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Coma Resistance and Adrenalæmia in the Insulin Treatment of Schizophrenia

By M. S. JONES, M.R.C.P.E.

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WHILE treating schizophrenic patients by the induction of hypoglycæmic coma with insulin, I have been interested in the enormous individual variation to the dose of insulin required. Some patients have had satisfactory comas with 36 units, while others have shown no clouding of consciousness with 300 units.

The existence of "insulin-resistant" cases of diabetes mellitus has long been recognized (Lawrence, 1928; Root, 1929).

Himsworth (1936) considers that diabetics can be divided into an insulin-sensitive type and an insulin-insensitive type. These two types are differentiated on the basis of an insulin-sensitivity test, which is carried out by comparing a routine glucose tolerance curve with the curve following the administration of a certain dose of insulin intravenously to the fasting patient together with a glucose drink. In the insulin-sensitive group the insulin considerably depresses the level of the blood-sugar, and the curve given by glucose + insulin is lower than that given by glucose alone, while in the insulin-insensitive group the normal glucose tolerance curve is not appreciably lowered by the addition of the small amount of insulin intravenously. Himsworth believes that insulin insensitivity is due to the lack of an unknown factor which sensitizes the body to insulin. In brief, Himsworth believes that not all cases of diabetes are due to lack of insulin, but that some, the insulin-insensitive group, might be due to a lack of the sensitizing factor in the presence of normal amounts of insulin.

De Wesselow and Griffiths (1938) could find no evidence for the existence of two distinct types of diabetic patient, and found that it was possible, by means of carbohydrate and insulin, to convert a diabetic from the insulin-resistant to the insulin-sensitive state. They (1936) believe, however, that the sera of certain elderly obese glycosuric patients have the property of inhibiting the fall of blood-sugar which occurs normally after the intravenous injection of 0·2 unit of insulin into the rabbit. In this respect the sera behaved similarly to extracts of anterior pituitary gland.

Young (1936) has described a "glycotrophic" factor present in anterior pituitary lobe extracts which abolishes the hypoglycæmic action of 2 units of insulin given intravenously to the fasting rabbit: this effect could also be demonstrated in the adrenalectomized animal, which suggests that the glycotrophic factor does not produce its effect through stimulation of adrenaline from the adrenals. This is important, because Cope and Marks (1934) have suggested that the insulin resistance of the pituitary injected animal might be due to the liver glycogen stores becoming unusually susceptible to the mobilizing action of adrenaline, so that the development of hypoglycæmia is prevented by the increased production of glucose by the liver.

Cases which result from undoubted overactivity of the anterior pituitary, e.g. acromegaly and Cushing's syndrome, and are associated with hyperglycæmia, show an insulin-insensitive type of response to the insulin-sensitivity test (De Wesselow and Griffiths, 1938; Flaum, 1938).

It is apparent from the foregoing remarks that very little is yet known about insulin resistance, and certainly there is no conclusive proof that an insulin-antagonistic substance can be demonstrated in the blood or urine of insulin insensitive diabetics, acromegalics, or cases of basophil adenoma of the pituitary.

Little has been done in studying cases with a normal glucose tolerance but who demonstrate an excessive insulin resistance. Hall (1938) describes a case undergoing insulin shock treatment, in which the initial injection of 20 units of insulin caused the blood-sugar to fall from 88 to 70 mgm.% in two hours, but who developed such a resistance to insulin that a coma could not be obtained: 1,000 units of insulin given in one injection reduced her blood-sugar from 115 to 80 mgm.% in two hours, while the serum showed a definite ability to inactivate insulin.

We have found several cases in which 300 units of insulin have been unsuccessful in inducing a deep coma after four to five hours, and have studied two such cases in some detail.

