

ISONIAZID IN THE TREATMENT

OF SCHIZOPHRENIA

By

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INTRODUCTION

Schizophrenia is one of the gravest diseases affecting mankind. Ellery writes that it claims more victims than either cancer or tuberculosis. In the United States of America, each year 30,000 - 40,000 young people succumb to it, and he adds that in proportion Australia is similar for at least one quarter of the patients admitted to mental hospitals are suffering from Schizophrenia.⁽⁴⁾ It affects the young before the majority have even reached the prime of life and most of these young adults spend the best part of their lives in institutions. The worst sufferers come to lead what is almost a vegetative existence. Skottowe's findings, in an investigation of 949 consecutive unselected admissions of psychotic patients to the Buckinghamshire Mental Hospital in the five year period 1936 - 1940 drawn from a population of 309,600 persons, show that 94 men and 87 women were suffering from Schizophrenia. These represented 22.5% of the male admissions and 16.3% of the female admissions. 90% of all the patients were under 40 years of age.⁽³⁹⁾ In view of its chronic nature, the majority of the mental hospital population consists of schizophrenics - Henderson and Gillespie estimate the figure at 50% to 60%.⁽¹¹⁾

It is doubtful whether any other illness causes so much human distress or entails so much unproductive expense. This economic side to the problem is also vast. The cost to the State of maintaining a patient in Knowle Hospital is £4. 1. 1d per week. There is in addition the loss of the victim's earning capacity and, in many cases, further expense to the State in assisting to maintain his dependents. A study in Massachusetts some years ago showed that ten cents of every State-tax dollar went for the care of schizophrenics.

It is generally agreed that spontaneous remissions do occur particularly in the early stages of the illness. However, it is very difficult to assess the extent of this remission. Ellery finds that the figures vary from 2% to 39%, and adds that many of the remissions in the higher claims are temporary or of short duration. He quotes Müller as believing the figure for spontaneous remissions to be between 15% and 20%, but he comments that Müller gives no indication as to what percentage of these may be permanent or what percentage may be complete.⁽⁴⁾ Smith states categorically that spontaneous recovery in Schizophrenia occurs in less than 10% of cases.⁽⁴⁰⁾

In a condition like Schizophrenia in which the aetiology and the abnormal physiological and

pathological factors - if any - are unknown, any treatment must be empirical. Many organic treatments were tried in their turn but all failed. In the beginning of this century some workers attributed the cause to focal sepsis and recommended operations on tonsils, teeth and other possible sources of infection, but such procedures were eventually proved to be of no value. Treatment with various vaccines, autovaccines and sera of recovered schizophrenics proved unsuccessful. An aseptic meningitis produced by means of horse serum introduced into the subarachnoid space was tried by Carroll. Various glandular products have been used but all with unpromising results.

The first real progress in organic treatment of mental illness was made following the clinical observations of recoveries of mental patients during intercurrent infections. This led to various fever-producing methods. The production of a sterile abscess with turpentine oil was especially used in France, while in other European countries the sulphosin method of Schroeder was widely applied in Schizophrenia. In 1917, Wagner-Jauregg introduced malarial treatment in general paresis, the first successful treatment of a mental illness on a purely

organic basis. However, the use of malaria and of typhoid fever, and later of heat-producing agents of a physical nature, failed in Schizophrenia.

In 1922 continuous sleep treatment with barbiturates was developed by Klási. Results in Schizophrenia were poor. It is moreover a dangerous therapy, carrying a high mortality rate. Sargent and Slater comment, "Continuous narcosis is a symptomatic method of treatment appropriate with certain syndromes and on certain occasions. It is fundamentally an interim procedure from which permanent benefits can only be expected if the natural powers of recuperation will be sufficient to bring about recovery, given a breathing space of a fortnight or so."⁽³⁷⁾ However, it can be considered as the most important predecessor of the so called "shock treatments" and many authorities consider that their modes of action are similar.

Hypoglycaemic coma treatment with insulin in Schizophrenia was introduced by Sakel in 1933. Since then, a great deal has been learned about the treatment but the basic technique employed by Sakel is the one still most commonly used. Although statistics vary greatly, it is generally accepted that insulin coma therapy is a valuable adjunct in

the treatment of Schizophrenia. This is endorsed by the fact that in the twenty years since its inception it has become the most widely used treatment throughout the world for this illness. In 1935 von Meduna reported on his treatment of Schizophrenia by epileptic convulsions artificially induced by cardiazol. He claimed a most impressive remission rate especially for cases treated in the early stages of the illness. However, although it has proved a valuable treatment, von Meduna's high claim of success in Schizophrenia has not been borne out by subsequent findings. The beneficial effect of hypoglycaemic convulsions in insulin treatment led Georgi to recommend combined insulin-convulsive treatment. Time and experience have proved that, although not necessary in every case, this combined treatment is very valuable in certain cases resistant to insulin treatment alone, and in other selected cases. In 1938, Cerletti and Bini demonstrated, in Rome, the use of an electric current passed through the brain as a method of inducing convulsions. Its development followed extensive experimental work in electrically induced seizures in animals. This method has now largely replaced pharmacological convulsive treatment.

These new methods, while having their limitations, have introduced a little light into the

dark recesses of the treatment of Schizophrenia and have given some hope for sufferers from this illness to be able possibly to lead comparatively normal lives.

From 1947 - 1952 as a specialist in psychiatry in the Royal Navy, I was in charge of the psychotic ward. In this time I treated 115 Schizophrenic patients with deep insulin coma therapy. The immediate results were very good but all these patients were young physically fit men, struck down before having reached even the prime of life. On the completion of treatment they were all automatically invalided from the Service, the careers of their choice being ruined. Since coming to Knowle Hospital as Assistant Psychiatrist in 1952, I have been in charge of the insulin unit and have treated more than 40 cases suffering from Schizophrenia with this treatment. My impression is that a large number of the now chronic hospital population have, at one time, received insulin coma therapy which has failed, and that several admissions have previously had this treatment and have relapsed.

In a recent paper in the British Medical Journal on "The Effect of Isoniazid on Carbohydrate Metabolism in Controls and Diabetics", Luntz and Smith

found that the administration of isoniazid produced a temporary elevation of the blood-sugar level. They showed that isoniazid itself, although a reducing agent, was not responsible for the rise in blood-sugar levels and therefore postulated that a disturbance in carbohydrate metabolism could be inferred.(21)

My interest was aroused in the effect of using isoniazid in mental disorders, in particular in Schizophrenia, with the object in mind that it might possibly affect the metabolism of nerve cells. The food of nerve cells is carbohydrate and one of the theories for the beneficial effect of insulin and convulsive therapies is that they disturb the metabolism of the brain cells.

In the present thesis, the author proposes to give the results of his experience of the value of isoniazid in about sixty cases of Schizophrenia.

HISTORICAL SECTION

Insulin was first used in psychiatry as a sedative in agitated states especially in delirium tremens and catatonic excitement, and it was also used to overcome refusal of food and to build up debilitated patients. However, the dosage in these treatments was small. Haak did comment in 1929 that he was surprised that a case of catatonic stupor could be influenced by large doses of insulin. In 1928, Sakel produced hypoglycaemic states to overcome the withdrawal symptoms in the treatment of morphia addiction, and he also used this method in the symptomatic treatment of psychotics. He noted that deeper hypoglycaemic states, occurring unintentionally, frequently had a beneficial effect on the psychosis itself. He therefore began to induce hypoglycaemic coma with insulin in the treatment of schizophrenia, and his first report on this work was presented in Vienna in 1933. His technique was soon being widely used throughout the world and it was introduced into this country in 1936 by Strecker. This original technique was so carefully and skilfully worked out that it is, apart from a few minor modifications, still the one most generally used. Sakel, in his 1935 monograph on insulin treatment, warned against

the danger of epileptic seizures occurring during hypoglycaemia, but he later fully recognised and stressed their therapeutic value, stating that hypoglycaemic shock may consist of either a coma or an epileptic seizure.

In 1935, von Meduna reported on his treatment of schizophrenia with artificially induced epileptic convulsions. He first used 25% camphor in oil injected intramuscularly. The main disadvantages of this method were the impossibility of anticipating the time between the injection and the convulsion which could vary from 15 minutes to three hours, and the possibility that several convulsions might occur or none at all. Von Meduna therefore began to use a soluble synthetic camphor preparation, pentamethyl-entetrazol, known in this country as cardiazol and in the United States of America as metrazol. This is injected intravenously and was first used in a 20% aqueous solution, but this strength often caused pain and thrombosis of the vein at the site of the injection on account of which it has since been used in a 10% solution. This treatment was introduced into Great Britain in 1937 by L.C. Cook.

Combined insulin-cardiazol therapy was originally advocated by Georgi following his observations that a sudden improvement often resulted

after a convulsion during hypoglycaemia. The endeavour to overcome the fear and anxiety associated with cardiazol and the belief that hypoglycaemia decreases the convulsive threshold for cardiazol were other reasons for the use of the combined treatment.

In the early years of this century various workers produced stupor, general anaesthesia, catatonic states and convulsions with an electric current. Cerletti and Bini first applied the method to individuals suffering from mental disease in 1937 and reported on their findings in 1938. In an attempt to overcome the repellant prodromata of drug induced convulsions and the practical difficulty of repeated intravenous injections in patients with sluggish circulations, they began experimenting with animals and found that very large electric currents could be passed through the brain without producing histological signs of damage provided the exposures were not longer than about one second. Using an alternating current with a frequency of 50 cycles, they then applied the electrical method of inducing convulsions to human subjects, producing one thousand fits without accident. They obtained results at least as good as those claimed for the chemically induced convulsion therapies. Electric convulsive

therapy is really a technical modification of pharmacological convulsive therapy which it has largely replaced.

SCHIZOPHRENIA

Towards the end of the last century, Kraepelin described a series of cases which arose mainly during the later years of adolescence and which, although differing in many individuals, possessed certain features in common. The chief of these were detachment from the outside world, incoherence of thought, impairment of judgment, loss of feeling and various peculiarities of behaviour. He found that the majority relapsed and ultimately passed into a state of permanent mental enfeeblement. He therefore named the condition Dementia Praecox. He differentiated three principal types which he termed hebephrenic, katatonic and paranoid. He later added a fourth variety described as simplex.

In 1911, Bleuler, approaching the condition from the psychological aspect, explained it as the result of a splitting of the intrapsychic life which did not necessarily end in dementia and which might arise in adult life. He therefore suggested the term Schizophrenia, and this has gradually superseded the

older one of dementia praecox. Both Tredgold and Ellery point out that the terms are not synonymous and that while cases of dementia praecox evince the schizophrenic type of reaction, all cases of schizophrenia are not dementia praecox.⁽⁴⁾

(44) Tredgold states that dementia praecox is always followed by permanent mental deterioration. Although in some instances this process may undergo arrest, the patient is usually left on a definitely lower mental plane, while in many cases it gradually progresses to dementia.⁽⁴⁴⁾

Practically all the symptoms occurring in mental illnesses may occur in schizophrenia, but certain symptoms are more pronounced and are common to all the varieties. Probably the most frequent symptom is failure of affect or emotional blunting showing itself in apathy and indifference. There is a lack of initiative, spontaneity and ambition. There results a progressive withdrawal from the outside world to an inner world of phantasy, and a consequent loss of active attention. The patient loses his pride in his personal appearance gradually becoming more untidy and slovenly. In many cases as the deterioration proceeds, his habits become faulty and degraded.

Another important diagnostic symptom is emotional incongruity or disharmony between the mood and the thought. Happenings or situations in which the schizophrenic patient finds himself, which would normally have a profound emotional affect, produce only indifference or occasionally the opposite to the normally expected affect. Frequently there are sudden causeless outbursts of laughter or a silly vacant grin in which there is no real mirth. The schizophrenic's laughter is not infectious as is the manic's. Many of these patients have delusions which are accompanied by a completely inappropriate emotional tone.

Schizophrenic thinking is said to be autistic and katathymic, that is, it is introverted with little or no attempt to transfer thoughts into real tangible acts and it is directed along the lines determined by some complex. It is often obvious that the schizophrenic patient is experiencing considerable difficulty in thinking and occasionally the stream of thought is completely interrupted for no obvious reason (thought blockage). Speech may be stilted, stereotyped, affected or childish. It may be incongruous and frequently shows irrelevancies; neologisms or words of the patient's own making are

occasionally present. It may consist of a stream of words unrelated in meaning but rhyming or similar in sound, or in a mere meaningless incoherent jumble. Writing often shows similar features and large amounts of rubbish are frequently composed.

Ideas of reference, illusions, hallucinations and delusions constitute another group of symptoms. Ideas of reference are especially common. The patient is more sensitive and suspicious than normal and consequently believes that people are looking at him and speaking about him behind his back. Less frequently, this develops into the delusion that articles in the newspapers or topics on the wireless have special reference to him. Illusions I have not found to be common. Auditory hallucinations occur frequently. Sometimes the voices say pleasant things to the patient but more often they revile or accuse him. For a time they may not exercise much influence apart from his speaking back to them and the fact that he can sometimes be seen in a listening attitude, but often they dominate the patient and he acts in response to their suggestions and commands, frequently in a violent and impulsive way. Hallucinations of vision, smell, taste and touch are much less common than those of hearing. Delusions occur frequently,

and although it is said that the striking thing about them is their changeable and transient nature, I have not found this to be the case. In my experience, the schizophrenic patient often retains the same delusional beliefs for long periods and even indefinitely. However, they are very poorly systematized and are not accompanied by an appropriate emotional tone. Delusions of influence are very common. The patient believes that his thoughts are being read or that his mind and his actions are being controlled or influenced by some telepathic or hypnotic process, or by wireless or electricity. One case considered he was being controlled by cosmic radiation and therefore feared that he might be instrumental in setting off an atomic chain reaction.

The schizophrenic patient shows impaired judgment and a lack of proper appreciation of his position. In the majority of cases there is no insight or it is only very limited. The patient has no realization that he is ill and requires care and treatment, and he will give various reasons for his being in hospital such as that he was kidnapped and is being improperly detained, or that he just came along for admission because someone suggested it.

In the early stages of the illness these

symptoms occur in a setting of relative clearness. There is no real clouding of consciousness. It is said that there is no disorientation but I frequently find imperfect orientation to time which I consider due to the general apathy and indifference. The same reason accounts for the fact that the patient is often able to give only a poor account of himself and events leading up to his admission although his memory is usually good both for recent and remote events. The general intellectual faculties are unimpaired and there remains a good grasp of school and general knowledge. It is only later that, in many cases, a progressive mental deterioration sets in leading to a profound dementia.

