CARDIAZOL TREATMENT OF SCHIZOPHRENIA.*

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SCHIZOPHRENIA.

THE term " schizophrenia " was first introduced by Bleuler (1) as descriptive of the dissociation and fragmentation of mental processes which he regarded as the chief characteristic of the condition. There is " a detachment from the world without, and a breaking up of normal psychological connections within. The personality is not integrated as in normal people; thinking emotion, and conduct are discrepant and morbid, yet there is no impairment of formal intelligence such as is found, for example, in organic dementia " (Mapother and Lewis (2)). To quote Bleuler (1), " even though we cannot as yet formulate a natural division within the disease, nevertheless schizophrenia does not appear to us as a disease in the narrower sense but as a disease group, about analogous with the group of the organic dementias, which are divided into paresis, senile forms, etc. One should therefore speak of schizophrenias in the plural. The disease at times runs a chronic course, at times in shifts; it may become stationary at any stage or may regress a certain distance, but probably does not permit of a complete *restitutio ad integrum*. It is characterized by a specific kind of alteration of thinking and feeling, and of the relations with the outer world that occur nowhere else ".

With regard to prognosis there is now a considerable general measure of agreement. It is in all cases regarded as doubtful, but the following features are of hopeful import: abrupt onset of the illness; adequate precipitating cause; a pre-psychotic personality which was well adapted, had wide interests and showed a vigorous healthy reaction to difficulties; prominence of manic-depressive features; previous attacks with an interval of normality between (1) (2).

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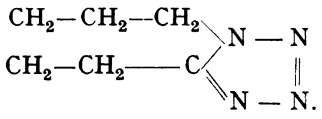
The Pharmacology of Cardiazol.

Pentamethylene tetrazol, or cardiazol, is a synthetic drug originally produced for use as a circulatory and respiratory stimulant. Its structure may be recalled here : *



The first reference to it in the literature is the paper of Schmidt, Hildebrandt and Krehl (3), who state that it stimulates the isolated frog's or mammalian heart, and has the pharmacological action of camphor with the advantage of being readily soluble in water. This is followed by an appreciation of its clinical value by Ruef (4). Papers testifying to its clinical efficacy in cases of acute circulatory and respiratory collapse soon appeared (Hinricks (5), Hemmerling (6), Kaiser (7), Pichler (8), Lange (9), Feriz (10), Waldbott (11), Henderson and Sparks (12)).

It was said to stimulate the isolated heart also by Hildebrandt (13, 14), Strube (15), Sanders (16) and Fahrenkamp (17, 18), but this was denied by Stross (19), Camp (20), Gremels (21, 22) and Leyko (23). Stross found that the effect on the blood-pressure was lost when the animal was decapitated, and Leyko that it had no effect on a heart-lung preparation. Barker and Levine (24) were alone in finding that it was without action on the cardio-respiratory mechanism, probably because their animals were too near death to respond. Helaers (25) and Schubel and Gehlen (26) found that the margin between the therapeutic (respiratory and circulatory stimulant) and convulsant dosage is narrow. The absence of secondary and depressant effects is emphasized by Hildebrandt (13), Adam (27), Buding (28), Tartler (29) and Kohn and Jacobi (30). Maloney and Tatum (31), however, find in experimental animals that injection causes an initial fall in blood-pressure, followed by a rise, and in a later paper Maloney (32) describes the production of depression and death with large doses. Tinnitz and von Bergman (33) describe a prolonged rise of blood-pressure with no preliminary fall.

Analysis of its effect on the central nervous system was first attempted by Blume (34), who, working with decapitated cats, found that the reflex irritability of the cord was increased, the chief effect being on the receptor portion of the arc. He found that it was possible to produce convulsions in these animals with large doses. Camp, using frogs, found that convulsions could be produced as long as the connections between the medulla and spinal cord remained intact. He concluded that it acted specifically on the medulla. Knoefel

* The designation " cardiazol " is a proprietary name. The drug is marketed in America under the name of " metrazol ". It is also manufactured in Holland, Hungary and Switzerland under the names of " corvis ", " tetracor " and " pentazol " respectively.

and Murrel (35), after a sufficient amount of cardiazol, obtained co-contraction of flexor and extensor muscles by stimulation of a homolateral sensory nerve. Blume's results agree well with those of Muskens (36), who used the pharmacologically allied camphor monobromide to investigate the production of convulsions, finding that no one system or part of the brain was necessary, but that the presence of lesions, especially if they involved the pyramidal tracts, raised the convulsant dose. There is some evidence that it restores cortical function when it is depressed by drugs. Quoting Fulton and Keller (37, 38), " in experimental monkeys under ether or barbiturates cardiazol appears to be a specific stimulant to the cerebral cortex, restoring cortical excitability within 5 or 10 minutes after subcutaneous injection ". From the context it appears to convert an extensor plantar response to a flexor. Silver (39) describes a state of hypersensitivity to painful impulses produced by pernocton in the rabbit, in which merely touching the skin with a sharp point causes the animal to jump vigorously. He finds that cardiazol is adjuvant to morphine in abolishing this state, and it appears probable that this action is due to restoration of cortical control over the thalamus.

Increase in the respiratory volume has been demonstrated by Behrens and Reichelt (40) in rabbits, and in both the respiratory rate and volume in man by Steiniger and Gaubatz (41) and Hicks (42). Muller (43) states that it sends up the respiratory quotient. Eichler and Hildebrandt (44) find that it produces irregular changes in limb volume, due to stimulation of the vasomotor centre.