The first case is a boy aged 15 whose schizophrenic illness dates from nine months ago. Pubic hair appeared at the age of 10 and erections a year later. He started to shave when aged 13, and now does so every week. The penis and testicles are those of a well-developed adult, and the legs are extremely hairy. Other findings are a normal basal metabolic rate, negative Wassermann reaction, normal eye grounds, absence of glycosuria or ketonuria, and on X-ray examination the pituitary fossa was found to be very shallow and the anterior clinoid processes almost non-existent. The appearance was slightly suggestive of pressure from above, and in front of this area, though there was no evidence of actual bone erosion. The glucose tolerance after 50 grm. of glucose by mouth was, fasting, 88 mgm.%, and half-hourly estimations up to three hours show 95, 129, 134, 117, 106, and 106 mgm%. An insulin-sensitivity test, performed by giving the same amount of glucose plus 5 units of insulin intravenously, showed no significant drop when compared with the glucose tolerance test. The figures were: fasting, 84 mgm.%; after 10 minutes, 90 mgm.%; after 20 minutes, 90 mgm.%; after 30 minutes, 106 mgm.%; after 45 minutes, 113 mgm.%; after 55 minutes, 113 mgm.%; after 70 minutes, 110 mgm.%; after 85 minutes, 120 mgm.%; and after 100 minutes, 110 mgm.%.

He has shown no clouding of consciousness or loss of ability to do calculations after 300 units of insulin, although sweating and increase of pulse-rate, respirations, and blood-pressure, occur. After 100 units of insulin the blood-sugar fell to 56 mgm.% after two hours. After 300 units of insulin the lowest figure found has been 38 mgm.%, but four hours after the injection of 300 units of insulin the figure is usually over 40 mgm.%. On the evidence furnished by the insulin-sensitivity test and the hypoglycæmic response to large doses of insulin, it would appear that this patient shows some insulin insensitivity.

The clinical picture suggests the possibility of anterior pituitary overactivity, which might account for the insulin insensitivity. However, the basal metabolic rate was within normal limits, an assay of a forty-eight-hour specimen of his urine for gonadotrophic hormone showed that this was not present in excess (less than 20 rat units per litre of urine).

Fresh plasma showed no power to inhibit the hypoglycæmic action of 0·2 unit of insulin injected intravenously into the rabbit; the technique employed was similar to that described by Young (1936 *b*).

It is clear, therefore, that we were unable to obtain any indication as to the nature of the insulin resistance in this case, but the possibility of a pituitary or adrenal antagonist cannot be entirely excluded.

The second case, a male schizophrenic aged 24, showed no significant physical findings. His basal metabolic rate was normal, X-ray of the skull showed no abnormality, and there was no evidence of endocrinopathy.

A glucose tolerance test after taking 50 grm. of glucose by mouth showed fasting level 106 mgm.%, and half-hourly figures up to three hours were 124, 150, 130, 104, 99, and 84 mgm.%. With the insulin sensitivity test a marked sensitivity to insulin was shown. The fasting level was 70 mgm.%, and then at ten-minute intervals up to one hour the figures were 63, 52, 45, 34, 48, and 48 mgm.%, then rising to the original fasting level in two hours.

Blood-sugar curves after the injection of 100, 200, and 300 units of insulin gave very similar figures, the smaller doses giving, if anything, lower readings.

The lowest figure recorded at any time with this patient during hypoglycæmia was 18 mgm.%.

In spite of the fact that this patient showed no evidence of insulin insensitivity and gave a hypoglycæmic response to insulin comparable with cases in which coma was easily induced, he proved to be extremely " coma-resistant ". A deep coma was never achieved, and although he had 60 treatment days on 300 units of insulin, he was usually fully responsive at the end of four hours hypoglycæmia.

The problem here is not one of insulin insensitivity but an anomalous response of the central nervous system to hypoglycæmia. It seems necessary to distinguish such " coma-resistant " cases from " insulin-resistant " cases.

We now went on to consider, in a more general way, to what extent the adrenaline response to hypoglycæmia varies in different cases, and whether this might in itself be a factor in the prevention of coma. Cannon *et al.* (1924) have shown that hypoglycæmia calls forth an outpouring of adrenaline and mobilization of liver glycogen. Stewart and Rogoff (1916) state that splanchnic stimulation, continued over many hours, does not result in a failure of adrenaline secretion. Theoretically it might be possible to demonstrate this adrenaline-hyperglycæmic mechanism in any one of three ways: (1) indirectly by clinical observation, noting the occurrence of such evidences of sympathetic activity as increase of pulse-rate and blood-pressure, increased respirations, and dilatation of the pupils, (2) by frequent blood-sugar determinations, (3) by an attempt to measure the blood adrenaline.