Schizophrenia Simplex

The chief features of this type are an insidious onset with a gradual blunting of feeling and conation but without, as a rule, hallucinations, delusions or any great incoherence of thought. It frequently occurs in the "shut in", reserved schizoid personality when it is merely an accentuation of the existing personality defects. The onset is usually soon after puberty and rarely later than the twentieth year. The patient becomes increasingly dreamy, detached and asocial. He shows

little interest, spontaneity or ambition, and is quite content to remain in a sheltered hospital environment being incapable of making any concrete plans for his future. He will often do simple routine work. Emotional blunting and apathy are usually marked. Memory and grasp of school and general knowledge are usually well retained, and evidence of gross dementia does not set in until the lapse of many years.

Hebephrenic Type

The onset of this type is usually in the later years of adolescence. The main distinguishing feature is a marked emotional disturbance. There are sudden periods of wild excitement with impulsive, violent and often destructive conduct. Equally sudden periods of acute depression and tearfulness are liable to occur. Hallucinations of hearing and of sight are common and are usually vivid. Delusions are, as a rule, changeable and bizarre. Delusions of influence and ideas of reference are frequent. Great incoherence in speech is a prominent feature. The course tends to be gradually progressive. Habits become faulty and the general mental deterioration leads to dementia.

Katatonic Type

This type tends to occur first between the ages of twenty and thirty years. The onset is frequently said to be acute but closer investigation will usually reveal a history that, for some time, the patient has been vague, dreamy, apathetic and disinterested, with periods of odd, eccentric behaviour. Then, with very little warning, he passes into a state of dull stupor. If this is complete, there is mutism, refusal of food, and he sits slumped in a chair in one position for prolonged periods or he lies curled up in bed. He is insensitive to painful stimuli. There is either incontinence or retention of urine and faeces. He has to be dressed and undressed. He usually has to be tube-fed as food, placed in the mouth, is generally not swallowed. He may assume strange, statuesque postures which are maintained for long periods. Flexibilitas cerea is common. If the stupor is less marked, the patient may perform a series of stereotyped actions or he may show a marked degree of negativism or automatic obedience. Perserveration is common. Mannerisms may occur. In this state of stupor the patient understands what is going on around him but his apathy is so great that he takes no part in it.

Suddenly the picture may change. The patient begins to take notice of things, to reply to questions, and to make spontaneous remarks. He can often give a full account of what has happened during his period of stupor. He gradually returns to a condition of apparent normality.

The second characteristic feature of this type consists of sudden periods of wild excitement with great impulsiveness. The patient may, without warning, suddenly become extremely violent and destructive, and actively homicidal or suicidal. These actions may be in response to hallucinatory commands but are not necessarily so. This state of impulsive excitement may last from a few hours to days or weeks, and then suddenly subside.

Kraepelin reserves the name Katatonia for cases in which there is the conjunction of this peculiar wild excitement alternating with katatonic stupor, but, in my experience, it is now common to meet cases in which only the katatonic stupor occurs.

The katatonic type is usually characterised by remissions and recurrences, the majority of patients eventually passing into a state of chronic semi-stupor or chronic excitement, ultimately becoming demented.

Paranoid Type

This type tends to develop later in life than the other forms. It rarely arises before thirty years and may begin after forty years of age. The characteristic features are delusions, hallucinations and ideas of reference. The delusions are multiple, unsystematised and usually fantastic and illogical. They are said to be changeable but I frequently find the same delusions retained for prolonged periods. They may be of persecution, grandeur, depression, or of influence. The most notable feature is the lack of emotional tone concerning them and the marked incongruity between the delusional belief and behaviour which allows, for instance, the man claiming high titles and degrees to perform menial tasks in the ward. The hallucinations are usually aural and the voices are frequently annoying, accusing or threatening. These patients also show the general schizophrenic symptoms of incoherence of thought, detachment and withdrawal from reality with impaired judgment and insight.

Prior to the onset of this type, many patients have shown no gross mental abnormality and have good school and work records. At the beginning there may be short remissions and relapses but the general course is a gradual deterioration to eventual dementia.

Aetiology

There are two main schools of thought in the controversial question of the causation of schizophrenia. One group considers that the defect is primarily psychological and the other that it is essentially organic.

Adolph Meyer considered that the disease is due to a failure in adaptation of the individual to the stresses of life. He believed that it occurs in the schizoid personality whose characteristics are hypersensitiveness, instability, poor initiative, lack of aggressiveness, and a tendency to daydream and to seek refuge in evasions rather than face the difficulties of life. In such a person, any environmental stress against which he cannot contend may result in a withdrawal from reality and the symptoms of schizophrenia. Hoch and Jung have each expressed similar views.

The organic viewpoint has been put forward by various authors and mainly concerns theories of abnormality in the functioning of the brain cells or the endocrine glands. Kraepelin believed that dementia praecox was due to auto-intoxication from a disordered secretion of the sex glands which acted on the brain cells. Mott supported this view. He

found post-mortem changes in the cortical nerve cells which he considered were indicative of either suppressed or diminished function and evidence of a diminution of the oxidation processes. He also described evidence of a disordered action in the whole endocrine system with particular reference to the gonads, adrenal medulla and pituitary gland. He claimed that, in the majority of schizophrenics, there was a complete arrest of spermatogenesis with regressive atrophy of the cells of the testicular tubules, and, in female patients, he described changes in the ovaries. Lewis claimed that schizophrenics suffer from a state of aplasia of the circulatory system and an atrophy of the sex glands, and Gibbs reported that a large number of his cases had abnormal hair distribution and hair texture. A recent research in which biopsy specimens were taken from the testes of schizophrenics, supported Mott's findings. However, Mott's claims were disproved by Morse's investigations and by subsequent workers, and it is now generally held that, it has not yet been proved that there is any specific cellular pathology in the brain in schizophrenia and that, while the evidence of frequent abnormal endocrine function is very suggestive, no definite causal relationship between the abnormal

function and schizophrenia has been proved.

Hereditary predisposition does play a part. Only 3 - 5% of the siblings and parents of schizophrenic patients have an outright schizophrenic illness, but the liability to the illness is 14.7% in dizygotic twins and 85.8% in monozygotic twins. Kallmann reports that the predisposition to schizophrenia, that is, the ability to respond to certain stimuli with a schizophrenic type of reaction, depends on the presence of a specific genetic factor which is probably recessive and autosomal.⁽¹⁸⁾

Hill states that the natural periodic short remissions and post-mortem findings seem to show that the brain cells are neither destroyed nor even harmed, but are deprived of some substance which is necessary for their function. In the remission, for some reason, the capillary walls suddenly become more permeable to the substance necessary for the functional activity of the brain cells.⁽¹²⁾

Stockings considers that schizophrenia is a manifestation of a single organic cerebral disorder consisting of a profound derangement of the oxygen-glucose metabolism of the brain cells which affects principally the centres concerned with the higher thought processes, affective and intellectual functions.

This condition, at first reversible, may if long continued lead to permanent cerebral damage. He further postulates a "dysoxic" or oxygen disordered type and a "dysglycolytic" or glucose disordered type. (41)

Many believe that schizophrenia is due to a functional disorder in the hypothalamic region. Morrow quotes the work of Finkelman and Stephens who found that schizophrenics averaged a heat loss of 0.8°F . during exposure to cold compared with a loss of 0.2°F . in controls, and that the normal reactive hyperaemia of the skin after exposure was missing in schizophrenic patients. They pointed out the similarity of these findings to those seen in animals with hypothalamic lesions and therefore suggested a physiological disturbance in that region in schizophrenia. (27) Hoskins states that Ransom believed that the secret to the causation of the illness was most likely to be found in the hypothalamus and cites the work of Brookhart and his collaborators of the Ransom's Institute. They showed that, by hypothalamic puncture, it was possible to eliminate sexual behaviour and hence reproductive capacity from guinea pigs of both sexes while the reproductive apparatus, endocrine and otherwise, remained microscopically normal. (13)

Hoskins, in a summary of the abnormal biological findings in schizophrenia, stresses the following points:-

1. A relative deficiency of catalytic iron has been found. He regards this as of special importance in view of the various evidence of deficient oxygen uptake in the psychoses. He further stresses the importance of all the catalytic systems of the body and states that almost any symptomatology in schizophrenia might be accounted for by defects in the enzyme systems.
2. His own uncompleted studies point towards rather marked deficits in the tissue vitamin stores and he underlines the important role played by the vitamins in the enzyme systems of the body.
3. He emphasises the influence of the various amino-acids on cell processes and functions. In some of the lower organisms, the maturing processes and those leading to cell specialization are determined by d-glutamic acid and l-proline. As immaturity is an outstanding feature of schizophrenia, he considers that the immaturity, and hence the psychosis itself, might ultimately prove to be fundamentally due to an aberration in amino-acid metabolism.
4. He mentions the evidence of endocrine deficiencies

in schizophrenia and states that the defect is not necessarily one of levels of hormone production but might be due to inadequate reactivity to the hormones. He considers that the hormone defect might be the basis for the schizophrenic immaturity and gives in support of this theory the evidence that thyroid deficiency can hold an organism, such as the tadpole, in an immature state of development for long periods, that early deprivation of the pituitary prevents maturation, and that the sex hormone has an important influence on the maturation of an adult behaviour pattern in puppies.

Hoskins concludes that schizophrenia represents an end result of a generalised failure of adaptation that arises from defective evolution of the maturity processes, and that the accessory symptoms can be regarded as constituting secondary adaptations to the difficulties arising out of the primary defect. As an alternative theory, he states that the psychosis itself or the postulated immaturity may be due to a specific pathology which might exist in abnormalities of one or more enzyme systems of the brain, in an aberrant amino-acid metabolism or in a disorder in the hypothalamic region.⁽¹³⁾

Finally it can be mentioned that schizophrenia may be due to a disorder in glucose metabolism in the

brain resulting in the production of a toxic breakdown substance akin to mescaline or lysergic acid.

The wide divergence of these various theories on the aetiology of schizophrenia and the absence of any positive evidence towards a definite pathology, brings home our lack of knowledge on the disease and emphasises the difficulty of the whole problem. This is especially apparent in the field of treatment and it accounts for the numerous empirical methods which have been tried, the majority with but limited success.

INSULIN COMA TREATMENT AND CONVULSION THERAPY

INSULIN COMA TREATMENT

Technique

Soluble insulin is injected intramuscularly at 7.0 a.m. each morning from Mondays to Fridays. Saturdays and Sundays are rest days. The patient has had no food since supper on the previous evening. The commencing dose of insulin is 20 units, which is increased on subsequent days by 20 units until coma occurs. If the dosage reaches 200 units without producing coma, the method of "swinging" is used to overcome the insulin resistance. The dose is dropped to the initial dose, the next day 100 units is given, and on the third day 200 units. This procedure is repeated for several days and if a coma is not produced the patient is given an electrically induced convulsion whilst in hypoglycaemia in an attempt to break down the following day's insulin resistance. By these methods it is seldom necessary now to exceed 200 units to induce coma, whereas previously I often had to continue the increase to 400 units or more. The initial coma dose is kept constant for one week and is then reduced by 10 units daily until the minimum satisfactory coma dose has been found. This is maintained for seven to ten treatments after which

the dose is again diminished by 10 units to see if any further reductions are possible in the minimum coma dose. I find that, in the majority of patients, insulin sensitivity increases during treatment, and, if this method of reducing the dosage is neglected, the danger of irreversible comas is much increased.

The treatment room must be kept at a warm, even temperature as the patients perspire profusely. Beds supplied with removable padded sides are used. The patient's temperature, pulse and respiration rate are taken before the insulin is injected, and again in the evenings. The pulse and respiration rates are recorded half hourly during treatment. On this daily treatment chart are also shown the onset and amount of sweating, the patient's colour, restlessness, state of consciousness, the onset of sopor and coma, and remarks on general behaviour and neurological and other abnormalities in sopor and coma. The insulin dosage and amount of glucose necessary for interruption are included on this chart. In addition to this individual record, a general treatment chart is kept which contains the names of all the patients under treatment, the times of onset of sopor and coma, the time when each patient is due to be interrupted, the actual time of interruption and the time of his

awakening. Finally an insulin dosage book is necessary for entering the following day's dose of insulin.

There is much difference of opinion about the use of the word "coma". Some workers use it to mean loss of consciousness and others say it is not present until the corneal reflex has disappeared and the plantars show an extensor response. I have used the criteria of coma given by Kupperts as reported by Sargant and Slater. He differentiates the stages of loss of consciousness into sopor or precoma and true coma. The onset of sopor is indicated by the loss of a normal response to speech and impairment of orientation. Responses are confused. The onset of coma is shown by the loss of all purposive responses even on careful testing. There are no responses from visual, auditory or tactile stimuli. Painful stimuli may produce some movements but these are not directed towards removing the stimulus. Tests should include raising and dropping the patient's arm, passing a hand quickly before his eyes, and pressure on the supra orbital nerve.(37)

If no sopor has occurred by 10 a.m. hypoglycaemia is terminated by giving the patient one and a half pints of 33.1/3% sugared tea to drink. Sopor

is allowed to continue for one and a half hours before being interrupted if no coma supervenes. When the patient begins to go into coma, the coma is increased from five minutes on the first day to ten minutes on the second, twenty minutes on the third, and then thirty minutes on subsequent days. In sopor and coma, interruption is carried out by a nasal tube. After withdrawing gastric juice and testing for acidity with litmus paper to ensure that the tube is in the stomach, a pint and a half of warmed 33.1/3% glucose solution is poured in. If the patient is not awake twenty minutes after the usual feed, intravenous 33.1/3% glucose is given. 40 ccs is generally sufficient to rouse the patient. As soon as possible after awakening, the patient has a breakfast of high caloric value.

At the onset of coma an airway is inserted and before interruption, gr.1/100 of atropine is injected to facilitate absorption of the feed and diminish the risk of vomiting.

The following complications are taken as calling for an immediate intravenous interruption of treatment:-

1. Evidence of circulatory failure shown by cyanosis, poor peripheral circulation, a persistently irregular pulse, or a pulse rate of above 120 or below 50 in coma.

2. Laryngeal stridor persisting after insertion of the air-way.
3. Evidence of respiratory distress.
4. Vomiting either before or after nasal interruption.
5. Epileptic fits occurring in coma or late sopor.
Fits in the earlier stages of hypoglycaemia indicate interruption by the oral or nasal method.
6. Persistent undue restless leading to exhaustion.
7. Waves of extensor tonus in coma in the presence of a free air-passage.
8. Generalised tremor when the patient is not cold.

