HISTAMINE AND INSULIN IN THE TREATMENT OF SCHIZOPHRENIA AND OTHER MENTAL DISEASES.*

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EARLY WORK.

ABOUT twelve years ago, apart from mental work, I had occasion to use insulin to some considerable extent for the treatment of diabetes and the preparation of diabetic cases for operation, and acquaintance was thus made with hypoglycæmic shock. Most of us have had that experience. Insulin has been tried more recently in a large field, being used as a remedy in conditions of all sorts, even as a dressing for septic ulcers. But the writer's scope has been more confined, the extent being limited to mental cases.

Later on, during special examinations of the urine in different cases of mental disease, many specimens were found to contain ketone bodies. These cases were given insulin and glucose. Most of them showed improvement at once. Others resisted the treatment, and many devices were tried, one of the methods being the administration of insulin without glucose. Although the ketone bodies did not entirely disappear in some cases, the patients' condition improved to a noticeable degree.

In the light of present-day knowledge, one should have recognized what is now known to be a fact, namely, that the improvement was due to the resulting hypoglycæmia, without shock—an important point, not appreciated at the time. For lately, in several quarters it has been stated that a longer and slower hypoglycæmia, without shock or coma, might in the end prove more beneficial in schizophrenia and other mental diseases.

After that, insulin was tried in a considerable number of mental cases without ketonuria, with varied and indefinite results, some cases improving and some not, for no apparent reason. The only point to emerge at that time was that cases which had recently had very acute symptoms seemed to improve under this treatment.

Since the introduction of insulin, insanity from diabetes seems to have become very rare ; and here, again, we have an instance of the hypoglycæmia produced by insulin lessening or preventing mental symptoms.

Later still the shock treatment of schizophrenia by insulin was introduced and the action of insulin was then considered in this new light.

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Investigation of the Insulin Shock Method.

Observers have reported that during shock treatment patients have suffered from epileptic fits, *status epilepticus*, coma, migraine, laryngeal and bronchial spasm, convulsions, cramps, tetany, sepsis, exhausting sweating, loss of reflexes, stridor, aphasia, paralysis of the heart and respiration, profound collapse, violent restlessness, great salivation, great fear and terror and other alarming phenomena, including grimacing and senseless laughter, giddiness, hemiplegia, flushing of the face, tremor and twitching of limbs, deathly pallor, lockjaw, racing pulse over 140, Cheyne-Stokes breathing and œdema of the lungs. Death sometimes takes place, and is due to faulty doses of insulin, or to the coma being allowed to last too long, or coma coming on too early or too rapidly, with no sweating, starting of the insulin dose too high, or increasing it too quickly.

This is a formidable list, and seems to be a disorderly sequence of rather meaningless names As a matter of interest these names are kept in the exact order in which they were originally written down After studying this list for some time, it appeared that a number of the symptoms could be attributed to the action of toxic doses of histamine, which is known to be formed in all cases of shock. The list can, therefore, be divided into two, one being a list of symptoms caused by toxic doses of histamine, the other list comprising the symptoms caused by hypoglycæmia. Insulin, as will be seen later, may augment the action of histamine, and vice versa.

Action of Histamine.

Histamine is present in every variety of shock, including anaphylaxis, surgical shock, the shock of acute intestinal obstruction, and the shock of extensive burns. It has been established that all nervous stimuli (including shock) evoke a chemical substance which translates for the tissues the messages received from the nerves, and in the case of shock this appears to be histamine.

Histamine is a peculiar substance. It even acts differently in animals of the same species, and under different experimental circumstances. It contracts the capillaries of a cat, but dilates the capillaries of all other species. Even in the cat this action may be reversed under different circumstances.

Again during anæsthesia its action may be reversed. Under some conditions it has great physiological activity; some of its effects can be seen in solutions as weak as one in several millions. There is also a peculiar paradox about its action on the blood-pressure, for although it stimulates plain muscle-fibres intensely, there is a profound fall of blood-pressure. This has been proved to be due to the fact that the great arteries and veins are emptied. The veins are constricted and the capillaries widely dilated, their walls being made more permeable and the plasma of the blood exudes through. Thus it will be seen that under different conditions histamine is notoriously fractious

and contrary in its action, and springs surprises, but it always acts in the same way under the same circumstances. It is the circumstance which alters its action, and insulin is such a circumstance. The amount of histamine liberated under insulin shock is large, probably because there may be an alteration in the permeability of the walls of the muscle-cells leading to a liberation of intracellular histamine.

