of the cat lead him to favor (ii) and he discusses at length the manner in which he believes Dibenamine may act.

Comments

The above review of the literature on this interesting new drug shows that there is still a good deal of controversy as to the practical uses to which it may be put, e.g. there is no general agreement as to how useful it may be in treatment of certain conditions as hypertensive disease, peripheral vascular disease, shock, ventricular arrhythmias in patients under anesthesia, etc. However, it seems apparent that it will be useful in the diagnosis and the treatment of some, at least, of these conditions, perhaps to be displaced later by other members of its own family, once their pharmacology and therapeutic indices are also fully worked out. Dibenamine does seem to have certain advantages in specificity of action, long duration and completeness of blockade, and wide margin of safety over

some of the drugs currently in use as adrenergic blocking agents, e.g. Yohimbine, Priscol, the Fourneau benzodioxone componds, tetraethylammomium, etc.

Interesting new vistas of speculation and experimentation are opened up by the discovery of so active a drug, quite apart from its immediate practicality. The whole field of autonomic activity can be reviewed with fresh interest and Dibenamine can be used as a convenient tool in the attempt to elucidate more of the mysteries of the sympathetic and the parasympathetic systems.

New possibilities of investigation may also arise from the central effects of Dibenamine, and psychiatry gain new knowledge. It is interesting to note that one experimenter, Medinets (11), has already announced certain discoveries with regard to the catatonic state of schizophrenic patients, in this case making use, however, of the adrenergic blocking action of the drug.

The workers on Dibenamine, scattered in laboratories and clinics over most of the continent, have gradually built up a large store of information on this drug in the last three years. Further coordinated studies on it and its congeners should soon prove tremendously worthwhile both for the field of Medicine and the field of Pharmacology itself.

Summary

Dibenamine, one of a new series of potent, specific and long-lasting adrenergic blocking agents, has been investigated by laboratory and clinical workers since 1946. Chemically related to the nitrogen mustards, it must be carefully administered, preferably by the intravenous route, to avoid causing tissue necrosis similar to that caused by these related substances. Its systemic effect is to cause blockage of all excitatory adrenergic functions, thereby often throwing into relief concurrent but previously invisible inhibitory adrenergic functions which it is unable to block. A variety of experiments which have been performed on both laboratory animals and human subjects to demonstrate its pharmacodynamics are then described. These pertain chiefly to Dibenamine's action on the cardiovascular system for it is here that the most dramatic and potentially the most clinically useful results of its opposition to epinephrine and/or sympathetic nerve stimulation are apparent. It is notable that Dibenamine does not affect the chronotopic or positive inotopic effects of epinephrine on the heart; it opposes chiefly the peripheral vasoconstriction which epinephrine induces.

The acute toxic effects of Dibenamine are local tissue necrosis and central excitation, both of which can usually be avoided by a careful and slow intravenous administration of the drug. Chronic toxic effects are usually not noted as there is only slight cumulative toxicity. The therapeutic ratio, although not high, compares favorably with that of other adrenergic blocking agents.

The possible mechanism and site of action of Dibenamine, the duration of effects and the dosage used are discussed. Possible clinical and

laboratory uses for the drug are suggested and a comparison of its effectiveness with that of other adrenergic blocking agents is made.

BIBLIOGRAPHY

1. Acheson, G. H., Farah, A. and French, G. N. Some effects of dibenamine on the mammalian heart. Federation Proc. 6:305, 1947.
2. Console, A. D. Diagnostic and therapeutic use of tetraethylammonium and dibenamine. Am. J. Med. 5:164, 1948.
3. Garb, S. and Chenoweth, M.B. Studies of hydro-carbon-epinephrine induced ventricula fibrillation. J. Pharmacol. & Exper. Therap. 94:12, 1948.
4. Goldenberg, M., Pines, K. L., Baldwin, E. F., Greene, D. G., and Roh, C. E. The hemodynamic response of man to nor-epinephrine and epinephrine and its relations to the problem of hypertension. Am. J. Med. 5:792, 1948.
5. Goldenberg, M., Snyder, C. H., and Aranow, H. Jr. New test for hypertension due to circulating epinephrine. J. A. M. A. 135:971, 1947.
6. Haimovici, H. and Medinets, H. E. Effect of dibenamine on blood pressure in normotensive and hypertensive subjects. Proc. Soc. Exper. Biol. & Med. 67:163, 1948.
7. Hecht, H. H. and Anderson, R. B. The influence of dibenamine (N,N - dibenzyl-beta-chloroethylamine) on certain functions of the sympathetic nervous system in man. Am. J. Med. 3:3, 1947.
8. Hecht, H. H., Focht, F. S., Abildskov, J. A., Burns, T. W., and Christensen, R. O. Further observations on the action of dibenamine in human subjects. Am. J. Med. 3:124, 1947.
9. Loew, E. R., and Micetich, Audrey. Adrenergic blocking in decreasing epinephrine toxicity in mice. J. Pharmacol. & Exper. Therap. 93:434, 1948.
10. Marsh, D. F., and VanLiere, E. J. The effect of adrenergic blocking agents on the vasconstriction produced by acute oxygen lack. J. Pharamacol. & Exper. Therap. 94:221, 1948.
11. Medinets, H. E., Kline, N. S., and Mettler, F. A. The effect of N,N-dibenzyl-beta-chloroethylamine hydrochloride (dibenamine) on autonomic functions and catatonia in schizophrenic subjects. Proc. Soc. Exper. Biol. & Med. 69:238, 1948.
12. Moe, K., Malton, S. D., and Freyburger, W. The role of arterial pressure changes in the induction of epinephrine—cyclopropane idioventricular rhythms. J. Lab. & Clin. Med. 32:1415, 1947.
13. Nickerson, M., and Goodman, L. S. Pharmacological and physiological aspects of adrenergic blockade, with special reference to dibenamine. Federation Proc. 7:397, 1948
14. Nickerson, M. and Goodman, L. S. The pharmacological properties of a new adrenergic blocking agent, N,N-dibenzyl-beta-chlorosthylamine (Dibenamine). J. Pharmacol. & Exper. Therap. 89:167, 1947.
15. Nickerson, M., and Goodman, L. S. The pharmacology of a series of new sympatholytic agents. Proc. Am. Federation Clin. Research, 2:109, 1945.
16. Nickerson, M., and Nomoguchi, G. M. Locus of the adrenergic blocking action of dibenamine. J. Pharmacol. & Exper. Therap. 93:40, 1948.
17. Raab, W., and Humphreys, R. J. Protective effect of adrenolytic drugs against fatal myocardial epinephrine concentrations. J. Pharmacol. & Exper. Therap. 88:268, 1946.
18. Remington, J. W., Wheeler, N. C., Boyd, G. H. Jr., and Caddell, H. M. Protective action of dibenamine after hemorrhage and after muscular trauma. Proc. Soc. Exper. Biol. & Med. 69:150, 1948.
19. Rockwell, F. V. Dibenamine therapy in certain pschopathologic syndromes. Psychosom. Med. 10:230, 1948.
20. Roth, G. M., and Kvale, W. F. A tentative test for pheochromocytoma. Am. J. M. Sc. 210:653, 1945.
21. Spear, H. C.,and Griswold, Dwight. The use of dibenamine in pheochromocytoma. Report of a case. New England J. Med. 239:736,1948.
22. Wiggers, H. C., Roemhild, F., Goldberg, H., and Ingraham, R. C. The influence of prolonged vasoconstriction on the transition from impending to irreversible hemorrhagic shock. Federation Proc. 6:226, 1947.
23. de Vleeschhower, G. R. On new adrenolytic compounds. Proc. Soc. Exper. Biol. & Med. 67:298, 1948.