Many workers have demonstrated an antagonism between it and almost all narcotic drugs (Schoen (45), Henderson and Sparks (12), Mehl (46), Tartler (29), Philips (47), Orestano (48), Maloney and Tatum (31), Maloney (32), Schlaepfer (49), Fulton and Keller (37, 38), Gros (50), Tinnitz and von Bergman (33), Gros and Haas (51), Lendle (52), Zipf and Hoppe (53), Albus (54), Koll (55)). This is shown in several ways : the lethal dose of either may be greatly raised if the other is administered along with it ; the convulsant action of cardiazol may be inhibited by narcotics or their narcotic effect may be diminished by cardiazol. The relationship between the narcotic and anticonvulsant action of drugs has been investigated by von Nyary (56), Jackson (57), and Biehler (58), using cardiazol as the convulsant. They demonstrate conclusively that these two effects are almost independent, and that a drug may have a high anticonvulsant but a poor narcotic action and vice versa. On the other hand, it is clear from such experiments as those of Albus (54) and Zipf, Windshus and Kokoschka (59) that cardiazol has a marked antinarcotic or " waking " action. Jackson's work suggests that depressed functions are the first to be stimulated.

Hoffman (60), working with narcotized rats, found that in their effect on the blood-pressure cardiazol and ephedrine were adjuvants, but Biehler (58) found that ephedrine had no influence on the convulsant action of cardiazol. Labes, Wedell and Soehring (61) demonstrate the adjuvant action of cardiazol and cyanides as convulsants. Flossbach and Weber (62) state that if cardiazol

be given along with quinine, the concentration of the latter in the blood will rise higher and persist longer than if it be given alone. Johnston (63) observes no change in an electrocardiographic record following its administration. Zunz and Tremonti (64) believe that it stimulates the respiratory centre directly, in contrast to coramine, which acts through the carotid sinus and is without effect when this is denervated. Rice and Isenberger (65) find that when it is injected intracisternally it has no effect.

De Morsier, Georgi and Rutishauer (66) were unable to find any lesions in the brains of rabbits killed after a series of cardiazol fits or by one lethal dose. Stender (67) found very indefinite signs of damage to the ganglion cells of the cornu ammonis and occasional small subpial hæmorrhages.

The significance of susceptibility to cardiazol convulsions has been discussed. Langeluddeke (68) produced fits in post-encephalitics, schizophrenics and other types of patient, finding no great difference in susceptibility between epileptics and non-epileptics. He concluded that it was of diagnostic value in fits of doubtful nature, as, if they were truly epileptic the fits produced by cardiazol would resemble them. Schönmehl (69) believes that epileptics react with smaller doses than non-epileptics because their "convulsion centre" is more excitable. He is supported by Stern (70), and Grubel (71) goes further, stating that it not only measures susceptibility to convulsions in general, but also hereditary predisposition to them. Kruger (72) and Ganz (73) find it of no diagnostic value.

I cannot find any adequate investigations into the mode of excretion of cardiazol. Voss (74) believes, on inadequate evidence, that the kidneys are the chief organs concerned.

It is clear that cardiazol has a profound and widespread action on the central nervous system, excitability and conductivity being greatly increased. The result is first a stimulation and restoration of depressed functions, rapidly passing to unco-ordinated activity and convulsions.

The Physiology of Convulsions.

Our knowledge of the physiological changes underlying and accompanying convulsions is extremely unsatisfactory, but it is perhaps not out of place at this point to review any work which may conceivably shed light on the mode of action of this treatment.

Wortis, Coombs and Pike (75) described the effect of camphor monobromide in the cat and, concluding that the fits produced were very similar to those of idiopathic epilepsy in man, proposed that the drug should be used as a standardized convulsant for experimental work. They appear to be identical with cardiazol fits. Muskens (36) had previously carried out extensive experiments with camphor monobromide on cats with various central nervous system lesions, with the results previously referred to. Coombs and Pike (76),

using this drug, found a preliminary fall of blood-pressure, arrested and converted to a rise when clonic convulsions appear. The rise is produced entirely by muscular action, and is prevented by the previous administration of a paralysing dose of curare or by transection of the spinal cord above the level of the third dorsal segment. If the blood-pressure is low, clonic convulsions do not appear, but if adrenaline is administered they will begin as the blood-pressure rises. Respiration is accelerated by subconvulsive doses, but with high doses respiratory failure may ocur. Death, when it occurs, is due to a great fall of blood-pressure, which can usually be arrested by intravenous adrenaline. They consider that the cause of the convulsion is the direct excitation of the motor cells of the cerebrum. Coombs and Cope (77) find that the intravenous administration of acetylcholine will stop the clonic convulsions, presumably owing to fall in blood-pressure, but has no effects on the tonic stage. Denny-Brown and Robertson (78), working with fits induced by overbreathing in epileptic subjects, found that changes in the blood and cerebro-spinal fluid pressure were limited to a rise produced by involvement of the thorax in the convulsions and asphyxia. Gibbs, Lennox and Gibbs, (79) using the same material, inserted a thermocouple into the internal jugular vein to measure the cerebral blood-flow, and found no disturbances preceding or in the early stages of the fit, although as the convulsions became violent the rate of flow tended to increase.

These results contrast sharply with Drabkin and Ravdin's (80) work on hypoglycæmic convulsions, which they found to be produced by the following cycle: severe hypoglycæmia ; anhydræmia ; rise of cerebro-spinal fluid pressure to a critical level ; convulsions. Measures designed to prevent the anhydræmia, such as the administration of sodium arabinate, would prevent convulsions, although quite ineffective against oil of wormwood—a drug closely allied to camphor, which they consider to be a direct cerebral irritant. If the animals were previously dehydrated, the rise in cerebro-spinal fluid pressure was diminished and convulsions did not occur.