The most important and serious complication of insulin coma treatment is the occurrence of a prolonged or irreversible coma. It occurs most often when the hypoglycaemia is unduly prolonged or is allowed to become too deep. It is generally agreed that it is not simply a state of hypoglycaemia and various theories as to cause have been suggested such as acidosis, vascular impairment, hyperinsulinism, and exhaustion of the nerve cells which consequently are unable to utilize glucose even though there is an adequate amount of it present in the blood stream. Severe cases may involve days of unconsciousness, while, in milder ones, wakening is delayed until the late afternoon. Prompt treatment is essential and I adopt the following procedure. If a patient does not

respond to the usual termination of the hypoglycaemia and does not waken within five to ten minutes after the injection of intravenous glucose, 100 ccs. of a 33.1/3% glucose solution is given intravenously and, if the patient does not show signs of awakening, the injection is continued up to 250 ccs. At the same time 2 ccs. of coramine is given. Hot water bottles are applied and a 5% mixture of carbon dioxide in oxygen is used. Should the patient come out of coma and become restless and excited, gr. $\frac{1}{4}$ of morphia and gr.1/100 of hyoscine is injected subcutaneously. If he remains in coma for an hour after the last injection, a further 250 ccs. of 33.1/3% glucose solution is given intravenously, and then 500 ccs. of 5% glucose in saline is administered by a slow intravenous drip. At the same time a further gr.1/100 of atropine is injected, the stomach contents are drawn off by a nasal tube and one and a half pints of 33.1/3% glucose solution is run into the stomach. This procedure of intravenous glucose in saline, an injection of coramine and tube feeding is repeated every four hours until the patient is awake. If there is no response in twelve hours, blood transfusions are given.

The doctor should be present in the insulin treatment unit throughout the period of coma and

awakening. Before coma, one nurse is necessary for every three patients and during coma one nurse for every two patients. It is best to have the same team throughout treatment, and it is most important that the sister or nurse in charge should be highly trained and experienced in this work.

Treatment is continued for fifty to sixty comas although, if it is going to be successful, an improvement is usually apparent after the first few comas, or even before the coma stage is reached. The benefit at first may only occur for an hour or two after treatment, gradually becoming longer until the improvement is maintained. A prominent feature is a marked improvement in rapport, sociability and friendliness occurring after wakening, and advantage should be taken of this for general supportive psychotherapeutic measures.

Psychotherapy, indeed, is a most important adjunct to the treatment and many workers maintain that it is more beneficial than the actual chemical effects of the insulin. It should include repeated explanations and reassurances, a discussion of the patient's problems in a general broad way, and when the time comes for his discharge from hospital assistance and advice on his rehabilitation and fears

about facing the outside world. The treatment situation is actually a type of group psychotherapy, and there is a strong feeling of comradeship and sympathy among the patients undergoing the treatment. Advantage should be taken of this. In the afternoons and evenings arrangements are made for them to take part in occupational therapy, to go on walks and other outings, and to participate in social functions as a group. They should be in charge of a nurse who carries a supply of glucose tablets and who is experienced in detecting the early signs of hypoglycaemia.

The most important contra-indications to insulin coma therapy are cardio-vascular disease, active pulmonary tuberculosis, diseases of the kidneys, liver, pancreas, thyroid or adrenal glands and diabetes.

Variations in Technique.

Sakel varies his terminations according to different psychotic manifestations of schizophrenia. In the paranoid forms he uses the classical deep coma method. For stuporose catatonic patients, the insulin dose is raised until an activation of the stupor is achieved. This usually occurs in the phase of building up to the coma dosage. At this stage the hypoglycaemia

is terminated. After the stupor is broken through, the patient receives the usual coma treatment. Patients showing catatonic excitement are given only sufficient insulin to quieten them and hypoglycaemia is terminated before they reach a coma dosage. It is, however, generally agreed that these rules for termination have not been sufficiently established, and I agree with the majority of other workers that states of catatonic stupor and excitement are best treated by convulsive therapy before or during insulin coma treatment.

Insulin, according to Sakel's original method, is given six times a week with one rest day. This procedure is followed by many therapists. Sargent and Slater give full treatment on five days, half doses of insulin on the sixth day and a rest day on the seventh. (37)

There is some controversy over the ideal duration of treatment, but most workers apply fifty to sixty comas before discontinuing insulin. The majority of patients who are going to respond show signs of improvement early in the treatment, often before coma dosage is reached, but even in these cases who recover after a few comas it is wiser to continue until a full course of 50 comas has been given as one feels that this lessens the danger of a relapse.

Experiments have been made in the intravenous use of insulin but it is generally agreed that this has no great advantage over the intramuscular technique. In addition, it has been found that patients develop late shock more readily, that allergic reactions occur more frequently and convulsions more often in coma with intravenous insulin. With patients who are very restless and excited in the early stages of hypoglycaemia it is, however, useful to give the insulin in divided dosage, one injection intramuscularly at 7 a.m. and the other intravenously one to two hours later.

Kraulis favours the protracted form of coma treatment, prolonging a state of deep coma for twelve hours and upwards, at the same time feeding small amounts of sugar either two hourly by a nasal tube or by a continuous intravenous drip of 5% glucose in saline. However, the majority are opposed to this method mainly on account of its increased mortality rate and because of the danger of permanent brain damage.

Hill gives small doses of insulin and histamine and claims that his percentage of successes is about the same as with insulin shock therapy and even that his technique has far more effect in chronic cases

than insulin.⁽¹²⁾ However, his series of cases is very small and his findings have not received subsequent support.

CONVULSION THERAPY

Various machines are available for electroconvulsive therapy (ECT) but all are based essentially on Bini's original design. Alternating current from electric light circuits having a frequency of 50 cycles is used. A volt meter regulates the voltage to be applied and most machines have a time measure graded in fractions of a second. The original apparatus had a second low-voltage current circuit for preliminary measurement of the resistance of the patient's head, but this has now been dispensed with as it has been found that there is no true correlation between the resistance reading and the convulsion threshold.⁽¹⁰⁾

Most operators adjust the setting beginning with, for example, 100 volts for 0.2 seconds until a satisfactory convulsion dose is reached. I give 130 volts for one second with all co-operative patients, as this produces a fit in almost every instance thereby cutting out the unpleasantness of an abortive response. I also consider that this dosage diminishes the risk of fracture. Where the patient is particularly tense or actively resistive, I use a

smaller dose sufficient to induce a stun which ensures relaxation and I then follow it with the convulsion dosage.

Cardiazol (pentamethylenetetrazol) is injected intravenously as rapidly as possible in a 10% solution using a wide bore needle. The initial dose is 3-5 ccs. If no convulsion results within one minute, another dose 1 cc. greater than the original dose is immediately given. If this also fails to evoke a seizure, the dosage is increased by 1 cc. on the following morning, and so on until a satisfactory convulsive dosage is found. The fatal dose is between 25 and 30 ccs.⁽²⁰⁾ In Neustatter's opinion, the maximum dose should not be above 12-15 ccs. depending on the weight of the patient.⁽²⁸⁾

The preparation and the control of the patient during the fit is the same with both ECT and Cardiazol induced seizures. No food is given for three hours. Before treatment the patient receives an injection of gr. 1/100 of atropine and he empties his bladder and, if necessary, his bowels. Dentures, spectacles, hairpins and other metal objects should be removed. The clothing is loosened. A rubber gag covered with lint is inserted in the mouth to prevent tongue biting. The patient lies on a firm surface such as a hard

mattress with a board underneath it - I use a stretcher trolley which has a metal top covered by a thin mattress -, a firm pillow is placed in the small of the back and a small pillow underneath the head. With ECT, the electrodes are covered by pads of lint and these are soaked in 30% saline. The temples are cleaned and left moist with a strong saline in spirit solution immediately before the electrodes are applied. In order to prevent fractures and dislocations, the technique of holding the patient during the seizure is of the utmost importance. On no account must undue force be applied. A nurse at the head holds the mouth gag in place and the patient's chin firmly on the gag. This prevents a possible dislocation of the jaw. The arms should be held into the sides, a nurse's hands being placed round the deltoids so as to hold the shoulders in. The legs should be straight, lightly held together at the ankles, but once the convulsion starts no force should be used either to prevent the extension of the legs or to counteract the clonic movements.

With ECT the response is immediate. There may be a subshock of "stun" with a momentary loss of consciousness and possibly a degree of cyanosis for a few seconds; or an abortive fit or petit mal; or a

major convulsion of a typically epileptic type with a tonic phase lasting approximately ten seconds and a clonic phase lasting about thirty seconds. This is followed by a period of coma of short duration from which the patient awakens confused and drowsy. This state lasts from five to thirty or more minutes.

With cardiazol, the convulsion occurs three to thirty seconds after the injection during which time the patient does not lose consciousness, and he experiences an extremely unpleasant sensation of fear and anxiety. He becomes pale and rigid, and makes a few clonic movements following which there is a cry, opening of the mouth, loss of consciousness and then a tonic spasm of the whole musculature for about ten seconds. This is followed by the clonic part of the convulsion, lasting forty to forty-five seconds. The paroxysm ends with a period of apnoea with marked cyanosis for several seconds, and this passes into a comatose sleep of five to ten minutes' duration. There is then a period of confusion lasting half an hour or longer. If no convulsion takes place with cardiazol, the patient often experiences great discomfort, anxiety and restlessness which may continue for several hours.

With ECT there is subsequent amnesia for the convulsion and also for a varying time prior to the

treatment. When cardiazol is used, the patient has an amnesia for the fit but, unfortunately, he remembers the deadly fear which he experienced between injection and convulsion. This, and the unpleasant discomfort when no fit results, are the most unpleasant features of cardiazol treatment and they frequently lead to the patient's refusal to continue therapy. They are among the most valid reasons for the superiority of the electric method of producing therapeutic convulsions. (17)

Other advantages of ECT over cardiazol are summarised by Jessner and Ryan⁽¹⁵⁾ as follows:-

1. There is rarely prolonged psychomotor excitement as sometimes occurs after the cardiazol convulsion, and no vomiting.
2. There is no difficulty with veins. Cardiazol readily produces thrombosis at the site of the injection.
3. The fit is less violent with ECT and the degree and frequency of cardiac complications are much less.
4. Economy.
5. ECT can be used for outpatient treatment.

Shepley and McGregor found that cases which previously failed to respond to cardiazol equally

showed no response to ECT, and that cases previously showing response to cardiazol equally appeared to respond to ECT.⁽³⁸⁾ It would therefore seem that, therapeutically, cardiazol has no advantages over ECT and, on account of the drawbacks mentioned above, it has now been largely supplanted by the latter treatment.

The frequency and duration of convulsive treatment depends largely on the psychiatric condition. I consider that Sargant and Slater are too conservative about the spacing of treatment.⁽³⁷⁾ I agree with Kalinowsky and Hoch that two or three convulsions a day should be given to acutely disturbed patients who are threatened by the danger of psychotic exhaustion.⁽¹⁷⁾ I give stuporose cases treatment daily until they respond. Depressive illnesses usually only require two convulsions weekly. In other conditions it is generally necessary to apply treatment three times a week. However, I am of the opinion that it is better to avoid confusional states, and, if these are produced, ECT should be spaced at a longer interval for that patient. Many workers realized early that a frequent reason for the failure of convulsive therapy in schizophrenia was the premature discontinuation of treatment because of the disappearance of all

psychotic symptoms after a few convulsions.

Kalinowsky and Hoch quote Gerhardt as having found that the reinstitution of treatment after a relapse did not lead to the same favourable results as a long uninterrupted course of treatment, and Fröhn as showing that the majority of his relapses belonged to the group of remissions after treatment of short duration.⁽¹⁷⁾ In schizophrenia, it is therefore necessary to continue until twenty to thirty convulsions have been given even although the patient appears well after the first few treatments.

The complications of convulsive therapy are remarkably few. The most frequent are fractures and dislocations (1.1% incidence), particularly compressed fractures of the thoracic vertebrae, the great majority of which are not serious and necessitate little in the way of treatment. Memory defects are common and are usually slight and transient. Extreme depression of the respiratory centre sometimes occurs and calls for prolonged artificial respiration. Other complications have been reported but are extremely rare.

Contra-indications may be summarised as acute bodily diseases, chronic diseases of the heart, blood vessels, lungs or kidneys, diseases of bones or joints,

exophthalmic goitre and patients who have been confined to bed for more than one year. Practically all these can be overcome by giving treatment modified with scoline, the technique of which is as follows:-

The patient is prepared in the usual way. An injection of 5% sodium pentothal calculated by the formula $\frac{\text{Body Weight in lbs.}}{10 \times 3}$ ccs. is then given intravenously immediately followed by scoline $\frac{\text{Body Weight in lbs.}}{100 \times 2}$ ccs. injected through the same needle. The lungs are then inflated with oxygen for about a minute and the convulsion is then induced. It consists of gentle muscular twitchings. Afterwards, the lungs are again inflated with oxygen until normal breathing is reinstituted. Scoline is succinylcholine chloride dehydrate, a synthetic muscle relaxant of short action. It produces a paralysis lasting from two to six minutes. Very occasionally recovery from scoline is delayed and it is then necessary to apply gentle artificial respiration until the paralysis passes off. It has to be used sparingly in patients suffering from liver disease and malnutrition. With scoline-modified treatment, there are few contra-indications to ECT.

COMBINED TREATMENT

A combination of insulin coma treatment and convulsive therapy can be given in many ways. A course of ECT may be followed by insulin treatment or vice versa, convulsions may be administered on insulin rest days or they may be given during the various stages of hypoglycaemia. In the latter instance, I give ECT after the patient has been in coma for fifteen to twenty minutes, and immediately follow it with the intravenous method of interruption. Some other workers, however, prefer to administer convulsive therapy in the early stages of hypoglycaemia. I think it is important that one does not confine oneself rigidly to any of these methods. They are all of value and whichever one is used depends on the individual patient.

SELECTION OF CASES AND RESULTS

Insulin coma treatment was introduced for the cure of schizophrenia, and it is for this illness that it is now used. Experience has shown that certain cases are unlikely to respond and, in view of the limited facilities for applying this treatment, it is important that the most favourable cases should be selected. All workers are agreed that the duration of

the illness is of primary importance, that the best prognosis occurs when the duration is less than eighteen months, and that practically no remissions can be expected when it is over three years. Strecker found a complete and incomplete remission rate of about 60% in the first year, 30% in the second year and that, in the third and subsequent years, the percentage was again progressively halved.⁽⁴²⁾

Stockings, using insulin coma therapy and ECT for schizophrenia in the Army, where the cases are nearly all of recent and acute onset, claimed a complete remission rate of 70%, a definite improvement in 15%, and failure in 15%.⁽⁴¹⁾ Garmany's results are similar.⁽⁸⁾ My own findings during seven years of Naval psychiatry support this. For obvious reasons early signs of mental abnormality much more readily come to notice than in civilian life. Of 112 cases of schizophrenia which I treated with insulin coma - some with ECT in addition - less than 10% had to be certified and transferred to civilian mental hospitals, while over 90% became well enough to be invalided from the Service to their own homes. Of course this only refers to immediate results. Due to various difficulties, the main one being that these homes were scattered widely over the whole country, it was

impossible to carry out a follow-up study on the patients. I felt that several on leaving hospital would relapse, but even one of the worst of those had remained well and usefully employed, earning a good wage five years after being invalided from the Navy.