PORPHYRIA

By J. E. MULLENS, '49

PORPHYRIA is a name given to a group of conditions which are due to inborn errors in metabolism and characterized by the excretion of porphyrins in the urine. One must be careful to distinguish the term porphyrinuria (porphyrins in urine) from porphyria. Although porphyrins occur in the urine in porphyria, not all porphyrinuria is due to porphyria. Porphyria is a disease entity, while porphyrinuria is merely a symptom.

In the last few years a great deal of interest has arisen concerning the role of porphyrins in health and disease. As yet the subject is in a state of flux, and the center of much controversy. Therefore, this paper cannot be too dogmatic or authoritative, its main purpose being to stimulate interest in the porphyrins and their relation to clinical medicine.

Before the clinical aspects of porphyria can be discussed it is essential that a very brief reference be made to the chemistry of the porphyrins. A few facts must be known in order to have some idea of etiology, and of the detection of porphyrins in the urine—a clinical necessity.

Chemistry of Porphyrins

Every porphyrin is composed of 4 pyrrol nuclei joined by methene bridges to form a ring. Each pyrrol nucleus is a five membered ring with 4 carbons and a nitrogen and 5 replaceable hydrogens. When these are linked together to form the porphyrin nucleus there are 8 replaceable hydrogen atoms present. Individual porphyrins are determined by the 8 side groups which each may possess. Hans Fischer synthesized 4 aetioporphyrins, which have 4 methyl and 4 ethyl radicals. Four differing arrangements are possible and thus these aetioporphyrins are named I, II, III, and IV. All other porphyrins are named according to which aetioporphyrin their configuration corresponds, regardless of the substituted radicals.

All naturally occurring porphyrins belong to I or III. II and IV configurations or types have never been found in nature. The porphyrins of the respiratory pigments, i.e. hemoglobins, cytochrome, catalase, as well as the free protoporphyrin of the erythrocytes all belong to type III. Coproporphyrin I occurs naturally in meconium, feces, and urine. Type III, coproporphyrin, also occurs naturally in the urine. The prefix copro is used because it was first isolated from the feces.

It is important to note here that it is quite unlikely that a type I porphyrin could be derived from a type III porphyrin (or vice verse) in nature because this could only happen by the breakdown and resynthesis of the whole molecule. Thus the coproporphyrin I in urine cannot be derived from the respiratory pigments. This formation of 2 types of porphyrins in nature independent of each other is what Fischer called the "dualism of the porphyrins".

Uroporphyrin is a porphyrin first isolated from the urine and later from the feces. It occurs only in pathological states and is evidence of a constitutional biochemical fault.

Physics of Porphyrins

The name porphyrin comes from the Greek word porphuros, meaning crimson or purple. Porphyrins are reddish-brown to red, depending upon their solvent, and its pH.

The absorption spectra are characteristic but a very precise spectrometer is required. The old spectrometers were the cause of the artificial haemato-porphyrin being confused with natural porphyrins, as their absorption spectra are quite similar.

In the longer waves of ultra violet light there is intense red fluorescence. The emission spectra in ultra violet light is characteristic but does not separate the isomers. The identification of isomers depends upon (1) melting point of the crystalline methyl esters, (2) crystalline form, (3) fluorescence curves obtained from porphyrin solutions of varying pH.

PORPHYRIA

Clinically there are 3 types of porphyria. Gunther named these congenital, acute, and chronic. Recently the term "chronic" has fallen into disuse. Waldenstrom prefers the term "porphyria cutanea tarda" be substituted for the term chronic. He identifies it as a late form of congenital. Many do not mention chronic in their classification.

It should be noted here that the term haemato-porphyria is archaic and incorrect despite its persistence in some good texts.

I. Congenital Porphyria

This is inherited as a Mendelian recessive. It occurs usually in males and usually before the age of 15 years. It is much less common than acute porphyria. It runs a long and debilitating course, death finally being due to intercurrent disease or anemia.