Histamine increases the flow of gastric juice ; it is used as a test in gastric cases. It increases the movements of the stomach and intestines, and stimulates the gall-bladder, all of which tend to rectify the stasis so common in mental cases. The blood-capillaries of the brain, as well as those of the rest of the body, dilate and there is an increased flow of blood through them. Their walls become more permeable, and blood-plasma passes through them with greater ease, carrying what is necessary to the cells for their function.

This happens in histamine shock, and a good deal of the blood in the body is collected in the capillaries. The capillaries of the intestines and pancreas are specially dilated. Those of the arteries, great veins, liver and lungs are empty. The increased flow and permeability allows of the delivery of more oxygen, and this is also what mental cases require.

The health of the mind and the oxygenation of the brain are closely connected. This is shown in the failure of a diseased heart accompanied by delusions, and the elation felt by those diving under pressure. Deficiency in oxidation plays a part in the phenomena of schizophrenia ; it is generalized, and also affects metabolism, as noticed in the disturbed acid-base equilibrium, and in other ways also, as in the lowered basal metabolic rate. The decreased fragility of the red corpuscles may also be due to the general tendency to deficient oxidation.

Again, histamine increases lacrymal, bronchial, salivary and intestinal glandular secretions. It increases the flow of urine ; it increases the flow of adrenaline. This adrenaline in the presence of insulin and histamine may act more powerfully than usual, for it is possible that it produces the terror exhibited by those under insulin shock.

In medicinal doses the production of adrenaline by histamine would fall short of this toxic effect, and produce pugnacity—the very thing to shake a schizophrenic out of his apathy.

When applied to the skin histamine produces the phenomena known as the triad of Lewis. This could possibly be used as a test for the patient's reaction to histamine, and to form some idea as to whether the patient was over-sensitive. It increases the heart-beat. Flushing is a very common early symptom. Histamine stimulates the autonomic system and smooth muscle. The chlorides in the blood decrease. It does not affect the coagulability of the blood. It causes an increased flow of lymph from the thoracic duct. The first result of a big dose of histamine after the flushing is a big fall in blood-pressure by 50 or 60 mm. followed by a short rise, and then a slow gradual fall.

Local inflammation is nature's remedy for any local disturbance, and this has been imitated in curative methods, such as the heat of fomentations and of diathermy, or in passive congestion induced by a tight bandage. Histamine also seems to imitate nature's method by causing what might be described as "local inflammation" throughout the whole body.

Effect on Mental Cases.

The first trials gave encouraging results. Insulin was then given as well, and this hypoglycæmia, combined with the effects of histamine, has yielded up to the present results which compare favourably with the shock method according to published figures, with the addition that it seems to have a greater beneficial effect on cases of long standing. A change in the patient's mental state coincides with the hypoglycæmia and effects of histamine, and it seems that this change tends to last longer and longer as the treatment goes on, probably due to the fact that the permeability of the wall of the capillaries tends to become more permanent as histamine is used.

Dosage.

The dose varies in many cases. The standard dose is 0·5 mgrm. A poisonous dose can be anything from 2 to 8 mgrm. It is well to begin, if one is not used to the method, with 0·1 mgrm. and to remember that histamine acts differently under different circumstances, but always the same under the same circumstances. It is only by experience that one can gauge what is necessary. Again, histamine and insulin act differently when given together than when given separately.

The injections of histamine may vary from two a day to two a week, being given with insulin. The dose of insulin may be anything from 5 to 10 units or more, and may be given twice a day or twice a week. The recorded cases were given histamine and insulin, and the proportion of histamine to insulin in any given dose also varies.

The indications for correct dosage are the sensations of the patient, who should remain free from unpleasant sensations throughout the course; the analysis of the flush (it should not extend over the whole body); the progress made, and attention to the precautions mentioned in the paper.

Precautions.

The employment of histamine as a remedy at present will vary according to the requirements of individual cases, and as I have just mentioned, in the absence of any measurable indicators is largely a matter of detailed clinical analysis and not a little experience, owing, as we have seen, to the drug's

peculiar actions under different circumstances. Sensitiveness to histamine varies very much in each individual, and there are some contra-indications to its use.

The length of a course varies from one month to six weeks. It is most advisable to stop it, and if necessary repeat. On recommencing, the dose must always be smaller than the last one given. Every case appears to require a little adjustment in size of doses and spacing of doses.