Spiegel and Spiegel-Adolf (81) have investigated by means of polarization studies various factors known to produce increased excitability of the central nervous system. They conclude that two possible mechanisms exist: (*a*) a change in ion concentration on the surfaces of the nerve-cells, and (*b*) diminution of the density of the cellular surface films. If their work is valid it is probable that cardiazol acts in one of these two ways.

Asher and Takahashi (82) make the observation that the carbohydrate in the brain is never mobilized except in circumstances producing increased excitability. This is interesting in view of the known importance of carbohydrates in brain nutrition (Himwich and Nahum (83), Holmes (84)), the various attempts that have been made to attribute schizophrenia to a disturbance of carbohydrate metabolism, and the implication that cardiazol will produce such a mobilization. Prados y Such (85), working with camphor monobromide in cats, found that the convulsions increased the permeability

of the hæmato-encephalic barrier to trypan blue and other dyes, giving good reasons for supposing that this was not due to rupture of capillaries.

One may conclude that the epileptic reaction is dependent on physico-chemical changes in the nerve-cells, probably of the kind indicated by Spiegel and Spiegel-Adolf (81), and that all other effects are secondary to the resultant motor discharge. The mechanisms by which epileptic convulsions and those produced by analeptic drugs on the one hand and hypoglycæmic convulsions on the other are produced appear to be fundamentally different, this providing a rationalization for von Meduna's (86) view that the hypoglycæmic convulsion is undesirable in the treatment of schizophrenia. No one part of the central nervous system is necessary, and the use of the term "convulsion centre" by certain Continental writers is obviously quite unwarranted.

Technique of Treatment.

The technique followed at Bexley in the treatment of schizophrenia by cardiazol is that recommended by von Meduna, the originator of the method (82, 88). Cardiazol is marketed as a crystalline powder, and for injection is made up into a 10% aqueous solution, sterilized by autoclaving at 110° C. for 20 minutes and kept in airtight rubber-capped bottles. The solution should be freshly made up every 3 days. On the morning on which the injection is to be given, the patient is kept in bed and the drug is administered intravenously. As nausea and vomiting occasionally follow the fit, it is advisable to give no breakfast or only a cup of tea. In order to obtain the maximum convulsant effect the injection should be given as rapidly as possible, and leakage from the vein should not occur. If no fit results, a second injection, equal in dosage to the first, may be given immediately.

The management of the convulsion is the same as that of all major epileptiform attacks. At the beginning of the tonic stage the patient's head extends and his mouth opens. A nurse must be ready at this point to insert a gag between the teeth, taking care to push the tongue back into the mouth out of harm's way. A piece of stout rubber tubing bent into a U or a U-shaped wire covered with several layers of lint forms a suitable gag.

The method of steadying the patient so as to prevent him from rolling off the couch during the fit is important. At the beginning of the tonic stage the patient's knees will extend and his hips will flex, when he can be lightly grasped round the thighs by a nurse. His arms should not be held or restrained in any way, as the occurrence of joint dislocations is a very real danger.

After the convulsion the patient stays in bed for five or six hours. The usual commencing dose is 0·5 grm. of cardiazol or 5 c.c. of the prepared solution. If this does not produce a convulsion it should be increased by 0·1 grm. steps until 1·5 grm. or the convulsant dose is reached. It may be necessary to increase the dose during the course of the treatment, as the patient may develop

heightened resistance to the drug. If no fit occurs the injection may be repeated on the following day, but if a fit is produced no further injections are given for 3 days. The number of fits given by Meduna varied from 2 to 30, the usual being 15 to 20. The only permissible sedative during the treatment is hyoscine, as the others tend to prevent the occurrence of fits.

The only contra-indications to the treatment appear to be (1) cardiac inadequacy, since the fit imposes a considerably increased strain on the heart, (2) arterial hypertension, as a rise in blood-pressure may be produced, and (3) active or latent infection, for reasons which will become apparent later. A complete physical examination before the commencement of treatment is of course essential. If intercurrent infection occurs it is prudent to suspend treatment. Elaborations such as are described by Kennedy (89) appear to serve no useful purpose.

The first method used by Meduna consisted of the intramuscular injection of camphor in oil and showed many disadvantages over that just described, the chief being that the injection was painful, sterile abscesses often resulted, and the fits commonly did not occur until 20 minutes after the injection, during which time the patient had to be watched by a nurse. Meduna has also employed cardiazol intramuscularly in cases whose veins were difficult to inject. Approximately three times the intravenous dose is necessary, and the patient has to be watched for some time, as after camphor. This mode of administration has not been employed at Bexley. In experimental animals the oral route has proved effective in the production of convulsions (Schoen (45), Voss (74)), rather larger doses being required than in the intramuscular method, but no one has yet used it therapeutically. The difference between the dose required for intravenous injection and that for intramuscular injection is mainly due to the rapid elimination of the drug from the body, so that if absorption is slow a convulsant concentration in the blood is hard to obtain.

The Fit.

The fit produced by the intravenous injection of cardiazol is extremely constant in its form and in the nature of the different stages. The most frequent prodromal signs are cough, blepharospasm or clonus and twitching of the face, accompanied by an expression of surprise and alarm. Occasionally a cry or a gasp may occur. This is succeeded by myoclonic jerkings which pass into a tonic stage with rigidity, adduction of the limbs and extreme flexion of the wrists, the eyes being usually drawn upwards and to one or other side, the side varying in different fits in the same patient. The next stage is that of generalized and frequently violent clonus, during which the patient becomes as a rule deeply cyanosed. Finally the clonic movements cease and the patient lies flaccid and inert. There is always a marked autonomic discharge, shown by widely dilated pupils, flushing or pallor and pilomotor

phenomena such as "goose skin". The vasomotor changes may occur very early, namely at the same time as the prodromal signs. Urinary or fæcal incontinence is comparatively uncommon, but may occur either in the tonic, clonic or flaccid stages. In males seminal emissions are seen in a very large proportion of fits.