(1) Ten cases were followed continuously from the time of giving the usual coma dose of insulin until two hours had elapsed. There is a definite and constant pattern of reaction in the early stages of hypoglycæmia. The pulse-rate, blood-pressure, and respiration rate, change usually within a few minutes of each other, the whole occurring approximately 30 to 60 minutes after the insulin injection. The pulse and respiration rate quicken appreciably, while the blood-pressure shows an increased pulse-pressure, changing from, say, 118/87 to 148/60. This sudden alteration occurs when the blood-sugar has dropped to below 60 mgm.%, the range in this series being 38 to 59 mgm.%. No significant alteration in the size of the pupil was noted up to the time of onset of the above physiological changes, and on only two occasions did sweating start during this period.

These changes do not necessarily result from a sudden outpouring of adrenaline from the adrenals; as a control, 0·05 mgm. of adrenaline was injected intravenously into several cases in the early stages of hypoglycæmia, the result being a sudden rise of pulse-rate and blood-pressure, the response occurring immediately, and conditions returning to the pre-injection level within three to six minutes in the

five cases studied. In this type of response the blood-pressure rises suddenly from, say, 132/60 to 162/90 with no increase of pulse-pressure as occurs in the physiological response to hypoglycæmia.

However, previous studies of the blood-pressure response to subcutaneous injections (Jones, 1935) showed that when adrenaline is absorbed slowly in this manner, there is a tendency for the diastolic blood-pressure to fall, along with a rise of systolic blood-pressure. In other words, the increased pulse-pressure found in hypoglycæmic cases may result from adrenalæmia.

(2) In eight cases blood-sugars were taken at intervals of five to ten minutes after the injection of the usual coma dose of insulin, the pulse, respirations, and blood-pressure, being recorded continuously by a second investigator. When the blood-pressure, pulse-rate, and respirations rose, blood samples were taken as quickly as possible, i.e. at two to five minute intervals. No constant rise in blood-sugar was found to accompany the physiological change, but in four of the eight cases a definite rise of blood-sugar occurred twenty to forty minutes after the onset of the physiological response to the hypoglycæmia ; the rises were from 39 to 66 mgm.%, from 48 to 63 mgm.%, from 36 to 56 mgm.%, and from 38 to 59 mgm.%.

It is thus apparent that any reactionary rise of blood-sugar which may occur does so some considerable time after the onset of increased blood-pressure, &c.

The effect of the injection of 0·05 mgm. of adrenaline intravenously was now observed in five cases, the injection being given two and a half to three hours after the administration of the coma dose of insulin, i.e. when the patient was almost in coma. In three cases there was no rise in blood-sugar at all ; in the other two cases the rise was 34 to 95 mgm.% in six minutes, and 67 to 85 mgm.% in ten minutes.

However, when 0·5 mgm. of adrenaline was given subcutaneously to five cases at a similar stage of the hypoglycæmia, a steady rise of from 15 to 32 mgm.% was obtained in all cases within a period of forty minutes after the injection. This tendency for adrenaline to have less action in raising the blood-sugar when given intravenously than when given subcutaneously is well recognized (Grollmann, 1936).

Our results suggest that the response of the blood-pressure, respirations, pulse-rate, and blood-sugar to hypoglycæmia bear no close relationship to the responses obtained by the injection of intravenous adrenaline to the hypoglycæmic patient, but are somewhat similar to the response obtained when adrenaline is injected subcutaneously during hypoglycæmia. However, much further work is needed to establish this point.