A stable pre-psychotic personality is next in favour of a good prognosis. An open and socially well-adjusted person reacts better than one who has always been shy, introspective and odd. Another helpful feature is a sudden onset to the illness as this brings the condition sooner to attention and to treatment. Unfortunately, however, it often turns out that the so called sudden onset is merely an exacerbation of a more insidious process. Sargent and Slater quote Freudenberg's findings that the body physique is of some importance and that the pyknic or athletic habitus is more favourable than the asthenic or the dysplastic.⁽³⁷⁾ Schizophrenic illnesses in which there are definite precipitating factors are said to have a good outlook.

Gralnick⁽⁹⁾ believes that the type of schizophrenia is not a significant factor but most workers consider that it is of some importance, although opinions differ. Stockings⁽⁴¹⁾ thinks that the simple type is probably, from the beginning, an

example of a purely degenerative form of brain disease and most are agreed that this type has the worst prognosis. My own view is that the other three types should be given the benefit of insulin treatment if possible, depending, when selection is necessary, on the other prognostic factors mainly on the duration of the illness. It is generally agreed that the paranoid form shows the best response but Kalinowsky and Hoch quote Müller as stressing that this is only if it is treated in the first year of the illness.⁽¹⁷⁾ Strecker states that catatonic excitement is more responsive to insulin while catatonic stupor does better with convulsive therapy.⁽⁴²⁾ I agree with Kalinowsky and Hoch that the combined insulin and convulsive treatment should be used in the stuporose catatonic patients, and I consider that this method should also be used in cases of catatonic excitement. Stockings⁽⁴¹⁾ writes that hebephrenics do well with insulin if it is given early enough. This is contrary to the general opinion which is that the prognosis in this type is poor.

Mayer Gross gives a good summary for the indications for using the combined method of treatment.

1. Preparative - to achieve the co-operation of resistive, negativistic, restless, excited and

stuporose patients and those who refuse food or eat inadequately.

2. Provocative - to break down insulin resistive patients.
3. For combating affective admixtures of the schizophrenic clinical picture; depression, listlessness, drowsiness, general moodiness, manic features.
4. For speeding up recovery in those patients who, after initial improvement, remain on the same level for three to four weeks without further progress. (23)

The early claims for the success of insulin coma treatment were very high. Mason Smith in 1937 wrote that reports of European clinics showed that 75% of patients ill less than six months were completely recovered as a result of the treatment, and that more than 69% of those ill less than one and a half years became productive, socialised individuals able to resume work.⁽⁴⁰⁾ Ellery in 1937 quoted Müller's Swiss figures as 76% full remissions if the illness was under six months' duration, and 68% if the illness was under eighteen months.⁽⁴⁾ The results collected by the British Psychiatric Insulin Society and quoted by James, Freudenberg and Cannon in 1938

showed a complete and social remission of 86% where the illness was less than six months, and of 79% where it was less than eighteen months.⁽¹⁴⁾ More careful follow-up studies have not supported these findings. Gralnick writes that insulin is of definite value but by no means as effective as early enthusiastic reports led one to believe.⁽⁹⁾ Mayer Gross states that most workers agree with Müller who now reports that, in patients whose illness has lasted not longer than one year, the numbers of remissions in schizophrenia can be doubled. He adds that insulin coma treatment neither provokes nor prevents relapses and that the remissions after it are neither shorter nor longer than spontaneous remissions.⁽²³⁾ Finiefs's⁽⁷⁾ findings with a thousand cases of schizophrenia were as follows:-

1. 446 patients received no special treatment. 34.5% discharged with an average stay in hospital of 8.3 months.
5 years and over. Of those discharged, 40% kept well and 40% relapsed
2. 82 patients given convulsive therapy - 39% discharged.
3. 103 patients given the combined method - 54.3% discharged.

4. 378 patients given insulin coma therapy - 54.2% discharged, with an average stay in hospital of 5 months.

5 years and over. Of those discharged 62% kept well, 30% relapsed.

Bond and Shirley write that of 309 schizophrenic patients treated over a ten year period, 48.8% were recovered or much improved at the end of treatment, 43% at the end of the first year, and 37% at the end of five years. This compares with a recovery-much improved rate of 16% for control cases under hospital treatment without insulin or other shock treatment.⁽¹⁾

The mortality for insulin coma treatment is less than 1%.

Electro-convulsive therapy is undisputedly the treatment of choice for depressive and manic illnesses. There can be no doubt that it is extremely valuable as a symptomatic maintenance treatment in chronic schizophrenia, and it has revolutionalised the atmosphere of the chronic mental hospital ward. No longer does one see the groups of catatonic patients standing in bizarre attitudes or slumped in a semi-stuporose condition in chairs. It has almost abolished the need for prolonged tube feeding and for

restraint. It has diminished the burden of the nursing staff almost beyond belief.

The use of convulsive therapy alone as a treatment in early schizophrenia is much more controversial. Again the extravagant results of the earlier workers have not been substantiated. Von Meduna claimed a remission rate of 80% in early cases before the onset of permanent symptoms of mental deterioration. Jessner and Ryan quote Von Meduna's later figures when, with Friedman, he surveyed 3,000 cases of schizophrenia of under eighteen month's duration treated with cardiazol convulsive therapy which produced a remission rate of 52%, and a great improvement in an additional 20%. They add that these figures have been supported by other workers and cite Kennedy as saying that there seems little doubt that convulsion therapy has given considerably better results than the spontaneous remission rate for comparable case material. Jessner and Ryan conclude, however, that in schizophrenia it is not so effective as insulin.⁽¹⁵⁾ Mayer Gross considers that convulsive therapy cannot equal the results of insulin as to completeness and permanency of recovery in schizophrenia.⁽²³⁾ Rees is of the same opinion.⁽³²⁾ Cook, in the early days of the treatment, pointed out

that, if therapy was interrupted before completion, relapse was common. His view was that the remission rate for both convulsion and insulin coma treatments was at least twice as great as that to be expected from spontaneous remission and that, in addition, recovery was more rapid.⁽³⁾ More recently Fergus writes that ECT is definitely less satisfactory and relapses are more frequent when an insufficient number of treatments is given. With overactive, disturbed and markedly regressed patients, he gives three treatments on the first day, two on the second, one on the third and then three a week. Others are given three a week from the start. The majority receive three a week to at least thirty treatments. If there is marked organic confusion, treatment is immediately reduced.⁽⁶⁾ Wortis states that, if ECT is used in schizophrenia, the consensus of opinion is that treatment must be prolonged and intensive with at least sixteen to twenty treatments.⁽⁴⁵⁾ Kalinowsky and Hoch hold similar views. They remark that even although the question of whether insulin or ECT is superior in schizophrenia remains undecided in view of contrary statements and lack of comparative studies, the value of ECT in this condition is sufficiently answered. They quote Cook's survey of

all opinions and conclusions that between 55% and 60% of patients treated with convulsions in the first year of their illness may be expected to remit sufficiently to take their former place in society.⁽¹⁷⁾ Another group of workers consider that insulin is not sufficient as a sole form of treatment in schizophrenia. They found that ECT was effective in 15% of patients who failed to respond to insulin coma and that insulin coma was effective in 17% who failed to respond to ECT.⁽²⁹⁾

In 1938, Strecker concluded a paper as follows:-
"The results obtained with insulin and with convulsive therapy in the first years of illness show that they constitute a decided advance in the treatment of schizophrenia. It would be a mistake to neglect either method or to practise one to the exclusion of the other."⁽⁴²⁾ Little more can be added to this statement today. Although neither treatment nor both is a specific for schizophrenia, it can, I feel, now be considered proved that they give results much better than could be expected for spontaneous remissions.

THEORIES AS TO MODE OF ACTION

It is not known how insulin and the convulsion treatments exert their beneficial effect. No one theory has found universal acceptance, and it is only

possible to mention a few of the numerous suggestions that have been made. It is, however, generally agreed that both treatments have a similar mode of action.

Some workers believe that the somatic part of the treatment is only incidental and that the effect on the patient is essentially psychotherapeutic. Kalinowsky and Hoch quote Meier's view that the main effect is due to the more intimate contacts between the patient and the doctor and nurses, and Schatner's opinion that with the patient helpless and dependent, the physician becomes a mother surrogate, the patient establishes a better transference and therefore becomes more therapeutically approachable.⁽¹⁷⁾ I do not consider that one's general findings support this. With ECT, the patient requires little attention and outpatient treatment has given particularly good results in certain cases. Other methods of treatment, in which the patient receives much care, have not given similar good results.

Schilder and other workers stress the importance of the feeling of impending death, victory over it and the sensation of rebirth in all shock treatments.⁽³⁵⁾ Bychowski believes that, in psychotic patients, there is a struggle between the repressed normal ego and its pathological substitute and that hypoglycaemia

eliminates the pathological ego and its counter cathexis, thereby allowing the repressed ego and its repressed (or denied) reality to enter their rights.⁽²⁾ However, a conscious feeling of impending death is, in the opinion of most investigators, an uncommon feature of insulin coma and electro-convulsive therapies and, if these theories were valid, one would expect similar good results with such procedures as continuous sleep treatment and anaesthesia. Bychowski does not explain how hypoglycaemia eliminates the pathological ego. Kalinowsky and Hoch ask why it is that all the mediaeval tortures inflicted on the insane failed to produce impressive therapeutic results, especially when they were inflicted on a conscious person in whom the so-called emotional shock or death threat must have been much more intense.⁽¹⁷⁾

Others consider that the patient regards the treatment as a punishment administered by the doctor who is a father figure and that, after treatment which expiates his sins and sense of guilt, he can resume his normal position in life. But the majority of patients do not regard their treatment as a punishment or as anything fearsome, and this theory again does not explain why insulin and convulsive therapies should succeed where other types of treatment, such as

fever therapy and sleep treatment and the mediaeval tortures and punishments, failed.

Von Meduna's theoretical basis for the introduction of convulsive therapy that schizophrenia and epilepsy were antagonistic to each other has not received subsequent support, and evidence has, in fact, disproved it.

It has been suggested that these treatments act by destroying brain tissue and this view has received some support from the more recent successes of pre-frontal leucotomy in some cases of schizophrenia. But it has not been proved that histological damage results from insulin or convulsive therapies unless a prolonged coma has occurred, and clinically the treatments do not cause any permanent intellectual deterioration. Kalinowsky and Hoch mention Stief's theory that both forms of therapy produce spasms in the cerebral capillaries which eliminate diseased nerve cells, thereby bringing about the desired therapeutic results. They rightly point out the main objection to this view as the fact that in schizophrenia it has not been conclusively shown that there is histological evidence of any brain cell defect.⁽¹⁷⁾

Hill's opinion is that the abnormal cerebral function in schizophrenia is due to a pathological barrier to the normal passage of plasma situated in

the endothelial cells of the capillaries. He considers that insulin acts by liberating histamine which makes the endothelial cells of the capillaries more permeable to normal plasma, thus enabling the nerve cells once more to obtain the substances requisite for their normal function.⁽¹²⁾ His claims for the success of his treatment with small doses of insulin and histamine have not, however, been supported.

The effects of insulin and convulsive treatments have been attributed to cerebral anoxaemia, longer lasting in the former and of short duration in the latter. Some believe that this has a sedative effect and allows the brain to restart a normal rhythm of activity, while others believe that the benefit is due to a compensatory overactivity which follows on the period of anoxaemia. There is a further view that the anoxaemia causes a reflex stimulation of the sympathetic system. Changes in oxidation have been demonstrated during and after shock treatments, but if this was the entire answer to the cause of the improvement one would expect beneficial results from methods which simply limit the oxygen consumption to the schizophrenic patient, and this has not been found to be the case.

The food of the brain is carbohydrate, and on its metabolism depends cerebral function. There is no doubt that insulin coma treatment profoundly disturbs carbohydrate metabolism which is also upset to a lesser extent by convulsive therapy. Numerous investigators consider that this disturbance results in a stimulation of the metabolism of the central nervous system with a consequent improvement in function. The mechanisms of this stimulation is more difficult to explain. A high carbohydrate diet or the giving of large amounts of sugar either parentally or intravenously has no effect in schizophrenia. Parfitt remarks that findings suggest that the sugar level is controlled by hypothalamic centres.⁽³⁰⁾ Probably the majority opinion at the present day is that the benefits of both insulin and convulsive therapies are due to their effects on diencephalic mechanisms. Rapid changes in weight, sleep, appetite and the menstrual cycle are produced and changes in water metabolism and autonomic function have been demonstrated. Harris writes that it is well known that cardiazol and electro-convulsive therapy cause anterior pituitary secretion in rabbits, probably by exciting some part of the hypothalamus.^(43a) Reiss states that ECT apparently stimulates the production of all the hormones from the anterior pituitary, and the final

endocrinological change is a resultant of the antagonisms between the different quantities of hormones mobilised.^(43b) Various workers stress different anterior pituitary hormones as playing the most important part in the therapeutic effect. Wortis quotes Gellhorn's view that all shock treatments operate by stimulating the hypothalamic - sympathetic - adrenal system. In the case of insulin, the hypothalamic stimulation is a release phenomenon; in convulsive therapy, direct stimulation is involved.⁽⁴⁷⁾ Robie also believes that ECT acts directly upon the pituitary gland and, via electrochemical processes, a change is produced in pituitary biochemistry resulting naturally in changes in the thyroids, adrenals, gonads and other glands of internal secretion, these changes being presumably tonic in nature.⁽³³⁾ Other investigators, including those of the Pavlov Institute, consider that the common factor of these treatments is the production of cortical inhibition coupled with subcortical release or vegetative mobilisation. However, it has not been proved that schizophrenia is due to an abnormal vegetative regulation or to an abnormally functioning hormone. The clinical evidence of the altered autonomic activity such as improvements in

sleep, appetite, weight and circulation may well be due to the improved mental condition resulting from the treatment rather than the actual cause of the improvement.