In a series of 60 fits in 19 patients urinary incontinence occurred in 8 and fæcal incontinence in 1. In 58 of the fits the time elapsing between the injection and the onset of myoclonic jerkings varied from 8 to 20 seconds, the onset of the tonic stage from 10 to 30 seconds, the onset of the clonic stage from 15 to 40 seconds, and the onset of flaccidity or the end of the fit from 40 to 90 seconds, although in only 2 cases less than 55 seconds. In the 60 fits the duration of the myoclonic jerkings varied from 2 to 18 seconds, only in 1 case being more than 10 seconds, of the tonic stage from 3 to 20 seconds, and of the clonic stage from 20 to 55 seconds. Various auræ are described by the patients; for example, an apparent quivering of the ceiling, a sensation as if all the people in the room were rushing towards the patient, growing bigger and towering over her and some with an obvious delusional content, i.e., a patient who complained that she was influenced by electricity felt the electricity running through her body. Two of the fits were delayed, i.e., tonus did not occur until 40 and 50 seconds respectively after the injection, and the end of the fit occurred at 90 and 95 seconds respectively. Prodromal signs are often seen 6 or 7 seconds after the injection has been given, i.e., as soon as the drug has had time to reach the brain.

With subconvulsant doses *petit mal* attacks are frequently produced, characterized by impairment of consciousness and very frequently by myoclonic jerkings. They are commonly succeeded by a feeling of unrest, tension and malaise which is very unpleasant and of which the patients complain bitterly. Unlike the seizures of spontaneous epilepsy the major attacks are not succeeded in all cases by drowsiness and sleep, but actually the patients may appear extremely wide awake and active. This is probably due to the anti-soporific action of the drug. There is always a post-convulsive period of confusion, varying in duration from a few minutes to an hour or two. Many cases become terrified of the injection, in which case it is advisable to give hyoscine and morphia half an hour before (Cook (90)). The unpleasantness of the treatment can be completely eliminated by inducing a light hypoglycæmic coma with insulin before the injection is given, an added advantage being that the susceptibility to cardiazol is increased and a smaller dose required (Georgi and Strauss (91)). I have no experience of this method.

Physiological Concomitants of the Fit.

Meduna (87) has investigated the changes produced by the fit in (*a*) the urine and (*b*) the white cell count. He finds that the urinary acidity, ammonia content and phosphorus content are increased and the urinary

chloride is reduced, which in his opinion supports the view that the cardiazol convulsion and that of idiopathic epilepsy are physiologically the same, since these changes have been described in idiopathic epilepsy by Frisch (92, 93). Actually Frisch's findings have not been confirmed by other workers (Gamble and Hamilton (94), Byrom (95), Ostmann (96)), and his conclusions have not gained general acceptance. It appears probable that transient vasomotor changes and the muscular work, with consequent increase of lactic acid, are the chief factor in the production of these alterations, and that no fundamental mechanisms are involved.

Meduna finds striking changes in the leucocyte picture, namely a shift to the left in the Schilling count and a polymorphonuclear leucocytosis balanced by a lymphopenia, so that the total white cell count remains the same. This also occurs in patients in whom the injection has not produced a fit. He attaches prognostic significance to the degree to which this change takes place, stating that when the shift to the left is double the average of all treated cases a remission is to be expected. He gives no food on the morning on which the white cell counts are to be done, and takes precautions to keep the patients quiet and to avoid exciting them.

I investigated the changes produced in the leucocyte picture after 20 injections, using the same precautions as Meduna, namely keeping the patients quiet and fasting, with the results shown in Table I.

It will be noted that the shift to the left described by Meduna is very definite and is to be observed in nearly all cases. There appears to be little difference, however, between the response of cases who subsequently recovered and those who remained unimproved, and it does not seem possible to draw conclusions of prognostic value from these counts. It will be seen that, in contradistinction to Meduna's findings, changes in the total leucocyte count did occur, namely a mild leucocytosis in 19 cases, preceded by an initial drop in the white cell count in 9 cases. Georgi (97), Gross (98) and Heilbrunn (99) describe similar changes in the insulin shock treatment of schizophrenia, except that the leucocytosis produced is much greater; this is ascribed by them to an outpouring of adrenaline. The changes in the leucocytes in idiopathic epilepsy are a matter of dispute and there is an extensive literature on the subject. Lennox and Cobb (100) summed this up ten years ago in these words: "Evidently the leucocytic count and formula are essentially normal except at the time of seizures. At that time leucocytosis may occur, presumably as a result of muscular work involved in the seizure." Guirdham and Pettit (101) find that the increase occurs mainly, if not entirely, in the lymphocytes, so that it does not appear to resemble that produced by cardiazol.

Müller (102, 103) has conducted animal experiments on the reaction of the leucocytes to the injection of noxæ, finding that (*a*) they tend to withdraw from the peripheral circulation and migrate into the blood-vessels of the liver, and (*b*) that the bone-marrow responds by pouring out immature cells.

TABLE I.