Red urine is the first sign of the disease and may precede the skin lesions by weeks or years. Tests show the porphyrins are uroporphyrin I and coproporphyrin I. Isolated instances of type III porphyrins in the urine have been reported.

There is characteristically a hypersensitivity to light. This manifests itself in skin lesions of a bullous nature. The bullae are large, show no umbilication, and are distributed chiefly on the exposed portions of the body. It begins with itching or burning of the skin, photophobia and conjunctivitis. There may be oedema and hyperemia of the face. At the same time malaise, nausea and headache are common. When uncomplicated the lesions heal with little but definite scarring. Suppurative lesions occur in the presence of secondary infection, and when this is present, marked scarring, deformity, and disfigurement of the hands and face occurs. The scars become pigmented. This skin affection occurs typically in the spring and summer unless the patient is protected from sunlight

and is therefore called hydroa aestivale or vacciniforme. It must be noted, however, that all hydroa aestivale is not due to porphyria.

Ocular damage may occur from scarring and deformity. Such lesions as conjunctivitis, chemosis, bullae on the cornea, leukoma, posterior synechia, and symblepharon occur. The lids may be narrowed, or ectropion may result.

The fingers and nails are often deformed. The nails may be lost, and in some cases may be red in colour.

Erythrodontia, or red teeth, are an interesting feature of the disease. The colour, though, may range from distinct red or brown to normal.

Endocrine disorders seem common, e.g. toxic goitre, hirsutism, etc. Borst and Konigsdorfer found morphological changes in the endocrine glands.

Hepatomegaly and/or splenomegaly occur, more commonly splenomegaly. The splenomegaly may not be found in the young but usually appears as the patient grows older.

Anemia is a significant feature of the disease. Normoblasts, megaloblasts, punctate basophilia, and polychromasia have been seen. Megaloblasts are rare in the blood, and though they occur in the bone marrow, the colour index usually diminishes as in any secondary anemia.

The feces are not characteristic unless the porphyrin content is high, then they become black on oxidation. Both coproporphyrin and uroporphyrin are present.

Congenital porphyria has no heredity connection with acute porphyria, although Nesbitt and Katkins have seen a family where one member had acute porphyria and another had congenital porphyria.

Differential Diagnosis of Congenital Porphyria

The skin lesions are not pathognomic. The deforming character may resemble lupus or leprosy. Scleroderma may be simulated. The lesions may be confused with epidermolysis bullosa because trauma also raises vesicles in some cases of porphyria. A urine examination should be sufficient in most cases to differentiate, however, if the urine is negative for porphyrins it does not rule out congenital porphyria and the blood serum should be examined.

The skin lesions and the teeth may show fluorescence in near-ultraviolet rays if the porphyrin content is high enough.

Splenomegaly may be present but the spleen is not as large as in the splenic anemias. This could confuse due to the anemia which is often present in porphyria. Because the splenomegaly only appears with time it is presumed to be secondary.

The anemia present is often associated with signs of abnormal bone marrow activity, e.g. normoblasts, erythroblasts, megaloblasts, and erythrophagocytosis. Petry, the original classical case of congenital porphyria, showed the picture of pernicious anemia late in the course of the disease,

and an indirect Van den Bergh reaction. Here again the examination of the urine will usually differentiate.

II. Acute Porphyria

This disease is inherited as a Mendelian dominant with a low incidence of expression. Contrary to the name it is actually a chronic disorder. It is more common in women and in the third to fifth decades. There is usually a high mortality, after a relatively short duration, due to respiratory paralysis.

Some people distinguish a toxic and an idiopathic form. Gunther originally, and many authorities since, think that toxic substances only precipitate the symptoms of a condition already present. Toxic porphyria may be precipitated by lead poisoning, barbiturates, sulfonal, trional and other substances. There is no justification in recognizing a toxic form as the symtoms are identical and only the history can differentiate.

SYMPTOMATOLOGY

1. Abdominal symptoms: Severe abdominal pain of a colicy type is commonly one of the first symptoms. It is often in the lower abdomen but may become generalized. Radiation to the thighs is not uncommon. A case has recently been reported in which there was urgency of micturation during the acute attacks. The abdomen is typically soft. The attacks may be often seen post-partum, or associated with the menses.

   Nausea and vomiting are usually present and frequently severe. Constipation is nearly always present and may be quite severe. Diarrhoea occurs but rarely.
2. Jaundice occurs sometimes and is usually mild. This is to be distinguished from the commonly occurring diffuse skin pigmentation. This pigmentation occurs chiefly on the face and abdomen and may be in freckle or chloasma-like spots, especially on the face. This pigmentation does not involve the mucosal surfaces. There is often darkening of the hair. The acute attack may be preceded by years by the pigmentation, which may become worse during attacks. Incidentally the cause of the pigmentation is unknown.
3. Hypertension and tachycardia occur often and especially during attacks.
4. Oliguria is commonly present.
5. Neurological and Mental Symptoms: Porphyria may play a minor role in the production of the neurological symptoms as porphyrinuria may occur after the symptoms have been established. Contrary to the prevalent idea, Wildenstrom states that an ascending paralysis is not the commonest neurological symptom, although this Landry form of paralysis is common.

   There are often irregularly distributed paresis. There may be only a single group, or nearly all striated muscle may be affected.

   Symptoms similar to those of polyneuritis may be marked. Convulsions, delirium and coma are sometimes seen.

Hysteria is a common diagnosis because of the curious paresis and pains all over the body. There may be initially a feebleness which can be overcome by strong volition. This is a hysterical picture. The passing attack of blindness which can occur may be diagnosed hysterical amaurosis. Paralysis is usually preceded by nervousness, irritability, pain in the lower extremity, or discomfort and aching. Such sensory disturbances as hypaesthesia, or paraesthesia may be present. These symptoms may precede the abdominal pain by a few days to a few weeks.