Kalinowsky and Hoch quote the opinions of Georgi, Demole and Freudenberg who hold that alterations of the nerve cell membrane are responsible for the success of these therapies. Evidence of this membrane alteration is found in a reduction in the amount of sugar in the cell which is produced slowly in the hypoglycaemic state and quickly with cardiazol and electric shock.⁽¹⁷⁾ Others believe that the benefit is due to a compensatory increased metabolism which follows this reduction of the sugar content.

Wortis suggests that ECT probably effects a redistribution of brain acetylcholine. He states that most known convulsants, including ECT, insulin hypoglycaemia and carbon dioxide promote acetylcholine production, and most anti-convulsants inhibit it.⁽⁴⁶⁾ In a later paper, he comments that the frontal cortex of the chronic deteriorated schizophrenic seems to contain too much cholinesterase.⁽⁴⁸⁾ If these views were substantiated, they would be of considerable importance. Treatment of mental illness by acetylcholine injections, however, has given disappointing results.

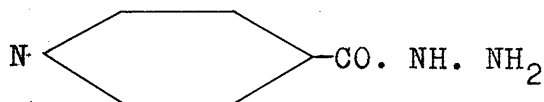
I consider that the line of investigation mentioned by Weil-Malherbe may be far reaching. He quotes the observations of Colowick, Cori and Slein on the inhibition of hexokinase by a pituitary factor and reversal of this inhibition by insulin. He himself has found substances in blood plasma which influence the activity of brain hexokinase in the direction of either inhibition or activation and, as the appearance of these substances is clearly correlated with the phases of carbohydrate assimilation, he assumes that they are of hormonal origin. Different groups of patients were found to show different patterns in response to a metabolic stress such as a glucose test dose. Patients suffering from schizophrenia of several years' duration often showed a flat glucose tolerance curve and a low fasting blood sugar, and were characterised by the absence of either inhibitors or activators of hexokinase in their blood plasma after the glucose test dose. (43c)

I feel that the functional mental illnesses may well be due to a defect in cerebral metabolism due to a fault in one or more of the enzyme systems. Whether a schizophrenic or a manic-depressive picture results would depend partly on the genetic constitution and partly on which enzyme systems were involved and the

level of the breakdown in metabolism. Insulin coma treatment and convulsive therapy could exert their beneficial action by an effect on the faulty enzyme thereby bringing the metabolism closer to normal. This action could be direct but is more likely to be mediated through an hypothalamic-pituitary mechanism.

ISONIAZID IN SCHIZOPHRENIA

Isoniazid is a new anti-tubercular drug. Its full name is isonicotinic acid hydrazide and it has the following structural formula:-



It is a white, crystalline solid, freely soluble in water at any pH.

Rubin and co-workers reported on the pharmacology of isoniazid in mice, rats and dogs. They found that it was rapidly absorbed after oral administration to mice and dogs. Approximately sixteen hours were required for the disappearance of the drug from the circulating plasma of dogs. Acute toxicity in mice and dogs was characterized by excitement and convulsions which were delayed in onset even after intravenous administration. Sub-acute toxicity in rats was evidenced by anorexia, loss in body weight, occasional convulsions and slight hepatic damage. Chronic administration to dogs resulted in anorexia, loss in body weight, ataxia, tonic and clonic convulsions, fatty degeneration of the liver and jaundice. Reversibility of these effects appeared possible upon prompt cessation of drug administration. (34)

Elmendorf and co-workers reported on studies of the administration of isoniazid to tuberculous patients. In man, the drug was promptly absorbed. After a single oral dose of 3 mgms. per Kgm. of body weight, the maximum concentration in the plasma (0.13 to 0.34 mgm. per cent.) was attained after one hour. A high percentage was excreted in the urine during the twenty-four-hour period after ingestion. The drug was also excreted in the saliva and the faeces. Appreciable concentrations of isoniazid were present in the cerebrospinal fluid within three hours of an oral dose of 2.0 to 3.0 mgm. per Kgm. in patients without meningitis. The administration of the drug for periods of four to sixteen weeks on 3.0 mgm. per Kgm. daily dose was not associated with any manifestations of drug toxicity in any of the patients studied. With patients on this dosage, there was no evidence of accumulation. Isoniazid possesses a high degree of activity against M. tuberculosis in animals and in the body fluids of man.⁽⁵⁾

A preliminary report on a large scale clinical investigation of isoniazid by the Medical Research Council⁽²⁴⁾ suggested that isoniazid was a very effective drug in pulmonary tuberculosis, but that when given alone it was not more effective than

combined streptomycin and paramino salicylic acid (P.A.S.). Bacillary resistance to isoniazid was found in 71% of cases at the end of the third month of treatment. Lack of progress could be related to the emergence of resistance. A second report to the Medical Research Council⁽²⁵⁾ studied the effects of various combinations of isoniazid, streptomycin and P.A.S. in the treatment of pulmonary tuberculosis. It showed that when isoniazid was combined with streptomycin, bacillary resistance to isoniazid at the end of the third month was reduced to 13%. It was concluded that, over a three month period, streptomycin 1 gm. daily and isoniazid 200 mgms. daily was clinically the most effective anti-tuberculous chemotherapy yet investigated, although its superiority to streptomycin 1 gm. daily and P.A.S. 20 gm. daily was not great. Streptomycin + isoniazid compared with isoniazid alone over a three month period was found to be considerably more effective in lowering the sedimentation rate, in suppressing tubercle bacilli in the sputum and also in improving the radiographic appearances. It was slightly more effective in resolving pyrexia. The two treatments produced equally striking improvements in the general clinical condition and in weight. Other workers stated that their patients reported a

sense of well-being when on isoniazid. A further report of the Medical Research Council showed that isoniazid + P.A.S. was a powerful addition to the acceptable drug treatments of pulmonary tuberculosis over a three-month period. (26)

Luntz and Smith state that isoniazid contains in its molecule a hydrazine residue which provides it with a two-fold action - a reducing action and the property of combining with sugars to form hydrazones and osazones. They quote Izume and Lewis as reporting that hydrazine derivatives induce hypoglycaemia by injuring the liver and thereby interfering with the formation of liver glycogen. Luntz and Smith, from their investigations, conclude that the administration of isoniazid produces a temporary elevation of the blood sugar level and makes both the rise and fall of an oral glucose tolerance test slower. They show that isoniazid itself, although a reducing agent, is not responsible for the rise in blood sugar levels, and therefore deduce that a disturbance in carbohydrate metabolism may be inferred. (21)

In view of these findings, I decided to observe the effects on the mental state of schizophrenic patients to whom isoniazid was administered. These cases were quite unselected except that they were

practically all of long standing, many of whom showed severe mental deterioration. The patients were from four different male wards in the hospital, one of which was the second refractory ward. Rimifon, the Roche preparation of isoniazid, was used in a dosage of 100 mgms. four times daily.

This study covers sixty cases of schizophrenia. In thirty-one, the drug was administered and its effect on the mental state assessed over a period of several weeks. In twenty-four cases, in addition to observing the effect on the mental condition, blood sugar estimations were carried out in the fasting condition and one, two and three hours after the ingestion of 100 gm. of glucose. This was done before commencing isoniazid therapy, one week after it was started and again three weeks later. In this group there were an additional five non-schizophrenic subjects. Finally, in five cases, blood sugar estimations were carried out in the fasting condition and then at half-hourly intervals to two and a half hours after the ingestion of 100 gm. of glucose in divided dosage by the Exton-Rose technique. This was done before isoniazid was started and again four and seven days later. On these days, the fasting cerebrospinal fluid sugar estimation was also done.

This group contained one additional non-schizophrenic subject. The plasma levels of isoniazid were not determined.

CASE 1

Age 24. Schizophrenia Hebephrenia. Admitted 27.2.53.

He was vague and detached from reality and unable to give an account of himself. His speech was slow and hesitant and showed evidence of thought blockage and confusion. He grinned and grimaced for no apparent reason. He was listless, apathetic and showed marked emotional blunting. He had no drive or initiative. He was untidy. He was deluded, believing that he was accused of murder and he alleged that people slandered him. He had ideas of reference and of influence.

He had a history of abnormal psychopathic behaviour dating back for seven years.

Electro-convulsive therapy produced only a limited response. He became cleaner and tidier and showed more interest, but otherwise his condition remained as above.

Isoniazid was started on 2.4.53. and he soon began to show a marked improvement. He became much more alert in speech and manner and his conversation no longer was confused or showed evidence of thought

blockage. He showed much more initiative, drive and spontaneity, and worked well in the ward. There was no obvious delusional system, and he lost his ideas of reference, persecution and influence. He remained, however, rather suspicious in attitude, emotionally blunted, and was unable to give an account of events leading up to his admission to hospital.

Isonaizid was stopped on 9.7.53. His improvement was maintained, and he was discharged to the care of his relatives on 30.9.53. His plans for the future were very vague and he lacked insight. It was considered that he had made a partial remission and that a future relapse was probable.

He gained 15 lbs. in weight while the drug was being administered.

This case was assessed as "improved" as a result of treatment.

CASE 2

Age 37. Schizophrenia Paranoia. Admitted 23.10.46.

He was morose, suspicious, solitary and asocial. He was manneristic, vague and detached. His answers to questions were often irrelevant and he could give but little account of himself. He was subject to auditory hallucinations, and was frequently noisy and violent in response to them. He had various

changeable delusions, and constantly believed that the wireless used a repetition of peoples' names combined with disgraceful language in order to make people stupid.

He had always been "irritable and apt to lose his temper". His illness began in 1945 when he was serving with the Army in India. He showed no response to insulin coma therapy and to two courses of ECT.

A prefrontal leucotomy on 9.5.53. relieved the aggressive and impulsively violent features, but he remained dull, lacking in initiative and spontaneity, untidy and slovenly, and hallucinated. He could give no account of himself.

Isoniazid was started on 8.10.53. He soon began to improve and when the drug was stopped on 12.12.53. he kept himself clean and tidy and showed some initiative and a little spontaneity. He worked in the ward on simple tasks under supervision, and he wrote letters home. He answered questions rationally, but his conversation was very limited and he could give no account of himself. He was no longer obviously hallucinated.

Some time after isoniazid was stopped he began to regress slowly becoming untidy and slovenly and completely devoid of initiative. He stopped working

in the ward and writing letters home.

He gained 1 lb. in weight while the drug was being administered.

This case was assessed as "improved" as a result of treatment.

CASE 3

Age 37. Schizophrenia Simplex. Admitted 2.5.52.

He was dull, vague, apathetic, detached and disinterested. He was solitary and asocial. He had vague ideas of reference and persecution. He was in a state of perplexity and stared dully in front of him, being unable to give any account of himself. He was capable only of the simplest routine tasks in the ward under direct supervision.

He was reported to have always been a shy, asocial person with a poor work record. He stayed at home for three years after the war, and in that time rarely spoke. He was previously a patient in this hospital, for five months in 1951. He showed only a temporary response to ECT.

Isoniazid was started on 26.2.53. He soon became much brighter, less lethargic, and showed much more initiative and spontaneity in speech and action. His work improved and he could be trusted to work without supervision. He took more interest in his surroundings and in his personal appearance, and he

began to mix with the other patients. He lost his perplexity and answered questions rationally and coherently. He became less blunted emotionally and smiled much more readily. His visitors commented on the improvement.

The drug was stopped on 22.4.53. and, for several months, he maintained his improvement. He then began to revert to his former state of disinterested apathy. He again became solitary and asocial with marked emotional blunting, and would only do a little work under close supervision.

He gained 4 lbs. in weight while isoniazid was being administered.

This case was assessed as "improved" as a result of treatment.

CASE 4

Age 50. Schizophrenia Catatonia. Admitted 1.4.49.

He was simple, childish and fatuous. His conversation was limited and often irrelevant. He had delusions of influence, believing that he was controlled by atomic energy directed by "the power behind the throne". He was aurally hallucinated, and had ideas of reference and of persecution. He showed marked emotional blunting. He was unoccupied and unemployable. He frequently became mute, inaccessible

and catatonic, refusing food for long periods. These stuporose phases responded to ECT but it was occasionally necessary to resort to tube feeding.

His illness began in the U.S.A. in 1941. He was a patient in mental hospitals there from 3.2.42. to 24.12.42. and from 7.2.44. until he was deported and admitted to this hospital.

Isoniazid was started on 26.2.53. He became brighter and more alert and a useful and willing worker in the ward without supervision. He showed good initiative. His conversation was rational and coherent, and he spoke more freely. His ideas of reference and of persecution were less marked, and he no longer would admit to the delusions noted previously. The drug was stopped on 22.4.53. and he quickly deteriorated to the condition he was in before it was started. It was recommenced on 27.5.53. and he again became much brighter and more alert, and generally improved as when he was on the drug before. Isoniazid was stopped on 15.10.53. and this time the improvement was maintained apart from the fact that he did not converse so freely. He has not had a phase of catatonic stupor since being on this treatment, which is the longest period he has been free from one for several years.

He lost 8 lbs. in weight while the drug was being administered.

This case was assessed as "improved" as a result of treatment.

CASE 5

Age 36. Schizophrenia Hebephrenia. Admitted 11.3.42.

He was inaccessible and almost mute. He was detached, solitary and asocial. He was apathetic with no interest in his surroundings, unoccupied and unemployable. He was manneristic, keeping his face covered with his hands and not looking at anyone. At times he was very destructive especially to his clothes. He was slovenly and untidy. He was depressed and hypochondriacal. He frequently grinned and grimaced for no apparent reason. At times his habits were faulty. He had had nine courses of ECT, to each of which he made only a slight and very temporary response.

His illness began in 1937. He was a patient in this hospital from 8.2.38. to 13.9.38.

Isoniazid was started on 25.2.53. and stopped on 25.4.53. He had become brighter, more alert and spoke much more freely. He was, however, agitated and very hypochondriacal and he asked for further ECT. He was therefore given eight treatments between

27.4.53. and 21.5.53. with little response, and by 10.6.53. his condition had deteriorated almost to that as noted in the first paragraph. Isoniazid was again administered. Within a week he was brighter and more alert, speaking more freely and showing more initiative and spontaneity. He continued to improve, began working in the ward and, on asking for a job to occupy his mind, he was sent to the occupational therapy department where he worked diligently and quite well. He remained in this phase until 15.10.53. when the drug was stopped. Thereafter he regressed, becoming withdrawn, solitary, unoccupied and unemployable. He was very depressed and said he was being subjected to mental tortures. He again kept his face covered with his hands. Isoniazid was once more administered from 14.11.53. and he quickly improved as before. He returned to working in the ward and at occupational therapy. He was bright and cheerful and spoke freely. His habits were clean, and he kept himself clean and reasonably tidy. He was no longer destructive. He did not cover his face with his hands but was sociable and friendly, and took more interest in things in general. At one of the Christmas parties, I saw him participating with fervour and with a keen spirit of competition in all

games, laughing, happy and obviously enjoying himself. The marked change was commented on by other medical officers who had known him previously. He remains on isoniazid and the improvement has been maintained.