Patient.	Result of injection.	Result of treatment.	Time.	Total white cells.	Mature polymorphs.	Juvenile forms.	Myelocytes.	Lympho-cytes.	Monocytes.	Eosino-phils.	Basophils.
E. W. C—	Fit	Recovered	Pre-injection	6,350/c.mm.	61·0%	10·5%	..	18·5%	9·0%	..	1·0%
			After 1 hour	4,900/c.mm.	56·0%	18·0%	..	16·0%	10·0%	..	..
			,, 2 hours	9,400/c.mm.	48·0%	27·0%	..	20·5%	4·0%	0·5%	..
			,, 3 ,,	8,350/c.mm.	54·0%	23·5%	..	12·5%	8·5%	0·5%	1·0%
			,, 4 ,,	6,000/c.mm.	58·5%	19·0%	..	14·0%	7·5%	..	1·0%
M. C—	,,	No remission	Pre-injection	9,800/c.mm.	71·5%	8·0%	..	12·0%	8·5%	..	..
			After 1 hour	6,300/c.mm.	69·0%	11·5%	..	14·5%	5·0%	..	..
			,, 2 hours	9,750/c.mm.	65·0%	18·0%	..	6·0%	11·0%	..	..
			,, 3 ,,	14,350/c.mm.	62·5%	23·5%	..	9·5%	4·5%	..	..
			,, 4 ,,	9,700/c.mm.	64·5%	20·5%	..	7·5%	7·5%	..	..
E. E. M. W—	,,	Temporary remission	Pre-injection	8,750/c.mm.	60·0%	14·5%	..	15·0%	9·0%	1·0%	0·5%
			After 1 hour	7,100/c.mm.	61·0%	14·5%	..	14·5%	9·5%	0·5%	..
			,, 2 hours	10,700/c.mm.	71·5%	13·0%	..	6·5%	8·0%	1·0%	..
			,, 3 ,,	12,300/c.mm.	70·5%	16·5%	..	6·0%	7·0%	..	..
			,, 4 ,,	13,200/c.mm.	74·5%	19·5%	..	2·5%	3·5%	..	..
E. E. M. W—	,,	Ditto	Pre-injection	8,400/c.mm.	68·0%	11·0%	..	11·0%	9·5%	0·5%	..
			After 1 hour	9,400/c.mm.	72·0%	11·5%	..	9·5%	7·0%	..	..
			,, 2 hours	15,100/c.mm.	60·0%	31·0%	..	5·0%	4·0%	..	..
			,, 3 ,,	12,600/c.mm.	56·0%	27·5%	..	6·0%	10·5%	..	..
			,, 4 ,,	11,900/c.mm.	52·5%	26·5%	..	11·0%	10·0%	..	..
E. F. S—	,,	,,	Pre-injection	5,950/c.mm.	54·0%	6·0%	..	20·5%	18·5%	1·0%	..
			After 1 hour	5,300/c.mm.	56·0%	13·0%	..	16·5%	13·0%	1·0%	0·5%
			,, 2 hours	8,650/c.mm.	70·0%	17·0%	..	9·0%	4·0%	..	..
			,, 3 ,,	11,600/c.mm.	62·0%	23·5%	..	7·5%	6·5%	..	0·5%
			,, 4 ,,	11,750/c.mm.	61·5%	19·5%	..	9·0%	10·0%	..	..
E. F. S—	,,	,,	Pre-injection	6,200/c.mm.	53·5%	7·0%	..	29·6%	9·0%	0·5%	1·0%
			After 1 hour	7,350/c.mm.	63·5%	10·5%	..	15·0%	10·5%	..	0·5%
			,, 2 hours	7,300/c.mm.	65·0%	21·0%	..	6·0%	8·0%	..	..
			,, 3 ,,	12,300/c.mm.	61·0%	23·0%	..	6·0%	9·5%	0·5%	..
			,, 4 ,,	8,400/c.mm.	62·5%	22·5%	..	5·5%	9·0%	..	0·5%
L. J. S—	,,	Recovered	Pre-injection	8,850/c.mm.	42·0%	9·0%	..	35·5%	13·5%	..	..
			After 1 hour	5,750/c.mm.	47·5%	20·0%	..	18·0%	14·5%	..	..
			,, 2 hours	8,500/c.mm.	53·5%	29·5%	..	11·0%	6·0%	..	..
			,, 3 ,,	11,300/c.mm.	49·0%	28·0%	..	17·0%	6·0%	..	..
			,, 4 ,,	9,750/c.mm.	57·5%	27·0%	..	11·5%	4·0%	..	..

TABLE I (*continued*).