Paresis and loss of reflexes in the legs and soon involving the arms is often seen. Complete flaccid paralysis may ensue. During this 2 - 3 week interval the patient may be irrational. Visual and auditory hallucinations are encountered, and delirium may alternate with apathy. there may be other psychopathic phenomena, e.g. maniacal or depressive states, or epileptiform seizures. A true Korsakoff's psychosis may develop, viz.: acute toxic psychosis with polyneuritis.

Waldenstrom points out that many porphyrics are in asylums. In studying the family history of porphyrics it seemed to him that there were more than an average number of manic-depressives and schizophrenics in the family. Watson suggests that it would be a good idea for someone to survey the clinical material in our mental hospitals as Waldenstrom did in Sweden, and doubtless many porphyrics would be discovered.

In the late stages of the disease bulbar paralysis and therefore dysphagia and dysarthria are commonly seen. Amaurosis and ocular palsies are also seen. Finally incontinence, coma and death ensue.

Mild cases have recovered and some others have had remissions and relapses.

6. The urine is usually a burgundy red or amber, becoming red on exposure to light. The appearance of the red colour is hastened by oxidizing agents. Originally it was said that the urine contained uroporphyrin III and I and in some cases coproporphyrin III. However, recent work has shown that what was formerly considered uroporphyrin III is actually uroporphyrin I with an unidentified type III porphyrin.

   The chromogen porphobilinogen is present in the urine and is specific for acute porphyria. It is stable when in alkaline urine but when acid it becomes porphobilin and what was formerly known as uroporphyrin III. Porphobilin was formerly known as urofuscin, and is simply a pigment. Some porphyrins in both acute and chronic porphyria are commonly excreted as complex metallic compounds—zinc especially.
7. Photo sensitivity has been reported but is extremely rare.
8. The following also have been noted:
   (a) Sudden development of Grave's disease
   (b) Obesity of the Frohlich's type

(c) Changes in the pituitary and adrenals
(d) Virgin secreting colostrum
(e) A man with swelling of the breasts during an attack
(f) A lesion of coeliac ganglion.

9. Remissions and exacerbations occur especially in the abdominal type. The neurological type has a mortality of 50-75 per cent. Mixtures of symptoms do occur commonly in any combination.

Differential Diagnosis of Acute Porphyria

1. Examination of Urine:
The urine may be red only on exposure to light, especially sun. Porphobilin may be responsible for most of the colour. It has been confused with urobilin. Watson and Schwartz have devised a simple test for the detection of urinary porphobilinogen. Equal parts of Ehrlich's solution, urine, and a saturated solution of sodium acetate are mixed. A few c.c.'s of chloroform are added. Porphobilinogen remains in aqueous solution and urobilinogen is extracted by the chloroform.

More chemical procedures for the detection of porphyrin isomers will be omitted here for brevity.

2. Abdominal Condition:
Laparotomies have been done for obstruction, appendicitis and gall bladder disease.

There is in this condition (porphyria) a leucocytosis of 15-20,000 and a temperature of 100-102°.

Gunther's triad of vomiting, colic, and constipation is almost invariably present.

The x-ray shows bowel spasm especially in the ileum. The stomach and colon may be dilated.

When an ascending peripheral neuritis is present the diagnosis is complete, but this is not always present.

3. Neurological:
Some of the entities with which it has been confused are poliomyeliitis, progressive muscular atrophy, periarteritis nodosa, cerebral tumour, hysteria and various psychoses. Should a suspicion of porphyria be present, the simple test outlined above will decide the issue in most cases.

III. Chronic Porphyria

No genetics are known about this condition. The symptoms of both congenital and acute may be present in a milder form. Waldenstrom believes it is a form of congenital porphyria.

The skin is somewhat sensitive to light. Abdominal or neurological symptoms may be present singly or in combination. Severe neurological symptoms are not present.

Coproporphyrin I and III and uroporphyrin I and III are excreted in the urine. Gray, Rimington and Thomson mention only uroporphyrin III.

Chronic porphyria develops later in life, and a sclerodermic tendency is noticeable.

Before studying the etiology the pathology should be summarized:

Pathology

1. Congenital Porphyria:

   The skin lesions show necrosis of the epidermis due to capillary damage in the corium. It is not primarily epithelial, therefore, but vascular.

   The teeth vary from red to normal and contain uroporphyrin I. Uroporphyrin I and coproporphyrin I are found in the cells of the bone marrow. Uroporphyrin I is also deposited in the bones. There is hemosiderosis of the bone marrow, spleen, and liver.

2. Acute Porphyria:

   Hepatic damage has been noted frequently. Recently Gray, Rimington and Thomson noted significant changes in the hippuric acid test when jaundice was present. In addition to disturbed liver function, disturbed calcium and cholesterol metabolism have been observed.

   Abrahams, Gavey and McLagen reported a case in 1947 in which low serum chlorides and serum sodium were present. To their knowledge these determinations have not been done in other cases. They noted that during exacerbations the symptoms were much like adrenal insufficiency though at autopsy the adrenals were anatomically normal, and therapeutically adrenal cortical extract and sodium chloride did not avert death.

   Prunty observed liver damage, hemosiderosis of liver and porphyrin in the liver cells. The kidney and the costal cartilages also contained porphyrins. Waldenstrom has found arteriolar medial sclerosis and necrosis.

ETIOLOGY

A. General

Porphyria has a universal distribution, and is not peculiar to humans. Typical congenital porphyria has been found in pigs and cattle. It is interesting, however, that nearly all of Sweden's porphyrics reside in one province.

It has been said before that some porphyrins are in the urine normally. The source of coproporphyrin in urine and feces is not likely to be meat because it may be found in vegetarians. There is a possibility that excretion is related to hemotopoietic tissue because excretion rises when hemotopoiesis is increased. Watson says that both uroporphyrin I and coproporphyrin I are formed in the erythrogenic cells of the bone marrow. Coproporphyrin I excretion increases in pernicious anemia and in hemolytic jaundice.