He gained 7 lbs. in weight while the drug was being administered.

This patient was assessed as "improved" as a result of treatment.

CASE 6

Age 35. Schizophrenia Hebephrenia. Admitted 18.11.52.

He was simple and childish in speech and behaviour. He was emotionally unstable and falsely elated. His conversation was vague and flippant. He had delusions of bodily dysfunction and of influence, believing that he was controlled by electricity operated by some person. He was subject to auditory hallucinations, admitting that he heard God's voice speaking to him daily. He was devoid of insight and stated he came into hospital to test a theory. His judgment and appreciation of his position were grossly impaired. He kept himself clean and tidy, he was co-operative and well behaved, and he worked on simple jobs in the ward. He mixed freely with the other patients, and participated in ward games and some social functions. He showed little response to

a course of ECT.

He had a very poor family history. His illness began in 1940 and he was a patient in this hospital from 11.1.41. to 23.3.41., and from 13.8.45. to 27.8.45.

Isonaizid was commenced on 2.4.53. He became very much worse. He was over-active, restless, confused, bewildered and manneristic. He was untidy and slovenly. He was no longer co-operative and he began to interfere with the other patients. He was unemployable and could not take part in ward games and social functions. He was fatuous and showed marked emotional incongruity.

Isonaizid was stopped on 19.5.53. and he became much steadier, reverting to his condition prior to treatment. He was quieter and again well behaved and co-operative. He kept himself clean and tidy. He worked in the ward, was no longer interfering and he mixed well with the other patients. He remained deluded and hallucinated, lacking in insight and in judgment, and was vague and flippant in speech.

He lost 3 lbs. in weight while the drug was being administered.

This patient was assessed to have "deteriorated" as a result of treatment.

CASE 7

Age 35. Schizophrenia Catatonia. Admitted 19.12.51.

He was completely mute and inaccessible, negativistic, resistive and unco-operative. He was asocial, disinterested, unoccupied and unemployable in the ward. He stood in one position or sat slumped in a chair for long periods in a typically catatonic manner. His attitude was uncertain, and he was occasionally impulsively violent probably in response to hallucinatory voices. He was untidy and slovenly in his dress and in his habits. He masturbated frequently and openly.

His illness began in 1946 and he was a patient in two mental hospitals from March to October 1947, responding to ECT. He was first admitted to this hospital on 31.3.49. when he was aggressive, violent, manneristic, restless, incoherent and hallucinated with many delusions of persecution. He responded well to a course of ECT being discharged on 11.8.49. However, he was re-admitted six weeks later after further violence. He made no response to deep insulin treatment and several courses of ECT. A prefrontal leucotomy was done on 2.6.51. after which he steadily improved until he was able to be discharged on 31.10.51. when he showed no gross mental abnormality.

However he soon relapsed and was re-admitted. His condition rapidly deteriorated to that noted in the previous paragraph.

Isoniazid was begun on 25.2.53. and he soon became more alert and active, responding quickly in his actions when spoken to. He no longer remained for long periods in catatonic postures. He stopped masturbating. He was still mute. Later he became tense and negativistic. The drug was stopped on 22.4.53. following which he resumed open masturbation. He became very suspicious, uncertain and aggressive and his habits were faulty. Treatment was re-started on 19.6.53. and he soon became much brighter and more alert, co-operative and no longer negativistic. His habits were clean and he stopped masturbating. He remained mute and suspicious. Rimifon was stopped on 25.8.53. and he soon reverted to his former state. It was again resumed on 20.10.53. and this time the improvement was even more marked. He began to speak freely and answered questions rationally, coherently and briskly. He was alert and co-operative, and it was possible to employ him usefully in the ward. He started to dress himself and to look after himself, and his habits were clean. He stopped masturbating. He took more interest in things in general, and

played football for the patients' team. He did, however, remain at times suspicious and uncertain in his attitude.

He gained 4 lbs. in weight while the drug was being administered.

This patient was assessed as "improved" as a result of treatment.

CASE 8

Age 38. Schizophrenia Hebephrenia. Admitted 28.11.41.

Chronic Mental Defective.

He was simple, childish, dull and retarded. He was emotionally facile and would often smile and laugh foolishly for no apparent reason. He could give no reliable account of himself. He was untidy, slovenly, and his habits were faulty. He was aurally hallucinated. He was unemployable, destructive and frequently impulsively aggressive. He required every nursing care and attention. He made only limited and temporary responses to ECT.

He was always feeble-minded and in 1936 he became unmanageable at home and was committed to a Mental Defective Colony for six months. In 1941 when serving in The Pioneer Corps he was admitted to a Military Hospital as he was unable to carry out his duties, and he required attention to see that he

washed and dressed. He had a mental age of 9 years. He began to show schizophrenic features and he was therefore transferred to this hospital on 28.11.41.

Isoniazid was started on 25.2.53. following which he improved considerably. He became quiet, co-operative and easy to manage. His habits were clean and he would dress himself, although he remained slovenly and untidy. He was no longer destructive or violent. He answered questions rationally. The drug was stopped on 22.4.53. and he soon deteriorated to his previous state. It was re-started on 17.6.53. and he again improved, becoming quiet, co-operative, clean and tidy, with clean habits. He lost his destructive and violent tendencies. Rimifon was stopped on 25.8.53. and once again he reverted to his former condition. It was resumed on 20.10.53. but, this time, after responding as before for six weeks, he began to deteriorate and when the drug was finally stopped on 16.12.53. his mental state was as described in the first paragraph. He subsequently showed no change.

He lost 2 lbs. in weight while the drug was being administered.

This case was assessed as "improved" with treatment as he initially responded well to it.

CASE 9

Age 40. Schizophrenia Hebephrenia. Admitted 20.8.42.

He was dull, retarded, apathetic and almost devoid of initiative. His conversation was rambling and irrelevant, and his replies to simple questions were often contradictory. He was slovenly and untidy in his dress and habits. He exhibited various mannerisms and laughed in a fatuous way for no apparent reason. He was simple and childish. He expressed delusional ideas which were changeable and of brief duration. He had no insight and stated he came into hospital to look after the apple trees and the brick work. He had shown no response to a course of ECT given shortly after his admission.

He had a good, stable prepsychotic personality. His illness began in 1942 when he was serving in the Army from which he was invalided in June 1942, two months before his admission to this hospital.

Isoniazid was started on 25.2.53. He soon began to be very much tidier and took pride in his personal appearance. He developed a little initiative and worked in the ward under supervision. His conversation remained rambling and irrelevant. The drug was stopped on 22.4.53. and he maintained his improvement for four months, after which he gradually regressed to the state he was in before treatment.

Rimifon was re-administered from 15.10.53. and once again he soon improved. He became neat, clean and tidy, and took an obvious pride in his personal appearance. He worked well in the ward without supervision, following instructions although not showing much initiative on his own. He has played several good games of football for the patients' team. He was alert and no longer retarded. His mannerisms disappeared. He answered questions rationally although his conversation was limited. He enquired spontaneously whether he could have hospital leave.

He gained 2 lbs. in weight while the drug was being administered.

This patient was assessed as having "improved" as a result of treatment.

CASE 10

Age 56. Schizophrenia Hebephrenia. Admitted 22.7.27.

He was dull, retarded, simple and demented. He was apathetic and disinterested in his surroundings. He mumbled continually to himself and, although answering simple questions rationally, his conversation was frequently incoherent and he could give no reliable account of himself. He said the year was 1930 and that he had been in hospital for three years. He was almost completely unoccupied. He was aurally hallucinated,

but had not shown any impulsive or violent trends since 1930. He was inclined to be very occasionally noisy during the night.

He served in World War 1 and was "shell shocked" in 1917. It was reported that subsequently he was odd and peculiar being pre-occupied with his war experiences. The first florrid schizophrenic signs appeared in 1925 when he was away from work for nine months being very hallucinated. His illness recurred in March 1927 with auditory hallucinations, delusions of persecution and impulsive violence.

Isoniazid was started on 25.2.53. His condition soon deteriorated markedly. He became over-active, restless, interfering and very noisy. He was destructive, impulsive and violent. There was no change in his conversation. The drug was stopped on 22.4.53. and he remained in this state for three months, after which he began to improve slowly to the condition he was in before treatment.

He lost 3 lbs. in weight while the drug was being administered.

This patient was considered to have "deteriorated" as a result of treatment.

CASE 11

Age 41. Schizophrenia Catatonia. Admitted 4.7.52.

He was completely mute, negativistic and unco-operative. He was detached from reality, apathetic, disinterested, solitary, asocial and unoccupied. His attitude was inclined to be suspicious and uncertain.

He was always of a reserved, melancholy disposition. His illness began in 1951 in Canada, where he was admitted to a mental hospital for treatment on 24.9.51. A diagnosis of catatonic schizophrenia was made and he was deported in June 1952, after which he was admitted to this hospital. He showed no response to a course of ECT.

Isoniazid was begun on 26.2.53. Within a week he was brighter and answered questions rationally in monosyllables. He continued to improve becoming much brighter and more alert. He conversed rationally and freely, but only when spoken to. He had little spontaneity or initiative, but was more interested in his surroundings. He kept himself clean and tidy. He remained suspicious and negativistic in attitude. When I asked him what the month was, he replied that I knew it as well as he did. He was, however, less tense and anxious. The drug was stopped on 22.4.53. following which his conversation steadily dwindled

and he became less alert and more sullen and disinterested. Treatment was recommenced on 10.6.53. after which he again spoke much more freely and he showed a little spontaneity. He was brighter and more alert, but unoccupied and unemployable. He was more interested in things in general and he began to read the daily papers. Rimifon was stopped on 15.7.53. and after a few weeks he slowly returned to his previous state. He was completely mute, inaccessible and withdrawn. Isoniazid was restarted on 18.11.53. and again he improved as before. He was quiet, well behaved and much more co-operative, being less suspicious in attitude. He conversed rationally and coherently when approached. He remained asocial and unemployable.

He gained 10 lbs. in weight while the drug was being administered.

This patient was assessed as "improved" as a result of treatment.

CASE 12

Age 34. Schizophrenia Paranoia. Admitted 2.12.42.

He was simple, childish and emotionally facile. He was manneristic, detached, solitary, asocial, disinterested, unoccupied and unemployable. He frequently and openly masturbated. He was incapable

of sustaining a conversation and his answers to questions were often irrelevant. He expressed ill-formed, bizarre delusions regarding various females who persecuted him physically. He had since admission expressed many other fleeting, poorly systematised delusions, mainly of persecution and of influence. He was untidy and slovenly. He was very agitated and depressed with noisy periods. At times he was impulsive. He showed no response to ECT.

He was a backward child and was always regarded as reserved, peculiar, eccentric and unstable. He was a patient in this hospital from 19.6.42. to 26.8.42. He soon relapsed and had to be re-admitted.

Isoniazid was started on 25.2.53. At first he became restless, over-active and impulsive, and he went off his food. However, he soon settled, becoming quieter, less over-active and no longer impulsive. He stopped masturbating, took much more interest and was usefully employed in the ward. He was tidier and no longer slovenly. He was not agitated or depressed. The drug was stopped on 22.4.53. following which he again became very noisy, agitated, impulsive, difficult with his food, and he masturbated frequently. Treatment was re-started on 3.6.53. and he quickly improved. He was quiet and

co-operative, and took his food well. He was clean and tidy. He rarely masturbated. He again worked in the ward. After ten weeks he began to deteriorate. He remained quiet and he ate well, but he resumed his frequent masturbation, he became disinterested and withdrawn and he was occasionally incontinent. Rimifon was stopped on 25.8.53. No appreciable change followed.

He gained 3 lbs. in weight while the drug was being administered.

This patient was assessed as "improved" with treatment as he initially responded well to it.

CASE 13

Age 39. Schizophrenia Hebephrenia. Admitted 30.7.53.

He was suffering from a marked thought disorder with thought blocking and auditory hallucinations. He said the voices were "An echo of my pent-up thoughts such as I like wood and wood often talks to me". His conversation was vague, rambling and often irrelevant. He was manneristic and he grinned and grimaced at times for no apparent reason. He expressed ideas of reference and of influence. He was devoid of insight and had no appreciation of his position. He showed emotional incongruity. He was quiet but not over-co-operative. He was inclined to be suspicious.

He joined the Army in 1935. His illness began in 1944 when he was admitted to Banstead Military Hospital. After several weeks treatment he was invalided from the Army. His subsequent work record was grossly unstable and he was finally unemployed. He stole a small amount of coal and, as it was obvious that he could not appreciate right from wrong due to his grossly impaired judgment, he was admitted to this hospital under the Criminal Justice Act.

Isoniazid was started on 27.8.53. and, at the same time, a course of ECT. By his sixth convulsion on 21.9.53. his condition had markedly deteriorated. His mannerisms and his grinning and grimacing were much more frequent and pronounced. He became noisy. He often laughed aloud and he was continually conversing in a loud voice with his hallucinations. He was slovenly, untidy and unco-operative. ECT was stopped and he was continued on isoniazid alone. He began to improve. He became amenable and fully co-operative. His mannerisms diminished and he stopped grinning and grimacing. He was quiet and well behaved. He denied hallucinations, and he was no longer objectively hallucinated. He was clean and fairly tidy, and he worked on simple routine jobs in the ward under supervision. His thoughts were clearer

and he conversed more rationally and to the point, although, at times, he still rambled and introduced irrelevancies and he was incapable of sustaining a conversation. He remained falsely elated and rather flippant with emotional incongruity. He had very little insight, his judgment was grossly impaired and he had no proper appreciation of his position. Isoniazid was stopped on 30.10.53. and he maintained this improvement until 27.11.53. when he was transferred to another mental hospital.

He gained 6 lbs. in weight during the administration of the drug.

This patient was assessed as "improved" as a result of treatment.

CASE 14

Age 36. Schizophrenia Paranoia. Admitted 10.10.46.

For almost two years after admission he had expressed various ill-formed delusional ideas, mainly of influence and persecution, and his attitude was uncertain and suspicious. He was subject to auditory hallucinations. He showed only a limited and very temporary response to both electro-convulsive and insulin coma therapies. For almost four years before commencing isoniazid he had been very quiet, withdrawn, detached, solitary and asocial. He was

unoccupied and unemployable. He was untidy and slovenly. He showed no initiative or spontaneity in speech or in action. He was devoid of insight.