Patient.	Result of injection.	Result of treatment.	Time.	Total white cells.	Mature polymorphs.	Juvenile forms.	Myelocytes.	Lympho-cytes.	Monocytes.	Eosino-phils.	Basophils.
M. L—	Fit	No remission	Pre-injection	4,550/c.mm.	63·0%	13·5%	..	13·0%	7·5%	2·0%	1·0%
			After 1 hour	6,200/c.mm.	66·0%	22·0%	..	4·0%	7·0%	1·0%	..
			,, 2 hours	11,700/c.mm.	58·5%	28·5%	..	8·0%	5·0%	..	..
			,, 3 ,,	8,350/c.mm.	67·0%	25·0%	..	4·5%	3·5%	..	..
			,, 4 ,,	11,600/c.mm.	61·5%	21·0%	..	9·5%	5·0%	..	..
G. S. T—	,,	Recovered	Pre-injection	9,000/c.mm.	65·0%	6·0%	..	16·0%	11·5%	1·5%	..
			After 1 hour	9,400/c.mm.	67·5%	12·5%	..	13·0%	8·0%	1·0%	..
			,, 2 hours	13,200/c.mm.	64·5%	20·5%	..	9·5%	5·5%	..	..
			,, 3 ,,	16,900/c.mm.	68·0%	21·0%	..	6·0%	5·0%	..	..
			,, 4 ,,	14,700/c.mm.	68·5%	19·5%	..	3·0%	9·0%	..	..
E. J. H. B—	,,	No remission	Pre-injection	10,800/c.mm.	69·5%	12·5%	..	15·0%	3·0%	..	..
			After 1 hour	10,700/c.mm.	67·5%	21·0%	..	4·0%	6·0%	1·0%	0·5%
			,, 2 hours	14,750/c.mm.	63·0%	27·0%	..	2·0%	8·0%	..	..
			,, 3 ,,	13,250/c.mm.	68·0%	22·0%	..	5·0%	4·5%	0·5%	..
			,, 4 ,,	13,600/c.mm.	64·0%	25·0%	..	5·0%	6·0%	..	..
E. J. E—	,,	Recovered	Pre-injection	8,150/c.mm.	60·5%	15·0%	..	13·5%	9·0%	1·5%	0·5%
			After 1 hour	8,700/c.mm.	59·0%	26·0%	..	6·5%	7·5%	1·0%	..
			,, 2 hours	9,650/c.mm.	60·0%	29·0%	..	5·0%	5·0%	0·5%	0·5%
			,, 3 ,,	13,700/c.mm.	66·0%	22·0%	..	6·0%	4·0%	1·0%	1·0%
			,, 4 ,,	11,050/c.mm.	56·5%	21·5%	..	11·0%	9·0%	0·5%	1·5%
E. J. E—	,,	,,	Pre-injection	7,350/c.mm.	60·0%	16·0%	..	12·5%	10·0%	1·0%	0·5%
			After 1 hour	6,000/c.mm.	52·0%	26·0%	..	6·0%	15·0%	1·0%	..
			,, 2 hours	10,300/c.mm.	56·5%	31·5%	..	4·5%	6·5%	1·0%	..
			,, 3 ,,	10,300/c.mm.	56·0%	33·0%	..	6·0%	4·0%	1·0%	..
			,, 4 ,,	8,900/c.mm.	57·0%	21·0%	..	10·0%	9·5%	2·5%	..
G. T. H—	,,	No remission	Pre-injection	8,600/c.mm.	64·0%	7·5%	..	19·5%	7·5%	1·5%	..
			After 1 hour	9,300/c.mm.	67·5%	14·5%	..	9·0%	8·0%	1·0%	..
			,, 2 hours	10,850/c.mm.	72·0%	19·0%	..	3·0%	6·0%	..	..
			,, 3 ,,	10,550/c.mm.	66·0%	12·0%	..	10·5%	10·0%	1·5%	..
			,, 4 ,,	13,000/c.mm.	65·0%	10·0%	..	11·5%	12·5%	0·5%	0·5%
C. J. K. F—	,,	Ditto	Pre-injection	10,850/c.mm.	70·5%	9·5%	..	8·0%	10·0%	2·0%	..
			After 1 hour	9,450/c.mm.	73·0%	11·0%	..	7·0%	6·0%	2·5%	0·5%
			,, 2 hours	12,950/c.mm.	71·0%	21·0%	..	1·0%	7·0%	..	..
			,, 3 ,,	11,050/c.mm.	72·0%	17·5%	..	4·5%	5·0%	0·5%	0·5%
			,, 4 ,,	8,850/c.mm.	63·5%	24·0%	..	4·0%	6·5%	2·0%	..

TABLE I (*continued*).

Patient.	Result of injection.	Result of treatment.	Time.	Total white cells.	Mature polymorphs.	Juvenile forms.	Myelocytes.	Lympho-cytes.	Monocytes.	Eosino-phils.	Basophils.
K. A. H—	No fit	No remission	Pre-injection	14,800/c.mm.	67·5%	17·5%	..	9·5%	4·0%	1·5%	..
			After 1 hour	15,200/c.mm.	59·0%	32·5%	..	5·0%	3·5%	..	..
			,, 2 hours	16,950/c.mm.	55·0%	34·0%	..	6·0%	5·0%	..	..
			,, 3 ,,	13,950/c.mm.	59·5%	34·5%	..	3·5%	2·5%	..	..
			,, 4 ,,	15,950/c.mm.	61·0%	27·0%	..	11·0%	1·0%	..	..
K. A. H—	,,	,,	Pre-injection	7,300/c.mm.	64·5%	12·0%	..	16·5%	6·5%	0·5%	..
			After 1 hour	7,800/c.mm.	68·5%	10·5%	..	13·0%	8·0%	..	.
			,, 2 hours	7,250/c.mm.	72·0%	16·0%	..	6·0%	6·0%	..	..
			,, 3 ,,	6,750/c.mm.	66·0%	19·0%	..	8·5%	6·0%	..	0·5%
			,, 4 ,,	8,250/c.mm.	69·5%	10·0%	..	12·0%	8·5%	..	..
H. C. G—	,,	Temporary remission	Pre-injection	7,700/c.mm.	46·0%	8·0%	..	29·0%	15·0%	2·0%	..
			After 1 hour	4,650/c.mm.	55·5%	20·0%	..	16·5%	6·5%	1·5%	..
			,, 2 hours	9,500/c.mm.	59·0%	31·0%	..	7·0%	1·5%	1·5%	..
			,, 3 ,,	8,850/c.mm.	59·0%	24·5%	1·0%	6·0%	7·5%	0·5%	1·5%
			,, 4 ,,	7,900/c.mm.	56·5%	20·5%	..	17·0%	6·0%	..	..
O. H. D—	Fit	Recovered	Pre-injection	13,750/c.mm.	80·0%	9·0%	..	4·0%	5·0%	2·0%	..
			After 1 hour	17,400/c.mm.	70·5%	15·5%	..	7·0%	4·5%	1·5%	1·0%
			,, 2 hours	22,200/c.mm.	70·0%	27·0%	..	3·0%	..	..	..
			,, 3 ,,	25,300/c.mm.	52·0%	36·0%	..	4·5%	7·5%	..	..
			,, 4 ,,	23,800/c.mm.	62·0%	29·5%	..	3·5%	5·0%	..	..
K. H—	No fit	,,	Pre-injection	8,750/c.mm.	63·0%	15·5%	..	12·5%	9·0%	..	..
			After 1 hour	6,250/c.mm.	59·5%	17·5%	..	13·0%	7·5%	2·0%	0·5%
			,, 2 hours	6,300/c.mm.	54·0%	28·0%	..	9·5%	6·5%	1·0%	1·0%
			,, 3 ,,	5,850/c.mm.	55·0%	25·0%	..	17·0%	12·0%	1·0%	..
			,, 4 ,,	5,800/c.mm.	44·0%	26·0%	..	18·5%	11·0%	..	0·5%
E. H—	,,	No remission	Pre-injection	8,750/c.mm.	53·5%	28·0%	..	11·5%	7·0%	..	..
			After 1 hour	7,500/c.mm.	64·5%	19·5%	..	10·5%	5·5%	..	..
			,, 2 hours	10,450/c.mm.	61·0%	20·0%	..	11·0%	8·0%	..	..
			,, 3 ,,	9,000/c.mm.	70·0%	14·5%	..	10·5%	4·0%	0·5%	0·5%
			,, 4 ,,	10,000/c.mm.	69·5%	11·0%	..	12·5%	6·5%	0·5%	..