All of the porphyrins sensitize to light in varying degree but porphyrinogens and metallic salts of porphyrins do not. Uroporphyrin has the

most photodynamic action of all. They also produce smooth muscle spasm which is intractable to atropine. Intestinal colic, hypertension, oliguria, retinal vessel spasm and peripheral neuritis are regarded by some as porphyrinopathic whether it be idiopathic or toxic porphyria, e.g. lead poisoning. Porphyrins are excreted in large amounts in congenital porphyria, and less so in acute porphyria. This has been given as a reason for photosensitivity in congenital porphyria. But this would mean that there is something wrong with the porphyrinopathic theory of bowel dysfunction because there is none in congenital porphyria. Turner says that the difference lies in the fact that the porphyrins are metal complexes in acute porphyria and not in congenital porphyria. Yet Watson has demonstrated free porphyrin in the blood serum without photosensitivity.

Porphobilin also has been under suspicion as the cause of the pathology.

Berg believes that porphyrins may produce a block at neuromuscular transmissions and inhibit acetylcholine at the synapses. It may interfere with the hydrolysis of acetylcholine in its relation to choline esterase or it may interfere with the synthesis and release of acetylcholine. It is interesting to note that uroporphyrin occurs normally in foetal bones.

B. Porphyrins in Drug Ingestion

1. Lead Poisoning:
   Coproporphyrin III and a little coproporphyrin I are excreted in the urine. Increased light sensitivity has been reported. Calcium chloride administration clears the porphyrinuria and fluorescence from bones. The urinary coproporphyrin is rarely large enough to give red urine. Uroporphyrin III has not been observed. Yet the symptoms are practically the same as those of acute idiopathic porphyria. Even in ordinary lead poisoning the toxic manifestations have been attributed to porphyrinopathic sequelae. The lesser degree of symptoms corresponds to a lesser degree of excreted porphyrins. Thus the calcium given therapeutically may remove circulating porphyrins as insoluble calcium compounds and deposit them in bone.
2. Sulfonal and Trional Ingestion:
   Porphyrinuria here occurs almost entirely in women. Uroporphyrin I and III are reported as having been excreted.
3. Salvarsan Injections:
   An increase in urinary coproporphyrin III occurs in some patients receiving injections, and in salvarsan dermatitis, but not always.
4. Phosphorus:
   Causes an increase in urinary coproporphyrin.
5. Selenium and Mercury:
   May cause increased excretion of coproporphyrin and also uroporphyrin.

6. Alcohol:
   Increase in urinary coproporphyrin III.
7. Barbiturates:
   Controversial.

C. Secondary or Symptomatic Coproporphyrinuria

1. Jaundice and Liver Diseases:
   (a) Hepatic cirrhosis:
   The fatty cirrhosis following chronic alcoholism causes an increase in coproporphyrin III excretion, while non-fatty, idiopathic or post infective cirrhosis causes an increased excretion of coproporphyrin I. The reason for this is not clear. But it is known that acute alcoholism temporarily increases coproporphyrin I excretion.
   (b) In Infectious Hepatitis coproporphyrin I is excreted in increased amounts.
2. Poliomyelitis:
   There is excretion of urinary coproporphyrin III. Incidentally coproporphyrin III is present in the white matter of the central nervous system. This may or may not be significant.
3. Anemia:
   Aplastic and hyporegenerative types increase the excretion of coproporphyrin I and III.
4. Hodgkins' Disease and Leukemia also increase coproporphyrin excretion.
5. A class of patients who appear to have functional bowel complaints have increased coproporphyrin excretion. Watson poses the question, are the porphyrins responsible or are they indicative of a primary autonomic nervous system disturbance?

Where do porphyrins come from? It has been hypothesized that uroporphyrin III may arise from disturbed synthesis of respiratory pigments or abnormal destruction of hemoglobin.

Dobriner and Rimington separately have hypothesized that the formation of porphyrins is under enzymatic control. If a porphyrin ring is split transversely two dipyrromethane rings are formed. Designate these X and Y and assume they can occur separately in the body. Then

$$X + Y = \text{type III porphyrin}$$
$$X + X = \text{type I porphyrin}$$
$$Y + Y — \text{does not occur}$$

These reactions are under enzymatic control and normally III and I types are produced in a constant ratio. Porphyria could be a disturbance of this enzymatic control.

In summary, one sees porphyrinuria in many clinical syndromes. In considering the etiology of porphyria it is interesting to note all the foregoing data that it might shed some light on the cause. As yet, the details

of etiology are obscure but it does appear as though porphyria has some tie-up with the symptomatic porphyrinurias.

SUMMARY

Treatment of Porphyria

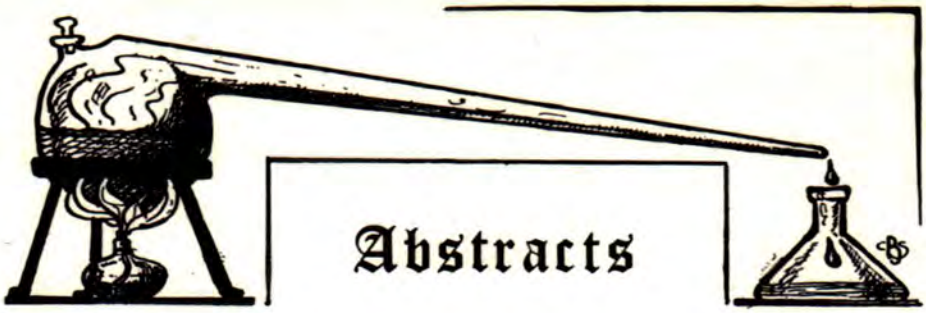
1. Avoid sulphonal, trional, lead, selenium, barbiturates, sulfonamides, arsenicals, alcohol and phosphorous.
2. Abrahams, Gavey and McLagan suggest kaolin be given to absorb porphyrins in the bowel, but Watson maintains porphyrins in the bowel have no relation to urinary porphyrin excretion.
3. Neostigmine and mecholyl have been used in acute porphyria with dubious results. Berg thinks they may actually be dangerous.
4. Liver injections have been used in chronic and acute types with controversial results. Theoretically the liver destroys porphyrins.
5. Demerol and atropine are useless in acute porphyria.
6. Alkalinizing the urine to decrease porphyrin excretion is useless. (Jorgensen and With).
7. Calcium chloride may or may not be of value.
8. Protect congenital porphyrics from trauma and sunlight.