(3) There are many difficulties in attempting to assay the blood adrenaline directly The biological method most frequently used for these determinations is open to many objections and the pressor response measured may not be wholly attributable to the adrenaline. In the living animal, Elliott (1905) found that 1 mgm. of adrenaline was inactivated by the liver in seven minutes, and Rogoff and Marcus (1938) state that when 25 to 50 times the normal output of the dog's adrenal per minute is given in a single injection, only 25% to 50% of the adrenaline may be detected in arterial blood one minute after the injection, while rarely could any adrenaline reaction be detected after two minutes. However, when large amounts of adrenaline were injected at a constant rate for an hour or longer, a small reaction was occasionally observed as long as twenty minutes after the end of the injection.

From these remarks it would appear that if adrenaline is released as a sudden outpouring when a certain hypoglycæmic threshold is reached, then any attempt to obtain a sample of arterial blood during the period of two minutes before the adrenaline is inactivated by the tissues is liable to fail.

Dr. Derek Richter has kindly assayed the adrenaline content of venous and arterial blood during the period when, as a result of developing hypoglycæmia, the blood-pressure, pulse-rate, and respirations, have been raised above the initial level.

The method used was the chemical method developed by Whitehorn (1934) and Shaw (1938), depending on selective adsorption and reduction of an arseno-molybdate reagent. This method is an improvement on previous chemical methods, being more specific for adrenaline and more sensitive. Its sensitivity is comparable with physiological methods.

Six determinations were made on arterial blood removed during the period of physiological response to the hypoglycæmia, and these were controlled by six determinations on venous blood removed after treatment. The figures obtained ranged from 1·5 to 5·9 parts per 100,000,000, with a mean of 3·4 parts per 100,000,000, for arterial blood, and 0 to 3·8 parts per 100,000,000, with a mean of 2·5 parts per 100,000,000, for venous blood. This difference between arterial and venous blood is probably not significant.

It cannot be taken as certain that these figures represent the adrenaline content of the blood, as other unknown reducing substances of this type may be present in blood, but the figures do show that the adrenaline content cannot be significantly higher than the figures given. It is impossible to give normal figures for blood adrenaline, as the methods available are all open to criticism, and it is not definitely established that adrenaline is present in measurable quantities in the general circulation.

0·05 mgm. of adrenaline was given intravenously to a patient in coma, a needle having been previously inserted into the femoral artery, and 10 c.c. of arterial blood was removed immediately after giving the adrenaline injection: this blood sample gave a reading of 2·9 parts in 100,000,000, as compared with a control of venous blood taken after the completion of treatment, which gave a reading of 2·3 parts per 100,000,000. Although such a dose of adrenaline given intravenously has a very definite effect on the patient's physiological condition, it really represents a very high dilution in the patient's blood; if one assumes a blood volume of 5 litres, then the adrenaline is diluted 1 part in 1,000,000,000 and the method used gives definite readings at a dilution of about 1 part in 10,000,000. Similarly, 1·0 mgm. of adrenaline given subcutaneously did not cause a significant rise in the blood adrenaline figure, even though the blood-pressure rose from 120/80 to 180/90, at which time the sample of the arterial blood was obtained. The figures for arterial and venous blood were the same: 2·9 parts per 100,000,000.

In brief, all attempts to obtain a sample of arterial blood in which adrenaline was present in significantly high concentration, either as a result of the physiological response to hypoglycæmia, or to injected subcutaneous or intravenous adrenaline, proved unsuccessful.

To summarize, a case showing normal glucose tolerance, which is insulin resistant judged by the insulin-sensitivity test and hypoglycæmic response to large doses of insulin, is described. In this case there is no definite evidence of anterior pituitary overactivity, and no evidence of " glycotrophic " activity in the blood.

A second case, not insulin resistant, and showing marked hypoglycæmia in response to large doses of insulin but demonstrating " coma-resistance ", is described.

No definite conclusion was formed as to the occurrence of an adrenaline response to hypoglycæmia during insulin treatment, but if this does occur, it appears to be more in the nature of a prolonged adrenaline hypersecretion than a sudden outpouring of adrenaline from the adrenals.

Adrenaline was not found in significantly high concentration in arterial blood when the clinical picture suggested the possibility of an adrenaline response to the developing hypoglycæmia.