A combination of these two processes affords the most probable explanation of the changes produced by cardiazol, which are due to the injection and not to the fit.

Bömer (104) and Demole and Bersot (105) find quite a high degree of hyperglycæmia in experimental animals during cardiazol fits, the former also finding increase in the blood lactic acid. Georgi and Strauss (106), in patients undergoing the Meduna treatment, find irregular fluctuations in the blood sugar in the pre- and intra-paroxysmal stages, with a post-paroxysmal rise in the region of 75%.

The effect of the injection of cardiazol on the fasting blood sugar was investigated in 12 cases, with the following result:

Blood Sugars in mgrm. of Glucose per 100 *c.c.*

Patient.	Pre-injection.	Flaccid stage.	¼ hour.	½ hour.	1 hour.	1½ hours.	2 hours.
K. A. H—	88	..	..	115	99	85	84
S. F—	73	..	..	81	83	76	74
A. J. S—	76	..	..	99	78	78	77
W. C—	81	..	..	108	93	85	84
E. M—	107	127	172	..	..	..	..
A. B. S—	117	135	169	..	..	..	..
A. E. H—	90	99	142	135	..	..	..
D. P. M—	90	112	150	136	..	..	..
L. L—	90	106	115	123	..	..	..
H. D—	104	125	152	158	..	..	..
F. C—	94	105	135	131	..	..	..
F. E. M—	95	103	117	122	..	..	..

There is a moderate rise in every case, with a rapid return to normal. Holmstrom (107) describes similar findings in idiopathic epilepsy. Lennox, O'Connor and Bellinger (108) state that in epilepsy any increase in the blood sugar during the convulsion is due to muscular exertion and asphyxia. Whether it occurs depends on the amount of readily available glycogen in the body. They do not discuss the mechanism by which it is produced. Kersten (109) is alone in finding fluctuations of great violence in spontaneous epileptic fits. The rise in blood sugar does not necessarily mean a predominantly sympathetic discharge, as Cannon's (110) work would suggest, various workers having shown that physostigmine and pilocarpine have the same effect (Hrubetz (111, 112), Nitescu and Benetato (113)) although in earlier work Macguignan (114) found that pilocarpine never caused a rise, but often after some hours a fall. Hrubetz believes that this action of pilocarpine is due to the stimulation of adrenal output demonstrated by Dale and Laidlaw (115), whose results,

however, were not confirmed by Stewart and Rogoff (116). Actually it is quite evident from the clinical description of the cardiazol convulsion that there is a mixed sympathetic and parasympathetic discharge, and it is extremely probable that this produces the rise in blood sugar.

Briner (117) describes a prolonged rise in blood-pressure following the fit, and Georgi (106) an increase in pulse-pressure during the fit. The experimental work of Coombs and Pike (76), Denny-Brown and Robertson (78) and Maloney and Tatum (31) suggests that this is a secondary effect. Blood-pressure readings were taken with the patients lying flat and kept as quiet as possible in 20 fits in 14 patients, with the following results :

Blood-pressure Readings. Pulse-rates italicized.

Patient.	Pre-injection.	Flaccid stage.	½ hr.	Result of injection.
R. M. M—	150/80 *80*	..	135/75 *80*	Major
A. B. S—	145/90 *90*	130/80 *80*	120/70 *80*	,,
F. A—	160/100 *110*	160/100 *110*	140/90 *100*	Minor
A. E. H—	140/90 *90*	170/100 *100*	130/80 *100*	Major
F. C—	190/100 *90*	140/90 *100*	150/80 *80*	,,
S. A. F—	170/90 *80*	160/90 *80*	160/80 *80*	Minor
D. P. M—	120/70 *90*	160/90 *120*	150/90 *110*	Major
A. E. M—	165/100 *90*	200/120 *120*	200/120 *120*	,,
F. C—	190/100 *100*	160/90 *110*	160/100 *80*	,,
A. B. S—	160/95 *100*	120/70 *80*	140/80 *100*	,,
H. D—	185/100 *120*	200/110 *120*	130/80 *90*	,,
R. M. M—	140/85 *70*	130/80 *120*	160/90 *110*	,,
F. E. N—	140/80 *80*	200/80 *120*	140/90 *80*	,,
H. F—	120/80 *70*	180/110 *120*	125/70 *80*	,,
D. P. M—	130/70 *80*	170/80 *110*	130/60 *110*	,,
A. E. H—	140/90 *80*	180/100 *110*	150/100 *90*	,,
L. L—	105/70 *70*	160/100 *90*	120/80 *90*	,,
O. C—	120/70 *70*	160/90 *100*	110/50 *80*	,,
H. A—	155/95 *90*	190/120 *100*	160/100 *90*	,,
R. J. H—	110/70 *70*	210/100 *100*	120/80 *100*	,,