Discussion

It is apparent that the investigations into a rare condition, porphyria, have opened up a vast new field for study in medicine, namely the role of porphyrins in health and disease. For example, what is their relation to liver disease, virus diseases such as poliomyelitis and infectious hepatitis, heavy metal poisoning, aplastic anemias, polyneuritis and mental disease? It has been the object of this paper to stimulate interest in porphyria so it may be recognized, and in the relation of porphyrin metabolism to other aspects of clinical medicine.

BIBLIOGRAPHY

Abrahams, A., Savey, C. J., McLagan, N., Brit. M. J., 2:327, 1947.
Berg, M., Arch. Int. Med., 76:335, 1945.
Brunsting, L. A., Mason, H. L., J. A. M. A., 132:509, 1946.
Chandler, F. G., Harrison, G. A., Rimington, C., Brit. M. J., 2:1173, 1939
Chu, E., Watson, C. J., Proc. Soc. Exper. Biol. & Med., 66:569, 1947
Dobriner, K., Rhoads, C. P., Physiol. Rev., 20:416, 1940.
Gray, C. H., Rimington, C., Thomson, S., Quart. J. Med., 17:123, 1948.
Jorgensen, J., With, T. K., Lancet, 252:54, 1947.
Linas, S., Solomon, M. L., Figgs, F. H. J., J. A. M. A., 132:509, 1946.
Nesbitt, S., Watkins, C. H., Am. J. M. Sc., 203:74, 1942.
Petrie, E., Brit. M. J., 1:296, 1948.
Prunty, F. T. G., Arch. Int. Med., 77:623, 1946.
Taylor, T. J., Solomon, M. L., Weiland, G. S., Figge, F. H. J., J. A. M. A., 131:26, 1946.
Turner, W. J., Obermayer, M. E., Arch. Dermot. & Syph., 37:549, 1938.
Waldenstrom, J., Acta Psychiat. et Neurol., 14:375, 1939.
Welcker, M. L., New England J. Med., 232:11, 1945.
Watson, C. J., Larson, E. A., Physiol. Rev., 27:No. 3, 1947.
Watson, C. J., Tr. & Stud. Coll. Physicians, Philadelphia, 16:No. 2, 1948.
Watson, C. J., Schwartz, S., Proc. Soc. Exper. Biol. & Med., 47:393, 1941.



NEW POSSIBILITIES IN PRIVATE PSYCHIATRIC PRACTICE

C. P. OBERNDORF

Am. J. Psychiat. 105:589-593, Feb. '49

After a brief account of the history of psychiatry and an evaluation of psychiatric methods, this article proceeds to consider certain problems and deficiencies in the practice of psychiatry. The psychiatrist, himself, is considered first. The isolating nature of the work of a private psychiatrist tends to limit his range and vision. To overcome this, the author suggests a part-time position in a sanitarium or other institution.

Next, the matter of cost of treatment is considered. At present, 90% of the population cannot afford private psychiatric treatment. A plan whereby private psychiatrists join in a "group practice" is advocated and the advantages of such a plan are enumerated. Under such a system patients in low income groups would be treated at reduced fees and this would be possible "through the circumstance that a younger man, whose practice in the early years is always uncertain, would be assured of a definite income for a given number of hours' work a week." "Half-way houses" for the intensive treatment of mild psychiatric cases are proposed as another facility in the private care of the mentally ill.

The old family doctor who knew the emotional setting of his patient is becoming extinct. A new and widening function of the psychiatrist is that of general family medical counsellor. This role is often attained only after the psychiatrist has treated some member of the family. The family psychiatrist is consulted to evaluate proposals of other medical specialists for treatment—especially in cases where emotional factors are involved. Advice is also frequently sought by the family in regards to choice of vocation and other personal matters.

The author believes that socialized or state medicine may eliminate the private psychiatrist. But if present trends remain the same in this country (U.S.A.), private psychiatric practice will prosper providing it offers better service at less expense.

—EWART SCHENCK, '50

GRAVES' DISEASE: TREATMENT WITH RADIOIODINE (I^{131})

MAYO H. SOLEY, EARL R. MILLER AND NADINE FOREMAN

J. Clin. Endocrinol. 9:29-35, Jan. '49

One of the most promising of the medical implications in the study of radioactivity is the application of radioactive iodine in treating Graves' disease. In effect, the intention is to perform a sub-total medical thyroidectomy. The authors report on the use of radioiodine (I^{131}) in Graves' disease.

Animal studies on rabbits and dogs showed an early decrease in the size of the thyroid—the arteries showed medial and intimal fibrosis, thickening and perivascular fibrosis. Of the acini, only a few remained, these at the poles. The amount of loss depended upon the uptake of I^{131} by the thyroid. In some instances, renal and tracheal damage occurred, with no changes in other organs.

To date, 68 true cases of Graves' disease have been studied, the majority of these with some thyroid enlargement. Dosages started with 250 microcuries of radioactivity, later were increased to 1000 and 4000 units, with a total dose up to 10,411 units.

The uptake of I^{131} was measured, using estimated weights of thyroid as judged by palpation and compared with actual weight of thyroid tissue removed in subtotal thyroidectomies. It was estimated that with no previous treatment, an average of 61% of I^{131} was taken up, whereas with those patients treated with Lugol's iodine or one of the thiouracils, an average of 48% was taken up.