[I wish to express my indebtedness to Dr. A. Walters, Dr. D. Richter, Mr. W. T. S. Smith, and Mr. A. H. Tingey, for much help in this study.]

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Dr. W. D. Nicol: The problem of schizophrenia as presented by Dr. Quastel is one of anoxaemia—the dominant facts as he sees them are (1) the demand by the brain for a continuous supply of oxygen and glucose for its normal metabolism and function and (2) the vulnerability and varying sensitivities of nerve cells to oxygen and glucose lack.

This deficiency of oxidative processes is not a new theory: it was postulated as long ago as 1909 by Koch and Mann [1], in their investigation of neutral sulphur.

In 1919 Haldane [2] delivered a lecture on the symptoms, causes and prevention of anoxæmia, which he defined as " a condition in which the rate of supply of oxygen to the tissues by the blood in the systemic capillaries is insufficient for the normal carrying on of life ". The clinical effects of anoxæmia on the nervous system are characteristic—to quote this article " the senses become dulled without persons being aware of it, and if the anoxæmia is suddenly relieved by administration of oxygen or other means the correspondingly sudden increase in powers of vision and hearing is an intense surprise. Powers of memory are greatly affected, and are finally almost annulled, so that persons who have never lost consciousness can nevertheless remember nothing of what has happened. Powers of sane judgment are much impaired, and anoxæmic persons become subject to fixed ideas which afterwards appear to them quite irrational, and to unrestrained emotional outbursts ".

I have risked quoting this clinical description at length because it brings out quite clearly that lack of oxygen in the brain is accompanied by mental symptoms, a fact of which perhaps some of us are unaware. The anoxæmic symptoms described above are immediately relieved by restoring an adequate supply of oxygen. Dr. Quastel himself uses the term anoxæmia somewhat loosely and states that it " denotes not only a state characterized by lack of oxygen but a state in which oxidative reactions are suppressed even if oxygen is freely available." Unfortunately the solution of the anoxæmia of the schizophrenic is not so simple. Loevenhart, Lorenz and Waters [3] in their studies on schizophrenic cases reported that lucid intervals varying from 4 to 20 minutes in catatonic patients could be produced by the administration of high percentages of carbon dioxide and oxygen. This lucidity followed a reaction resembling the fourth stage of anæsthesia. Subsequently Hinsie, Barach and others [4] had schizophrenics living in a converted dormitory for six weeks, during which the oxygen content of the atmosphere was raised to 45–50% and carbon dioxide only to 2–4%, but in all these patients no clinical changes of consequence were observed at any time following the cessation of treatment. Here it must be noted that in these second experiments the element of shock was eliminated. One suggestion put forward by Dr. Quastel is that the nervous tissues are unable to use the oxygen brought to them by the blood—this would correspond to the histotoxic

anoxæmia described by Hadfield and Garrod [5]. In this connexion it might be worth mentioning that Freeman [6] claims to have found a deficiency of catalytic iron in the brain of schizophrenics. Is it not possible, however, that a diminished consumption of oxygen in the schizophrenic might be due to the diminished requirements of the nervous cells in these patients for oxygen and not to any failure to utilize it.

Dr. Quastel puts forward as an alternative theory that " during periods of lowered oxidative metabolism certain nerve cells are destroyed or made inactive " whether in the course of hypoglycæmic shock or narcosis ; he asks whether these destructive processes have eliminated those cells which might have been responsible for the symptoms. It seems difficult to believe that any form of therapy could be so conveniently selective. It must, however, be generally conceded that deficient oxidation in the brain occurs in schizophrenia and extensive researches have been carried out showing the relationship between the respiration and the metabolism of the brain. Yet it would appear that the schizophrenic makes little effort to remedy his lack of oxidation ; on the contrary he shows a tendency to acidosis, shallow respiration is evident (as has been shown by Golla [7] and his co-workers), the thin pulse is not suggestive of increased circulation and on those rare occasions that one can see an autopsy during this disease process, the heart is fibroid, ill-nourished and almost infantile in size.

Dr. Goodall [8] in his Presidential Address to this Section in 1937 made a plea for team work in attacking these problems ; he deplored the fact that biochemical research in connexion with mental disorders is prosecuted in so few laboratories.