Histamine causes a fall of temperature, most noticeable in the rectum. This should be watched, so also should the blood-pressure. Asthma, increased blood-pressure, heart and liver disease are contra-indications. Blood-sugar and metabolic rates might be watched. Anæsthesia increases the danger of histamine shock.

I do not think that faulty circulation and cold extremities are contra-indications, although I have seen them quoted as such. The patient should be under observation and control, and have the services of a nurse.

Results.

There are 34 cases, and from this list it becomes apparent that histamine acts well in schizophrenia, and in cases coming on at the time of the climacteric in women. In this list there are 12 cases of climacteric mental disorder, 18 cases of schizophrenia (10 females and 8 males), and 4 in elderly men.

	Cases treated.	Well.	Improved.	Indefinite.
Climacteric	12	6	4	2
Schizophrenics	18	6	6	6
Elderly men	4	2	2	..

In investigating the case of the men the only common factor amongst them is that they have all suffered from prolonged worry or prolonged shock.

By saying that a case becomes well I mean that the patient is able to live a normal life outside an institution, and that those who previously had recurrences have been free from them for a longer time than before. By improvement I mean a decided change towards normality. In the case of schizophrenia it means a wish to come out into the open and mix with his fellow men, and an increased tendency to take an interest in all his surroundings and discuss his position.

Some cases appear to hang fire, and a new investigation is taking place with these cases, using protamine insulin or zinc protamine insulin instead of the simple insulin.

The following are illustrations of other types of mental disorder, included in the above table, which have been treated with success:

CASE 1.—Female, aged 45. Admitted October 16, 1936. Ferocious, savage and violent; she was murderous and suicidal. This lasted for about a month, when she began to get quieter. By December 15, 1936, the patient was beginning to be stuporose. In a fortnight she was oblivious to her surroundings, remaining stationary, whether standing or sitting. She never moved or took the slightest notice of anything. Her attention could not be attracted. She took no notice of Nature's calls. She could not feed herself, dress or undress, or perform the simplest act of toilet. She did not speak after Christmas, 1936.

She was given a short course with not much result. She had a second course, which was especially thought out and adapted. Her condition after the second course was completed was as follows:

She was no longer stuporose, but moved about the room and sat down naturally. Her attention was easily attracted, and she took notice of things going on around her. She went to the lavatory on her own accord. She fed herself, dressed and undressed, and did her hair. On March 29, 1938, she spoke for the first time for fifteen months, and asked for some more rice pudding, recognized a nurse, and called her by her nickname of "Micky".

This course was stopped about a month ago, and some of her symptoms returned. She is now once more on another course with different doses and different planning, and protamine insulin or zinc protamine insulin will be tried with large doses of histamine.

CASE 2.—Female, aged 49. Ill for a year; has a history of about five years. She was very difficult to manage before admission. She was obstinate and resistive. She had an ever-present delusion that her clothes were not her own, and that anything she ordered from a shop was never sent correctly. She had eternal rows with the shops, and was constantly ringing them up on the phone and accusing them of all sorts of things, at the same time having a row with the P.O. officials, saying that whenever she telephoned, the same voice cut in and interrupted her order, no matter where she telephoned. Things got so bad that eventually no one could stand it any longer, and she had to be certified for these and other reasons. She is now some way through her course. She is very amenable, reasonable, pleasant and grateful, and has a charming personality. She went for a long walk the other day, and her shoes rubbed one of her heels. She mentioned it to me, and did not take the opportunity to declare that that was one more proof that her clothes were not her own, and that even her shoes had been changed, hence the blister.

When I suggested that it seemed odd that her shoes should do that, she replied that she thought so too, as she had had them for years and they had never done such a thing before. That conveys to mind that the treatment is having a good tendency: it is, or appears to be, altering her personality back to normal. But this patient is not well enough yet to place on my list as improved.

CASE 3.—Manic-depressive. After treatment patient says that she has not felt better for years, that she is 100% better, and that during the winter she has put on a stone in weight. She walks a lot, rides in "point-to-points", drives her car, lives a perfectly normal life and is going to have a holiday abroad.

This case has a bad family history; father certified, mother neurotic and committed suicide; other relations have been in mental homes. She has had a great number of previous attacks, and always in the winter. She has been quite well since she left me last October.