The importance of the estimation was emphasized, though it was admitted that the margin of error was high, and that the concentration of I^{131} per gram of thyroid tissue was not directly related to the response.

Response is defined as satisfactory if in 4 months the signs and symptoms of thyrotoxicosis have disappeared, the thyroid has returned to normal size, and the basal metabolic rate, level of serum protein-bound iodine, and other laboratory findings are normal. Of the total, 42 patients were considered to have had good response, 4 showed a delayed response (these were more severe cases), 2 were given subtotal thyroidectomies (one for possible neoplasm, the other because of poor cooperation), 3 were considered "slow responses," 5 were unavailable for evaluation, one became pregnant and the remainder have not yet been evaluated.

The only complication mentioned was the development of myxoedema in 2 female patients. This occurred after a few weeks of therapy, with symptoms similar to those seen in the relapse of myxoedematous patients upon stopping thyroid therapy. It is stated that there may be some recovery in these patients, though follow-up is not yet complete.

The authors comment that time will permit resolution of the problems of selection of patients, dosage, and administration of dosage. They conclude that radioactive iodine (I^{131}) in adequate dosage will cause a subtotal destruction of hyperfunctioning thyroid glands in patients with Graves' disease, producing thereby satisfactory remissions of signs and symptoms of the disease. "Further studies ultimately will disclose its place in the therapy of Graves' disease."

—D. B. MELTZER, '50

EVALUATION OF THE VARIOUS CLINICAL SIGNS OF THROMBOPHLEBITIS AND EXPERIENCES IN THERAPY WITH ANTICOAGULANTS

DAVITT A. FELDER, M.D.

Surg., Gynec. & Obst. 88:337-350, 1949

Dr. Felder presents a very comprehensive paper on the subject, in which he presents 92 cases, representing 105 extremities with deep thrombophlebitis of the lower extremities.

Diagnostic signs and symptoms used were swelling, vessel tenderness, pain, increased temperature of limb, dilated superficial veins, cyanosis, pulmonary embolism and change in temperature and pulse.

The treatment used was:

1. Heparin and dicoumarol in 84 cases

   (a) Heparin used for 1-2 days for most patients. 50 mg. intravenously every 3 hours with clotting times (1½ hours after each dose) kept at 2 to 3 times the patient's normal clotting time. In some, the night therapy was given in one dose of 100 mg. at midnight. Heparin in Pitkin's menstruum was used in 7 cases (300 mg. in 1 dose/day with a vasoconstrictor given subcutaneously). Reports on coronamid prolonging heparin's action are encouraging.

   (b) Dicoumarol was given: 300 mg. the first day, 200 mg. the second day in 2 doses, and 100 mg. the third day in 2 doses. Prothrombin time was kept 1.5 higher than the control normal for the patient. In bleeding complications, 72 mg. Vit. K was given intravenously.

   The average treatment was for 14 days, but was extended to 21 days in cases of pulmonary embolism.

2. Bed rest—average 10.5 days.

3. Common femoral ligation was performed in 8 patients.

In this series the incidence of secondary pulmonary embolism was 2.17% and none of these was fatal. The complications of anticoagulant therapy are presented and discussed and do not appear to contra-indicate its use in most cases.

The therapy outlined appears to be adequate for most cases, but as Dr. Felder states, "The answer to the question of thrombophlebitis does not lie in perfecting the anticoagulants and their administration, but rather in the fundamental cause of abnormal blood clotting."

—EUNICE E. OESTREICHER, MEDS '49

MANAGEMENT OF CHRONIC PEPTIC ULCER

Lancet, 256:353, 1949

The article deals with the management of chronic peptic ulcer. Early treatment and diagnosis are very essential, and many can only hope for reasonably normal lives with minor relapses. It is pointed out that during acute relapses, bed rest is definitely required but not to the point of boredom for the

patient. The change from an active life should be gradual until the patient comes to accept his disability.

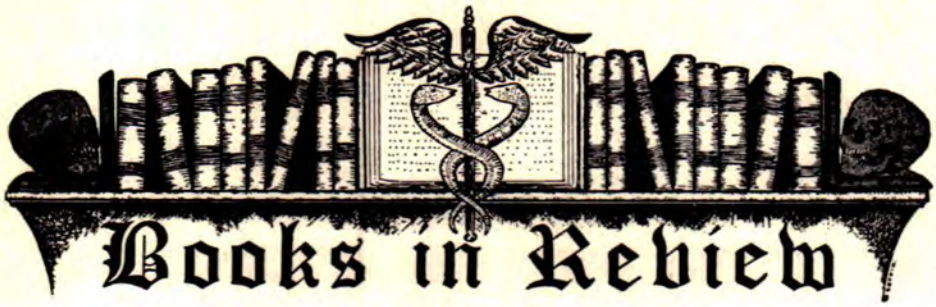
The drastic restriction on foods is felt to be open to question, and within reason the patient should eat what agrees with him. A little food, often, with proper timing and regularity is considered of prime importance.

There is no direct evidence that smoking is harmful. Schnedorf and Ivy have found that gastric acidity is not increased; if any effect at all, it retards evacuation and depresses gastric acidity.

The barbiturates are felt to be the only drugs of value in all stages of peptic ulcer. Belladonna in the form of l-hyoscyamine is useful in the acute stage, because it allays spasm and reduces painful gastric contractions, but it is of no use beyond this stage. The danger of haematemesis from insoluble aspirin is noted.

"The successful management of a peptic ulcer, then, requires on the patient's part an avoidance of excess, a minimum of fuss, and an acceptance of the inevitable. It asks of the physician a humble recognition of the limitations of therapy and a sparing and humane use of his veto."