These biochemical researches seem to spell chaos to the clinician, yet our own inexact methods must be equally confusing to the chemist. Only by patient research and by means of sifting scientific evidence by collaboration with the scientist can we hope to build up the foundations on which we can interpret this intricate neuropathology with all its inexplicable symptomatology.

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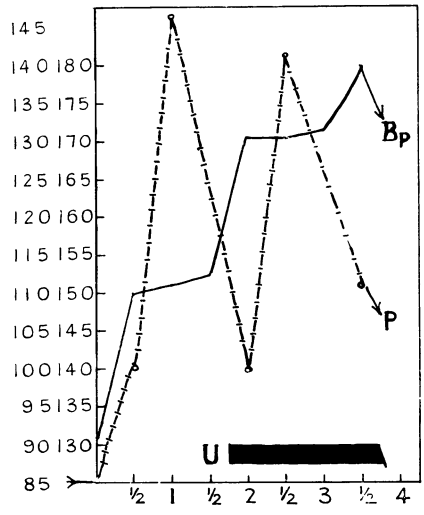
Dr. Francis Reitmann: The assumption that cerebral anoxia was the final agency in producing the results of shock therapy suggested trying the effect of anoxæmia induced directly by low oxygen supply. Dr. R. Fraser and myself undertook experiments on these lines at the Maudsley Hospital. Patients were made to inhale a mixture of 2% oxygen and nitrogen under normal atmospheric pressure. In the course of these investigations, which could not be pursued to a definite therapeutic result, some interesting observations on the clinical picture of pure anoxæmia were made which I should like to mention here, as the uncomplicated picture is not very widely known, and as it permits the drawing of some interesting comparisons with the cardiazol fit.

The diagram demonstrates the cardiovascular symptoms. The blood-pressure rises, the pulse-rate increases very irregularly, the respiration becomes more frequent. The patient's cyanosis is visible in the film. During the unconsciousness marked in the diagram by a black bar, the pupils are wide and do not respond to light. The most significant difference between the anoxic and the cardiazol effects was the complete absence of epileptiform fits from the former. Differences in the motor symptoms will be seen in the film. The vascular responses are very similar, though even there some differences could be found. Pulse-rate and blood-pressure returned to normal more rapidly after the termination of the anoxia than recovery from the cardiazol fit, and no irregularities of the pulse were seen.



The clinical comparison suggests the conclusion that cardiazol produces some other important changes that cannot be produced by severe anoxia of similar duration —most particularly evident in the production of an epileptiform fit. Therefore, although the anoxia may play a part in the pathogenesis of cardiazol effects, it presumably cannot be regarded as the most important mechanism of its action. Even if the effects of anoxia and cardiazol are similar, it does not follow, of course, that anoxia is the pathogenetic basis of its action.

Dr. E. Guttmann showed a film illustrating the clinical picture of anoxæmia as produced by Dr. Fraser and Dr. Reitmann in experiments with inhalation of low oxygen mixtures. The same patient was filmed during a cardiazol convulsion ; the differences in the pattern of neurological response and the different speed of recovery were demonstrated.

Dr. E. L. Hutton : It is with great interest that I have listened to Dr. Quastel's paper to-night. The possible role of anoxæmia as a causative factor in schizophrenia is one that cannot lightly be ignored. When I first became interested in the subject I was fortunate enough to be allowed to study the mental symptoms produced by low atmospheric pressures. By the kind permission of the Air Ministry I was allowed to visit the experimental chamber at Farnborough, where the atmospheric pressure could be reduced so as to correspond with altitudes up to but not exceeding 54,000 ft.

I have here a few notes written by one of the occupants of the chamber when the atmospheric pressure corresponded to an altitude of 17,000 rising to 22,000 ft. I was breathing oxygen from a cylinder, but the writer was not. Both objectively and subjectively the clinical picture he produced was one of alcoholic intoxication. He was originally elated, said he felt like drinking champagne, he thought his own jokes inordinately funny, and he wanted to fight another occupant of the chamber who was about twice his own size. He had some insight into his condition and, like the alcoholic, would occasionally try to pull himself together. I think this alcoholic effect is also shown in the notes.