He was always of a reserved, unsettled disposition. His illness began in 1942 with vague delusional beliefs and he was eventually admitted to this hospital on 18.5.43. He was treated with ECT but made only a temporary response, and he took his discharge on 6.7.43. showing no real improvement.

Shortly after isoniazid was started on 25.2.53. he became elated, euphoric, manneristic, restless and over-active. He frequently interfered with and upset other patients. His untidiness increased. His conversation was rambling, garrulous and often irrelevant. After two weeks he began to improve. His conversation became rational and coherent. He showed much more initiative and spontaneity. He began to take an interest in his personal appearance and kept himself clean and tidy. His behaviour, however, remained somewhat over-active and manneristic. The drug was stopped on 22.4.53. following which he became very quiet and withdrawn with very limited conversation, and no initiative or spontaneity in speech and action. His mannerisms disappeared. He continued to keep himself cleaner and tidier.

He gained 6 lbs. in weight while the drug was being administered.

This patient was assessed as "improved" as a result of treatment.

CASE 15

Age 29. Schizophrenia Paranoia. Admitted 20.12.52.

He was tense, agitated, suspicious and apprehensive with delusions of influence and persecution. He believed that the wireless was controlling him and that someone was disturbing him at night by blowing gas up the pipes round his bed, and that gas came up through the lavatories. He was subject to auditory hallucinations. He was confused and retarded, vague and detached. He was solitary and unoccupied. He spent his time scribbling on scraps of paper. He was devoid of insight and had no appreciation of his position. He improved considerably with insulin coma therapy but within two months he had relapsed. He was given ECT but after nine treatments his condition had deteriorated and it was stopped.

He was always a reserved and solitary child. In 1938 he was a patient in this hospital for nine months suffering from a schizophrenic illness which responded to cardiazol treatment.

Isoniazid was started on 27.8.53. and by 12.10.53. had produced little change. He was then given three treatments of electro-convulsive therapy in the ensuing week and, whereas previously he had deteriorated with ECT, he now improved rapidly. He conversed rationally, coherently and spontaneously. He was alert and cheerful with no tension, retardation or confusion. He kept himself clean and tidy. He began to mix with other patients, played games and attended social functions. He worked in the ward. He was no longer hallucinated and he did not express delusional beliefs, although he considered that his previous delusions did, in fact, happen. The drug was stopped on 21.10.53. and three weeks later he began to relapse. By 15.12.53. his condition was worse than that on admission. He was tense, agitated, disturbed, grossly hallucinated and deluded. He was given a further prolonged course of ECT, but this time there was no response whatsoever.

He gained 5 lbs. in weight during the administration of the drug.

This patient was assessed as "slightly improved" as a result of isoniazid treatment.

The above are examples of cases which received isoniazid. The entire study is summarised in tabulated form.

Diagnosis	Improved	Slightly Improved	Deteriorated	No Change	Total
Schizophrenia Simplex	3	1	1	4	9
Schizophrenia Hebephrenia	8	5	4	10	27
Schizophrenia Catatonia	3	0	0	2	5
Schizophrenia Paranoia	5	2	1	6	14
Schizophrenia Undifferentiated	0	0	0	5	5
TOTAL	19	8	6	27	60

TABLE I The response of schizophrenic patients to isoniazid.

From Table 1, it will be seen that 19 patients (32%) showed a definite improvement with isoniazid treatment, and a further 8 patients (13%) improved slightly. Case 15 was included under the heading of "slightly improved" in view of the fact that he did not respond until he had three treatments with ECT. As he had previously deteriorated with ECT and, after isoniazid was stopped, he relapsed and showed no response to ECT, it was held that the drug had played some part in his improvement. One case in which ECT

previous to drug treatment had had no effect improved considerably while on isoniazid. When it was stopped he relapsed and ECT again had no effect. Later he failed to respond to further drug treatment but did to ECT in addition to the drug. When either was stopped he began to deteriorate, but isoniazid + ECT kept him reasonably stable.

The improvement in every case was entirely symptomatic. No patient could be considered to have made a recovery. Even Case 1 who was discharged was only in a state of "partial remission" and the prognosis was thought to be poor. The influence of the treatment was most seen in its effect on behaviour with a stimulation of action and initiative and flow of speech. Many became cleaner and tidier, taking more interest in their personal appearance. The improved cases took more interest in their surroundings, were more inclined to work in the ward, and the quality of this work was better. They also became more alert and cheerful, and more amenable. In several instances aggressive, violent and destructive tendencies were relieved. Five patients who had been mute, or almost mute, began to speak, three of them quite freely. A further seven cases of complete or almost complete muteness, on the other hand, showed no response

whatsoever to the drug. The majority of patients who responded showed an amelioration in thought disturbances. They became less confused and their thoughts were much clearer. Thought blockage disappeared. They conversed rationally. Delusions were not markedly influenced. In six patients they were no longer present after treatment had begun, but my impression was that they were not far removed from the surface. Four patients were no longer obviously hallucinated. Several other cases, whilst retaining their delusions and hallucinations, were less preoccupied with them and their behaviour was less dominated by them.

Of the 27 cases who showed some improvement, twenty maintained it while isoniazid was being administered, almost all relapsing when treatment was stopped. Cases 5, 7 and 11 indicate dramatically the effect of the drug as they responded well when under treatment, relapsed when it was stopped, improved when it was restarted, again deteriorated on cessation, and for the third time improved when it was recommenced.

Six patients became worse while being treated. In every case, it was mainly behaviour which was affected. They became over-active, manneristic and inclined to be aggressive, impulsive, noisy,

interfering and destructive. One patient became confused and bewildered. In each instance, improvement set in on stopping isoniazid and all returned to the state they were in before receiving the drug, although this was sometimes a slow process and in three cases took three months.

During the administration of isoniazid, there was an average gain in weight of 2.1 lbs. Thirty-five patients put on weight, the maximum gain being 15 lbs. Nine showed no change and the remaining patients lost varying amounts of weight up to a maximum of 8 lbs. There was no correlation between changes in weight and the mental response to the drug.

	Venous Blood Sugar (mgms. per 100 ccs.)			
	Time in Hours			
	Fasting	1	2	3
Before treatment	81	87	66	72
After one week	81	94	76	73
After four weeks	82	93	78	76

TABLE II Average Blood Sugar Values before isoniazid treatment, and one and four weeks after treatment was commenced.

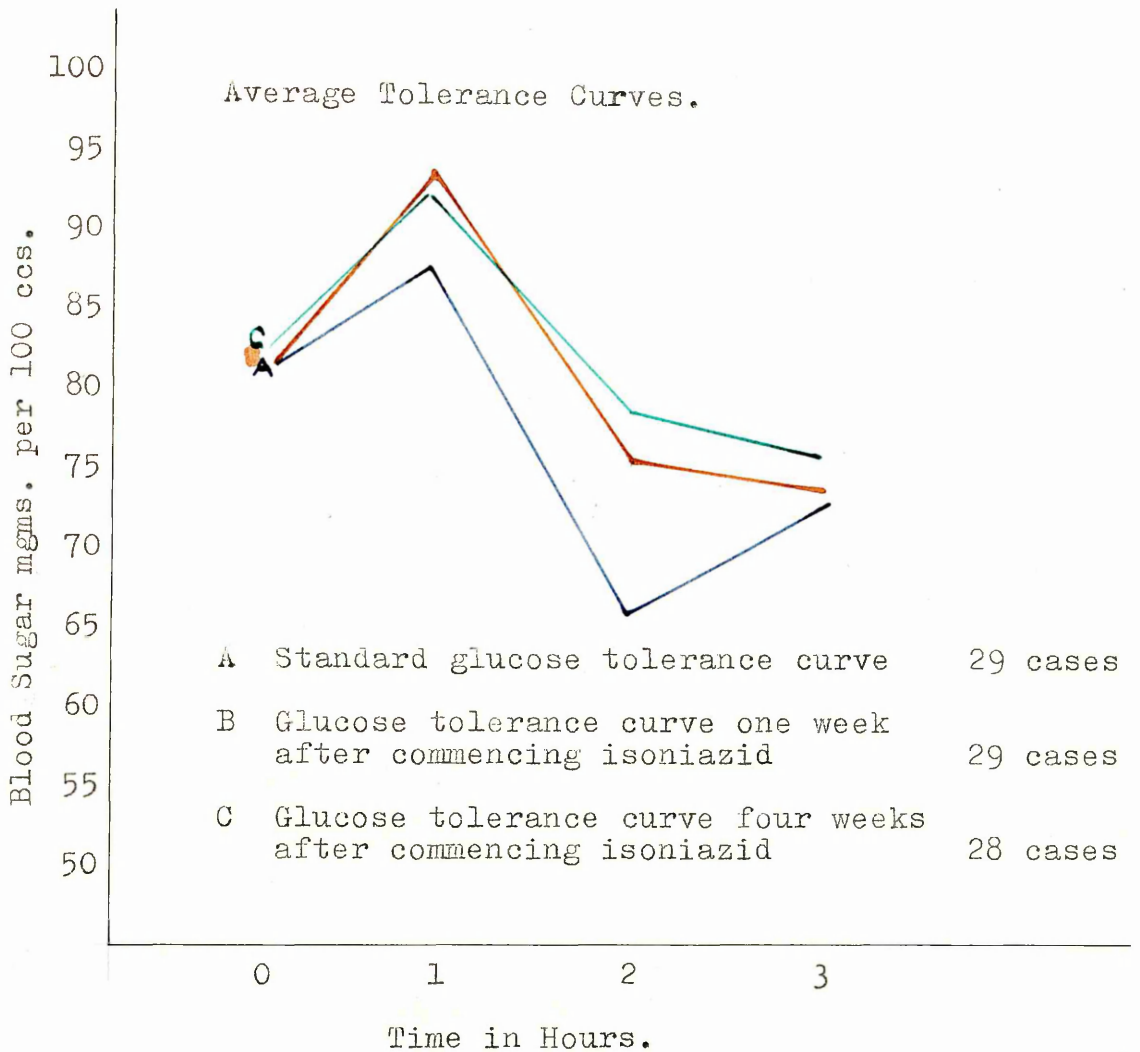


FIGURE I Composite glucose tolerance curves showing the effect of isoniazid one week and four weeks after administration.

From Table II and Figure I it is seen that, on the average, isoniazid caused a slight rise in the blood sugar values at one, two and three hours, although having no significant effect on the fasting

blood sugar. This tends to support the findings of Luntz and Smith, although they also claimed that isoniazid produces a significant rise in the fasting blood sugar. (21)

		Number of Cases			
		Rise	Fall	Equal	Total
Fasting	{ After one week	14	12	3	29
	{ After four weeks	16	11	1	28
1 hour	{ After one week	15	11	3	29
	{ After four weeks	18	9	1	28
2 hours	{ After one week	14	13	2	29
	{ After four weeks	15	12	1	28
3 hours	{ After one week	14	15	0	29
	{ After four weeks	16	11	1	28

TABLE III How individual cases responded in blood sugar values one week and four weeks after commencing isoniazid as compared with their blood sugar values at similar times before treatment.

However, Table III shows that out of 29 patients only 14 had a rise in the fasting blood sugar value one week after isoniazid was commenced,

and 16 after four weeks. For the blood sugar values one hour after the glucose test dose, isoniazid produced an increase in 15 cases and a decrease in 11 patients. The results for the other times were similar. It is therefore considered that these findings do not prove that isoniazid has any significant effect on the blood sugar values of schizophrenic patients.

There was no correlation between changes in blood sugar values and mental changes in response to the drug.

My findings confirmed the frequent abnormal glucose tolerance curves in schizophrenia as reported by other workers. Of the 29 curves carried out before isoniazid was administered, 14 or 48% were "flat" showing either no rise or an actual fall in the blood sugar values one hour after the test dose. Of the total of 86 curves done, 37 or 43% were similarly abnormal.

Table IV and Figure II show that, while, on the average, there was a general rise in the blood sugar curve four days after isoniazid, there was a distinct fall after seven days in all values apart from the fasting blood sugar. The individual response to the drug varied greatly with this group and the results

were similar to those of Table III. The results support my previous contention that isoniazid has no obvious effect on the blood sugar values of schizophrenic patients. These findings are similar to those of Keeping and Hutchings⁽¹⁹⁾ for their group of six non-schizophrenic subjects, and they do not support those of Luntz and Smith.⁽²¹⁾

	Venous Blood Sugars (mgms.per 100 ccs.) Time in Hours					
	Fasting	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$
<u>Before isoniazid</u>						
Case A	69	74	93	71	42	49
B	75	103	77	88	88	104
C	75	125	112	96	83	66
D	117	137	165	100	117	100
E	53	75	78	31	42	55
F	72	110	106	67	56	56
Average	77	104	105	75	71	72
<u>Four days after isoniazid</u>						
Case A	67	86	91	97	71	57
B	158	170	122	83	83	67
C	78	107	128	98	76	69
D	76	170	123	134	118	73
E	66	105	94	42	42	44
F	52	93	87	35	39	64
Average	83	122	106	81	71	62
<u>Seven days after isoniazid</u>						
Case A	65	68	65	43	43	42
B	82	84	132	78	76	80
C	65	99	102	73	51	39
D	170	160	148	124	94	88
E	67	67	68	42	54	65
F	72	92	74	52	46	66
Average	88	95	98	69	61	63

TABLE IV

Blood sugar values for six patients given a glucose tolerance test (Exton-Rose technique) before isoniazid and again on the fourth and seventh days of isoniazid treatment.