CASE 4.—The history of this case is similar. She also left me last October, and I saw her medical attendant last week and he told me that she had remained as fit as a fiddle, and had become very fat. It is peculiar that patients after this treatment often put on weight. This is that sort of case which goes on my list as "Well".

As time goes on one gets to know the type of case most likely to respond to treatment, and in compiling this list one might, by only including such cases, make these tables seem much more favourable. But no good purpose would be served by doing this, for it would only confuse the issue, and tend to discredit the method.

Seventy-five per cent. of the cases in my tables are or were certified.

Treatment of Early Cases.

It appears that the earlier this treatment is adopted the better the results, as it is in insulin shock, although this method has, in addition, marked effect in cases of five or six years' standing, and in other mental diseases as well as in schizophrenia.

General Survey.

With big doses of histamine the main cause of shock is the collection of blood in the capillaries, and the emptying of the main vessels. Medicinal doses still produce a great increase of flow through the capillaries, and especially increase the permeability of the walls but do not produce shock, and plasma flows through easily. This general change throughout the whole of the body is exactly what takes place in local inflammation, namely, the widening of capillary lumina, the opening up of channels normally empty, and the transudation of plasma through the endothelial walls, carrying to the cells of the brain and the body oxygen and chemical substances in solution necessary for their normal activity. It is this question of activity which I think is of importance.

It is well known to everyone that patients who for months have been incoherent, muttering, deluded and completely insane, may suddenly for two days or so talk and behave rationally and even go to a cinema and thoroughly enjoy it, only to go back just as suddenly to complete insanity. This seems to show that the brain-cells are neither destroyed nor dead, or even harmed (post-mortems bear this out), but are deprived of some substance which is necessary for their function. In these cases it seems that the cell is alive and its function alone prevented. For some reason the endothelial walls of the capillaries suddenly become more permeable to the substance necessary for the functional activity of the brain-cells, and the patient becomes rational.

Again, in cases which are perfectly normal by day, and deranged at night, the same thing is probably seen. The physical activities of the body by day are sufficient to keep the circulation and heart going with enough speed and force to maintain a sufficient supply to the cells. The barrier is weak and not difficult to overcome. At night, when fatigue is effective, and activities are in abeyance, the lessened circulation and the closing of channels normally open allow the barrier to have effect.

It appears that histamine acts by its power of making the endothelial wall of the capillaries more permeable to normal plasma, thus enabling the cells once more to obtain the substances requisite for their normal function which are carried in the plasma; the non-functioning of the cells being due to a pathological barrier to the normal passage of the plasma, this barrier being situated in the endothelial cells of the capillaries.

Conclusions.

It can reasonably be claimed that the method of treatment by histamine and insulin is natural and in accordance with physiological principles, and therefore on a rational basis. Toxic doses of these substances are not necessary. The results are good, the percentage of success being about the same as in the shock method, with the advantage that this method seems to have far more effect in chronic cases and is applicable to cases other than schizophrenia.

From what has been written it is obvious that this method is quite unsuitable for out-patients.

References.—Dale, *Journ. Phys.*, 1906, xxxiv, pp. 163–206.—*Idem, ibid.*, 1911, p. 182.—*Idem, ibid.*, 1918, lii, pp. 355 and 110.—*Idem, ibid.*, 1913, xlv, p. 275.—*Idem, ibid.*, 1926, lxi, pp. 282 and 185.—Dale and Laidlaw, *ibid.*, 1910, xli, pp. 318 and 344.—Editorial, *Lancet*, June 20, 1936.—Editorial, *Brit. Med. Journ.*, April 23, 1928.—Ewald and Salm, *Brit. Med. Journ.*, August 28, 1937.—Gillies, *ibid.*, April 10, 1937.—Harmer, *Heart*, 1924.—*Idem, ibid.*, 1926, xiii, pp. 381–394.—James, *Lancet*, May 8, 1937.—*Idem, Brit. Med. Journ.*, February 19, 1938.—*Journ. Med. Soc., New Jersey*, March, 1937.—Larkin, *Brit. Med. Journ.*, 1923.—Lewis, *Blood-vessels of Human Skin and Their Responses.*—Leyton, *Brit. Med. Journ.*, January 8, 1938.—Parfitt, *Proc. Roy. Soc. Med.*, xxxi, p. 137.—Russell, *Lancet*, March 27, 1937.—Wilson, *ibid.*, September 26, 1936.