These visits to the experimental chamber very strongly impressed upon my mind the undoubted fact that anoxæmia does produce very obvious psychological disturbance.

At the same time my attention was drawn to certain similarities between the physical and mental states in sleep and schizophrenia, which have been noted and recorded by various observers [1]. Of particular interest were the changes which occur in the respiratory and circulatory systems in these two states. In both there have been recorded a lowering of the basal metabolic rate, a reduction of the air intake due to slower and shallower respiration, a decrease of the circulatory rate and output, alterations in the acid-base equilibrium, and finally changes indicative of increased tonus of the parasympathetic nervous system.

A hypothesis of auto-asphyxiation seemed to offer a possible explanation of the mechanism of sleep. Dr. Quastel has shown us to-night that the oxygen requirement of brain tissue is high, and it is not improbable that the more highly developed the cell, the greater its oxygen need. If by means of a gradually increasing parasympathetic tonus the oxygen intake could be slowly diminished, one would expect the brain cells gradually to cease functioning, the cessation of function occurring first in the most highly developed cells and then descending the scale until only the vital processes were left functioning. As the parasympathetic tonus waned the oxygen intake would again increase and the cells would resume their function in an ascending scale until full waking consciousness is restored.

As regards the schizophrenic it seemed feasible that in their desire to avoid a painful reality they might be making a perverted use of a physiological mechanism already to hand, whereby they are able to eliminate unpleasant thoughts and feelings by refusing to let their minds function normally. It seemed to me an attractive theory, and I was loth to abandon it. I myself sought to prove the existence of a deficient oxygen intake in the schizophrenic. The technical difficulties encountered deterred me from completing the work and publishing the results, but I convinced myself that there was no arterial anoxæmia, and this has been confirmed by the work of Hinsie *et al.* in 1934 [2].

In 1926 [3] Segal and Hinsie published a paper in which they note " the oxidation of the venous blood in the lungs of our patients was manifestly incomplete ". In 1934, however, it is stated that " the earlier studies of Segal and Hinsie are thus not confirmed. Even in the presence of considerable peripheral anoxæmia, the arterial oxygen saturation was found to be normal ; i.e. the cyanosis must be a variety of stagnant anoxæmia ".

What is the explanation of the respiratory changes in the schizophrenic ? The processes of cell metabolism and cell respiration are as yet but ill understood. The changes occurring in muscle, both during the resting and working phases, seem to have been studied most fully. One may be led into making grossly inaccurate assumptions if one supposes that the metabolic changes in nervous tissue are analogous to those occurring in other tissues, but as even the most highly developed cells trace back their family tree to the same undifferentiated protoplasm, is it unreasonable to suppose that family likenesses do exist ?

Now in muscle the liberation of energy which can be converted into work is due to the breakdown of glycogen into lactic acid and of phosphagen into creatine and phosphate. This is an anaerobic change and occurs in the entire absence of oxygen during the resting stage and to a more marked extent during contraction, but under normal conditions it is checked before all the available glycogen or phosphagen is used up. In this way the tissues are normally prevented from entirely depleting themselves of their store of potential energy. The aerobic phase is concerned entirely with the restitution of the normal store of potential energy, i.e. with the resynthesis of glycogen and phosphagen. By suitable means the cell can be induced to release more of its stored potential energy or can be prevented from releasing so much, but ultimately unless its stores are replenished it finally ceases to function at all.

Is it not possible that oxidative processes throughout the body serve not catabolic but anabolic changes ? A. V. Hill [4] compared the activity of muscle with the function of an accumulator. The electrical energy which a charged accumulator delivers on closing the circuit originates in the end in the supply of energy in being charged. According to Hill, this charging up is being done in muscle during the recovery period when by the expenditure of oxygen potential energy is accumulated. May not this be true of nervous tissue also ?