—DONALD M. GOOD, '50



THE PROBLEM DRINKER

JOSEPH HIRSH

Duel, Sloan and Pearce, New York, 1949,

211 pp., Illust. 15

"Alcohol is a fact. We cannot hide it, we cannot avoid it. We have always had it. And as long as there is plant life on the face of the earth we cannot prohibit its existence. Alcoholic excesses and problem drinking are another matter. Their solution lies not in moralization, but in medical research, in treatment, in prevention, in honest education about how people function, and how alcohol functions—what it can do and does do to and for human beings."

This paragraph well expresses the theme of this interesting, matter-of-fact book on the age-old problem of alcoholism.

That excess drinking is an enormous problem is clearly demonstrated by the many recent statistics. The author points out, for example, that out of sixty million consumers of alcohol in the United States, there are over three and one-half million excessive drinkers, seven and one-half thousand of whom are true alcoholics. These excessive drinkers, through wage loss, accidents and expenditures of private and public welfare agencies, cost the United States over one billion dollars every year.

In his attack upon this problem, the author believes that many of our present laws are inadequate. Imprisonment and neglect, he points out, are not substitutes for treatment. The author offers many suggestions as to what may be done about the welfare of the alcoholic and about his rehabilitation.

Included in the book are excellent chapters on the history of alcohol; the pharmacology of alcohol; the relation of alcohol to crime, to accidents, to divorce and to venereal disease. One chapter is devoted to the organization and principles of Alcoholics Anonymous.

This book can be highly recommended as a useful and desirable book for any physician's library.

—KEN RITCHIE, '50

SOCIAL MEDICINE — ITS DERIVATIONS AND OBJECTIVES

THE NEW YORK ACADEMY OF MEDICINE INSTITUTE OF SOCIAL MEDICINE, 1947.
EDITED BY IAGO GALDSTON, M.D.

The Commonwealth Fund—New York 1949, 294 pp.

This extremely interesting book is composed of an edited collection of papers given before the Institute on Social Medicine formed in connection with the Centennial Celebration of the New York Academy of Medicine in the spring of 1947. The papers are printed in an orderly sequence and were given by many eminent authorities not only in the field of medicine, but also in the fields of history, philosophy, psychology, psychiatry, nutrition, economics, hygiene and public health, sociology and anthropology.

Medicine as it is practised to-day still tends to diagnose and treat an illness in an individual, neglecting many of the factors which may contribute to and help sustain the illness, such as economic and social conditions and many others. Although a great mass of facts is already known about the various aspects of environment which affect man's well-being and happiness, these facts are grouped into the separate fields named above. It was the purpose of this symposium to collect the opinions of various leaders in many fields of study regarding the useful knowledge which their respective fields are able to contribute towards a common pool of knowledge about the health of man, both as an individual and as a society.

This having been done, it was also their purpose to investigate means of integrating

the isolated fields into one study — social medicine — which would embrace the study of all contributions to the health of man. This is a positive study—to keep man happy and healthy as well as to treat him when he becomes ill; it embraces not only the ills of the individual patient, but also those of society, which are many, as evidenced by the frequency of wars, the wretched physical and social condition of so many of its members, and so on. The book continually stresses the role that the medical practitioner should play in social medicine. It is to be noted that this is not a book about socialized medicine as seen in Great Britain to-day; it is about social medicine and the distinction between the two is adequately described.

Anyone connected with the field of medicine will find much of great value in this relatively short book.

—DOUG. RICHARDSON, '50

HALLMARKS OF MANKIND

FREDERIC WOOD JONES

Bailliere, Tyndall and Cox, London, 86 pp.

The orthodox idea concerning the development of man is that he is the highest developed member of the order Primates. That is to say that the order Primates is made up of a number of closely related animals that represent an evolutionary sequence from "lowest" to "highest," the lowest being represented by the Lemurs and the highest by Man.

In this interesting little book, Wood Jones presents considerable anatomical evidence to show that this concept of man's development may be entirely wrong.

As a result of his studies in comparative anatomy Jones has come to the following conclusions: at an extremely early period, there existed a type of animal, perhaps unrecognizable as a monkey, which was destined to evolve into the Chimpanzee and Gorilla (African monkeys), the Orangs and Gibbons (Asiatic monkeys), and also Man. Through various natural forces a line of beasts, the Catarrini, developed. At a very early period a branch was produced from this main trunk which developed into Man. Some time later, after considerable specialization and polishing of the main trunk, a second branch was produced which became the Gibbon and Gorilla. After still more polishing and development the Chimpanzee and Gorilla were produced.

It will be seen that if this be true, Man is actually, in structure, a far more primitive beast than either Chimpanzee and Gorilla or Gibbon and Orang. The Gorilla, according to Jones, is the apex of anthropoid development rather than man. The less an ape has changed from its original form so much more human he appears.

Although the evidence for these ideas are not as yet completely convincing, they are stimulating and add further weight to the adage of Bacon, "that which the mind grasps upon with especial readiness is to be regarded wtth suspicion."

An interesting book for those interested in wandering along the byways of medical science.

—R. PRINCE, '50

Editorial

This is the first issue published by the 1949-50 staff of the Medical Journal. As is apparent, many changes have been made in the journal. These changes have been dictated by economic pressures which threaten the very existence of the journal. However, in spite of the limitations thus forced upon us we are striving to maintain a journal of high calibre which will bring articles of general interest to all our readers.

The editors wish to welcome the reorganized Osler Society to the Medical School scene. This society meets regularly to present papers on medical history. We feel that this is a very worthwhile study for medical students and graduates alike and we hope in the future to publish many of the papers presented at these meetings. In this connection we note with pleasure the appointment to the editorial board of the "Journal of the History of Medicine and Allied Sciences" of Dr. Lloyd G. Stevenson. Dr. Stevenson, a Western alumnus, is the author of "The Life of Sir Frederick Banting." We will await with pleasure the appearance in our journal of some of his articles on his return to Western.

Finally, we welcome at all times any suggestions from any of our readers which will improve the Medical Journal.