Average glucose tolerance curves

A. Standard glucose tolerance curve

B. Tolerance curve four days after isoniazid.

C. Tolerance curve seven days after isoniazid.

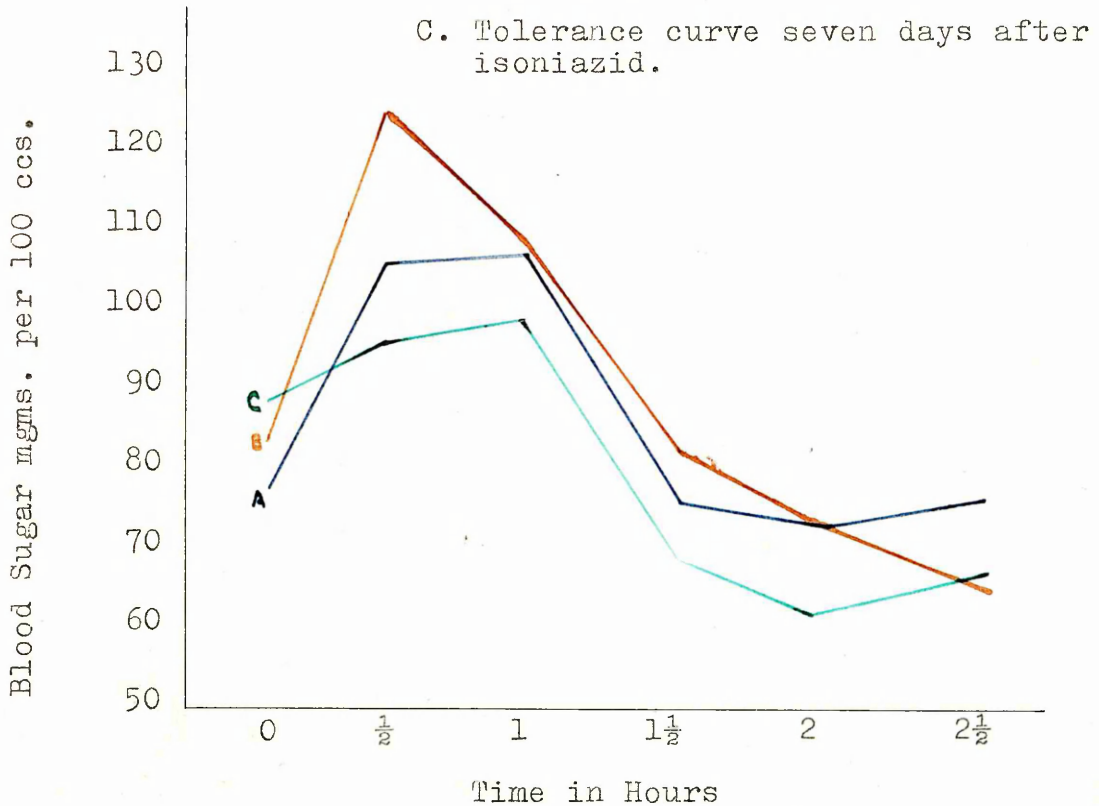


FIGURE II Composite glucose tolerance curves for six patients A before isoniazid, B after being on the drug for four days, and C after being on the drug for seven days.

	Fasting C.S.F. sugar values (mgms. per 100 ccs.)		
	Before isoniazid	After 4 days	After 7 days
Case A	50	53	48
B	61	65	68
C	71	55	48
D	60	64	68
E	53	59	37
F	54	52	56
Average	58	60	54

TABLE V Fasting cerebrospinal fluid sugar values
before isoniazid treatment and again on
the fourth and seventh days during the
administration of the drug.

Table V shows the effects of isoniazid on the cerebrospinal fluid sugar values. There were no significant changes and it was considered that no conclusions could be drawn. It would seem, however, that isoniazid has no marked or constant effect on the cerebrospinal fluid sugar.

DISCUSSION

My investigations indicate that isoniazid has a definite effect on the mental state of schizophrenic patients. Of sixty cases, thirty-three patients (55%) showed a definite response to the drug, 45% improving, and 10% deteriorating. The mental changes were considerable in all of the patients who deteriorated and in nineteen of the cases which improved. In every instance the illness was of long standing, the majority being of many years duration. It could, therefore, have been expected that they would not have responded to insulin coma therapy, and, in fact, many had had this form of treatment with no lasting benefit. The majority had also failed to respond to electroconvulsive therapy even as a maintenance symptomatic form of treatment. Five patients had been subjected to the operation of prefrontal leucotomy with little or no benefit, and three of them improved with isoniazid treatment.

It is difficult to compare my findings with those of insulin coma treatment used in chronic schizophrenia as there are few comparable reports in the literature. Ellery quotes Müller's results which were that, in schizophrenia of over eighteen months'

duration, there were practically no full remissions but 45% showed improvement.⁽⁴⁾ He does not mention whether this improvement was maintained. Kalinowsky gives similar figures for the effect of ECT in schizophrenia of over three years' duration - namely no complete recoveries but 50% were improved.⁽¹⁶⁾ Hemphill and Walter, reporting on thirty-seven cases of schizophrenia lasting more than two years, found that two (5%) recovered and thirteen (35%) were improved.⁽¹⁰⁾ These results are very similar to those I obtained with isoniazid therapy and it is probable that, on the average, my cases were of much longer duration.

Insulin coma therapy is an impracticable measure as a purely ameliorative treatment in chronic schizophrenia. The few beds available are needed for acute cases, it is time consuming, requires much skilled medical and nursing attention, and is not without risk. There is therefore, in my opinion, no doubt that in chronic schizophrenia isoniazid treatment is of very much greater value than insulin coma therapy.

ECT is undisputedly of great importance as a symptomatic maintenance treatment in long standing schizophrenic illnesses. In many cases it can control

violent, disturbed episodes, alleviate semi-stuporose and catatonic states and obviate feeding problems and the necessity for prolonged restraint. It is, of course, a simple treatment to administer. I have no doubt that, from a wide viewpoint, ECT is a much more powerful therapeutic weapon in chronic schizophrenia than isoniazid. On the other hand, as I remarked previously, the majority of the patients in my study had failed to respond to ECT and yet 45% of them improved with isoniazid. I consider that the drug had more effect than ECT in stimulating interest and initiative, and in making the patients more sociable.

Isoniazid cannot be considered to be the answer to the treatment for this distressing illness but, in the present state of our lack of knowledge, it does seem that it might have a place as a symptomatic measure in the chronic stages especially if ECT fails. It is a simple, safe remedy, which requires no supervision apart from seeing that the tablets are swallowed. The toxicity of the drug is extremely low and none of my patients showed any evidence of toxicity when on it. The dose I used, 400 mgms. daily, is considered to be towards the upper margin of a safe dose, but I feel it would be worth studying the effects of larger doses. An illness of such severity

as schizophrenia justifies the taking of some reasonable risks in treatment, and pharmacological studies of isoniazid have proved that any toxic changes are in all probability reversible, disappearing when the drug is stopped. From my investigations, I would say that a dose of 400 mgms. daily could safely be continued in most cases for prolonged periods, if not indefinitely.

As the results with isoniazid were approximately the same as those with ECT and insulin coma in the treatment of chronic schizophrenia, I consider that isoniazid is worth a trial in the early stages of the illness.

I mentioned previously two patients who had failed to respond to ECT and who showed no marked change with isoniazid but improved with ECT + the drug. Two further cases gave a similar response. This suggests a field for further study as to whether isoniazid might possibly augment the therapeutic action of ECT and even of insulin coma treatment.

Isoniazid is, as with the other forms of treatment in schizophrenia, an empirical method and therefore a discussion on its possible mode of action will have to be entirely theoretical.

The fact that my findings showed that isoniazid does not produce any significant rise in the blood

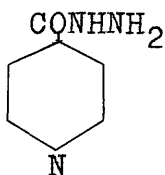
sugar levels of schizophrenic patients does not disprove the investigations of Luntz and Smith who claimed that the drug causes a temporary elevation of the blood sugar level, and makes both the rise and fall of an oral glucose tolerance test slower in diabetic patients and in non-diabetic controls.⁽²¹⁾ Many workers have reported on the frequency of abnormal responses to the glucose tolerance test in schizophrenia and my own results confirmed this. However, Luntz and Smith claimed a considerable rise in the fasting blood sugar with isoniazid while I found no marked change, and it is generally held that the fasting blood sugar of schizophrenic patients is within normal limits. This, and the report of Keeping and Hutchings⁽¹⁹⁾ on the effect of isoniazid on glucose tolerance tests in a small series of cases, would tend to throw doubt on the claims of Luntz and Smith. It would seem that, if isoniazid exerts its effect on the mental state of schizophrenia by disturbing the carbohydrate metabolism, it does so in a more subtle way than by merely raising the blood sugar level.

Isoniazid, in toxic doses in animals, has been found to be a central nervous system stimulant. Acute toxicity in mice and dogs is characterized by excitement and convulsions which were delayed in onset

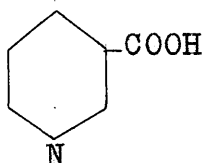
even after intravenous administration. Chronic administration to dogs resulted in anorexia, loss in body weight, ataxia, and tonic and clonic convulsions.⁽³⁴⁾ In man appreciable concentrations of the drug have been demonstrated in the cerebro-spinal fluid within three hours after oral intake.⁽⁵⁾ Selikoff has reported certain side effects occasionally occurring during the early weeks of treatment with isoniazid. They are vertigo, insomnia, constipation or difficulty in micturition which he suggests may be of autonomic origin and twitchings of the lower extremities and increased reflexes, which he considers point to an action of the drug on the central nervous system.⁽³⁶⁾ It is therefore possible that isoniazid acts in schizophrenia by a direct stimulation of the autonomic or central nervous systems, or both. In this connection, it must be remembered the widely held view that insulin coma and electro-convulsive therapies produce their effect by influencing diencephalic mechanisms.

Isoniazid in sufficient dosage is a convulsant drug. Wortis states that most known convulsants, including ECT and insulin hypoglycaemia, promote acetylcholine production and he suggests that they probably effect a redistribution of brain acetylcholine.⁽⁴⁶⁾

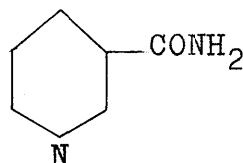
Isonicotinic acid hydrazide is closely allied chemically to nicotinic acid and nicotinamide as is shown by their structural formulae.



Isonicotinic acid
hydrazide



Nicotinic Acid



Nicotinamide

Hoskins' uncompleted studies point towards rather marked deficits in the tissue vitamin stores in schizophrenia, and he underlines the important role played by the vitamins in the enzyme systems of the body.⁽¹³⁾ Nicotinic acid and its amide are both thought to function physiologically by forming part of the molecular structure of several complex enzymes which act as hydrogen carriers in biological processes. The vitamin probably takes part in the metabolism of carbohydrate and it is essential for the normal functioning of the nervous system. The mental symptoms of pellagra are due to a deficiency of nicotinic acid with probably an additional deficiency of other members of the vitamin B-complex. I indicated earlier my opinion that schizophrenia may be caused by a defect in cerebral metabolism due to

a fault in one or more of the enzyme systems. I suggest that isoniazid, which is closely related to a known enzyme constituent, exerts its effect on the mental state of schizophrenia by replacing one of the missing or faulty constituents of the cerebral enzyme systems, thereby bringing cerebral metabolism closer to normal.

McConnell and Cheetham report one case of acute pellagra occurring in the course of isoniazid therapy.⁽²²⁾ Pegum has suggested that isoniazid may block the action of nicotinamide by competitive inhibition.⁽³¹⁾ Zabad also reports a case of mental symptoms developing in a patient on isoniazid who was immediately cured by stopping the drug and administering nicotinamide.⁽⁴⁹⁾ Both of these cases appear likely to have had a latent nicotinic acid deficiency before treatment. This pellagra-type of toxicity with isoniazid must be very rare as no mention of it is made in the reports to the Medical Research Council. McConnell and Cheetham remark that the amount of isoniazid which would compete successfully with nicotinamide in the formation of co-enzymes depends, by the law of mass equilibrium, on their relative concentration and their relative affinity for the co-enzyme residue and that, as no previous case of

fully developed pellagra had been reported during isoniazid therapy, its affinity is probably not great and its pellagra-producing effect depends on the patient's original nicotinamide level being low.⁽²²⁾ I agree with their remarks. In my series of schizophrenic cases, if isoniazid invariably disturbed the cerebral metabolism by blocking the action of nicotinamide thereby depriving the patient of this essential vitamin, one would have expected the majority of my cases to have deteriorated mentally, instead of which 45% actually improved. On the other hand this mechanism could explain the reason why six of my cases deteriorated. An incipient vitamin deficiency is always a possibility in the chronic population of a mental hospital. It is noted that five of these six patients lost small amounts of weight of from 3 to 5 lbs. and the group showed an average loss of 2.7 lbs. while under treatment as compared with the average gain of 2.1 lbs. for the whole series. In further investigations with the drug, it would therefore be advisable to combine its administration with that of nicotinamide.

I consider that the fact that schizophrenia is influenced by this drug is a further support for the view that the illness is due to an organic cause and particularly for the theories of a disturbed cerebral biochemistry.

SUMMARY

An account of the discovery and progress of insulin coma and the convulsive therapies is given. The symptomatology of schizophrenia is described and a review is made of the various theories of aetiology.

The technique of insulin coma treatment and of cardiazol and electric convulsive therapies is presented in detail. The results of these treatments are given and a discussion is made on the selection of cases. The theories suggested as to their mode of action are discussed.

An account is given of the pharmacology and therapeutics of isonicotinic acid hydrazide (isoniazid). It has been suggested that this drug produces a temporary elevation of the blood sugar level and causes a disturbance in carbohydrate metabolism. Sixty patients suffering from schizophrenia of many years' duration were treated with isoniazid administered for varying periods in an oral dosage of 100 mgms. four times daily. 32% showed a definite improvement, a further 13% improved slightly, while 10% deteriorated. In the remaining 45%, the drug produced no significant mental change.

In twenty-nine cases, blood sugar estimations were carried out in the fasting condition and one,

two and three hours after the ingestion of 100 Gm. of glucose. This was done before commencing isoniazid therapy, and one and three weeks later. In six cases, blood sugar estimations were carried out in the fasting condition and then at half hourly intervals to two and a half hours after the ingestion of 100 Gm. of glucose in divided doses by the Exton-Rose technique. This was done before isoniazid was started, and again four and seven days later. On these days the fasting cerebrospinal fluid sugar estimations were also done.

The results of isoniazid in the treatment of schizophrenia are discussed and compared with those for insulin coma and electro-convulsive treatments. Further possible uses for the drug in the treatment of mental illness are suggested. Theories as to its mode of action are discussed.

CONCLUSIONS

1. Isoniazid has a definite effect on the mental state of schizophrenic patients and the results of this treatment in chronic schizophrenia compare favourably with those of insulin coma and electro-convulsive therapies.
2. My findings also suggest that isoniazid might

possibly augment the therapeutic effects of ECT.

3. The investigation confirms the frequent abnormal responses to the glucose tolerance test in schizophrenia as reported by other workers.
4. The results do not support the contention that isoniazid produces a temporary elevation of the blood sugar level and causes a disturbance in carbohydrate metabolism.
5. Isoniazid is closely related pharmacologically to nicotinic acid and nicotinamide, and it is suggested that it acts in schizophrenia by influencing the enzyme systems concerned in cerebral metabolism.
6. While no evidence of toxicity was noted in this series of cases, it is recommended that, in future, nicotinic acid be administered with isoniazid.
7. The fact that the drug does have an effect on the mental state of schizophrenia is considered to be a further support for an organic aetiology for the illness, and particularly for the biochemical theories.

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