May we not consider sleep as a mechanism which has been evolved by the organism to prevent an excessive discharge of energy by the nervous accumulator, while providing suitable conditions for the recharging—and not only for the recharging but for the overhauling and reconditioning of the accumulator itself. If this is the case, any oxygen deficiency during sleep would defeat this object, and therefore on purely theoretical grounds becomes improbable.

Here I would repeat my suggestion that the schizophrenic is making a perverted use of the sleep mechanism ; that he uses it to inhibit painful and unpleasant mental processes—he uses it to prevent the discharge of nervous energy—and if the accumulator is but little discharged, there is equally little need for recharging, i.e. equally little need for oxidation.

Meyerhof [5] writes : " In the work of muscle the explosive formation of lactic acid is the decisive event, while the removal of lactic acid means recovery. Now it is evidently easier to obtain an instantaneous effect by increasing a chemical effect which is already under way than first to set it going. Respiration at rest is subservient to the readiness for work. We may compare it to the state of a cranked motor car standing still ! " Might we compare the schizophrenic to a driver whose previous driving experience has made him so apprehensive that he has tried to shut off his engine, and in some cases has throttled it down so successfully that it barely manages to tick over, and therefore later willy-nilly he cannot make the car go. In such a case, if the engine is violently cranked up and his fears of driving are removed by kindly advice and encouragment, this timid motorist may yet be able to make good use of his car. In the same way it is possible that shock therapy stimulates the retarded metabolism of the schizophrenic, while the subsequent psychotherapy, which has been found to be so useful an adjuvant, enables him to face with greater confidence the problems which led to his original breakdown.

In Dr. Quastel's experiments may not the anoxæmia found by him be the result of these violent metabolic changes induced by insulin and cardiazol, the principal factor being an excessive discharge of potential energy in the nervous system. If this be so, then the deficient aeration which occurs in schizophrenia and the altered oxygen consumption in insulin shock, cardiazol and narcosis are the results and not the causes of the physical and mental changes observed during this psychosis and its various methods of treatment. I should like to take this opportunity of thanking Group-Captain Struan Marshall for the assistance he has given me in these investigations on anoxæmia.

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3 SEGAL, L., HINSIE, L. E., *Am. J. M. Sc.*, 1926, **171**, 727.
4 HILL, A. V., quoted by O. Meyerhof, " Chemical Dynamics of Life Phenomena ".
5 MEYERHOF, O., *ibid.*

Dr. J. H. Quastel (in reply) said : I have not ventured to make any statement in this paper to the effect that schizophrenia is characterized by anoxæmia in the nervous system, or that the latter condition is a causative factor in schizophrenia. I know of no decisive evidence which would lead to either of these conclusions, and the experimental difficulties in the way of securing such evidence are indeed great. It is, however, well known that an anoxæmia in the nervous system does lead to mental symptoms resembling those encountered among psychotic subjects, and it is a plausible view that some of the psychoses, themselves, may owe their origin to a deficient oxidative metabolism somewhere in the nervous system. Such a view, however, is far from proved, and must be considered at present purely as a working hypothesis. I have tried to show that the experimental evidence points to the dependence of brain, for its normal metabolism and function, on a continuous supply of oxygen and glucose, lack of either of these leads to changes in the nervous system which may become irreversible and the extent of which depends upon the period of anoxæmia or hypoglycæmia. Yet the treatment of mental disorder by narcosis, insulin, or cardiazol therapy, appears to have a common factor, the production of anoxæmia, or of a suppression of oxidations in the nervous system. This may be quite fortuitous. If the securing for a short time of a lowered oxidative metabolism in the nervous system leads to beneficial results in certain classes of psychotic patients, it would be expected that the exposure of such patients to atmospheres poor in oxygen might lead to equally beneficial results. The clinical picture obtained in this form of treatment may well differ from that observed in cardiazol or insulin " shock " treatment, for the mode of securing " anoxia " differs greatly. The important matter, however, is whether the form of treatment in question can lead to an improvement in the mental state. Experiments on lines similar to these should eventually yield sufficient evidence to enable us to decide whether the improvements effected by present-day psychiatric therapy are definitely associated with alterations in the oxidative metabolism of the nervous system.