There is a post-paroxysmal rise in the majority of cases, but the changes are irregular. They are probably produced by the interaction of a variety of factors, cardiac and vasomotor, emotional and excitatory. Some cases showed high pre-injection readings, due to apprehension and emotional distress, but some of these showed a further postparoxysmal rise, and the cases showing a fall were not all in this group.

Meduna's Hypothesis.

Meduna (87, 88) believes that his treatment is effective because of a hypothetical biological antagonism between schizophrenia and epilepsy, so that the two cannot exist together for long in the same organism. If epilepsy is induced the biochemical and endocrine make-up of the patient is altered in such a way as to produce an unfavourable milieu for the development of the schizophrenic process. In support of this hypothesis he cites various authors who found that epileptic fits in schizophrenics are rare, and in a later publication (118) brings forward evidence from the literature that epileptics belong chiefly to Kretschmer's athletic type, and that the neuroglia is hyperplastic in epileptics, but aplastic in schizophrenics. He also states that carbohydrate metabolism is slowed in schizophrenia but accelerated in epilepsy.

Superficially the hypothesis is attractive, as the central nervous system may be believed to be over-excitable in epileptics and under-excitable in schizophrenics, but actually none of the points which von Meduna advances will bear critical examination. Kretschmer (119) regards the athletic type as also susceptible to schizophrenia, and Grundler (120) believes that epilepsy develops particularly in the schizothymic constitution. The question of organic changes in the brain of schizophrenics is notoriously controversial. There are many cases of combined epilepsy and schizophrenia in the literature (Notkin (121), Falsey (122), Vorkastner (123), Gruhle 124)) and such eminent psychiatrists as Kraepelin (125), Jelliffe and White (126) regard epileptic attacks as a common symptom in catatonic states.

As a result of a search through the case-records of all the schizophrenic patients at Bexley, 924 in number, I found 5 cases in which the combination of epilepsy and schizophrenia undoubtedly existed. Two of these cases had suffered from epilepsy prior to the development of their psychoses, their history being briefly as follows :

E. J. H—. Major epileptic fits from childhood. Admitted at the age of 32 in a solitary, hostile, hallucinated condition, with occasional outbursts of impulsive violence and delusions that his food was poisoned. He grimaced, struck grotesque attitudes and later decorated himself in a fantastic manner, being in a typical paranoid schizophrenic state in which he has remained for the past 19 years, at times degenerating into a stuporose, catatonic condition. He had one major epileptic fit two years after admission.

A. A. E. W—. Major epileptic fits since the age of 16 years. Admitted at the age of 26 five years ago in a foolish, irresponsible manneristic state, with many delusions of a bizarre and fragmentary character. Since admission she has deteriorated considerably becoming more and more stuporose with outbursts of impulsive violence. The fits have become less and less frequent, and now occur at about three-monthly intervals.

The other three have developed epilepsy subsequently to the onset of their psychosis, as these histories will show. None of them give evidence of vascular disease or of any other obvious organic basis for their fits.

E. T. S—. Admitted at the age of 33 in a garrulous, excited condition with very marked thought disorder and fragmentary, absurd, unsystematized delusions of a

religious and erotic character. She deteriorated steadily, becoming stuporose and oblivious to her bodily needs. After 5 years in hospital she began to suffer from typical major epileptic attacks, which have recurred at rather infrequent intervals for the past 8 years. Her mental state has shown little change for the past 13 years.

B. E. K—. Admitted at the age of 46, hallucinated and expressing absurd grandiose delusions, for example that she had saved the English Crown by writing a poem. She has remained in this condition with very little deterioration but occasional violent outbursts for the past 24 years. She had one typical major epileptic fit, in which she bit her tongue and passed urine, 19 years ago.

A. J. C—. Admitted at the age of 31 in an exalted hostile mood, with very incoherent speech in which fragmentary delusions could be discerned. She had shown no change during the 31 years that she has been in hospital. For the past 5 years she has suffered from occasional major epileptic fits.

Six cases gave a fairly convincing history of epilepsy which had ceased for some years prior to their admission. One case was admitted with a paranoid psychosis which was regarded as schizophrenic, but from the first showed several traits usually associated with epilepsy. The fits started two years after admission. In another recurrent catatonic case the history of a previous attack, received from the mental hospital where he had been treated, stated that he had had three major epileptiform seizures during his stay in hospital. He gave no other history of epilepsy, and made a good recovery with cardiazol treatment.

Therefore more than 1% of the schizophrenic cases, to make a conservative estimate, have at some time suffered from idiopathic epilepsy, namely epileptiform convulsions for which no cause can be found. More than ½% have undoubtedly had fits actually in the course of their psychoses, although they have been neither regular nor frequent in 4 of the 5 cases. The latter is a rather higher figure of incidence than that for the general population, as shown by the proportion of rejections for epilepsy by the recruitment boards in the last war (127).

Even if it were true that epileptiform convulsions are infrequent in schizophrenia the hypothesis would not be strengthened thereby. Lennox and Wright (226) found that the basal metabolic rate of epileptics was frequently below normal and that, if it was raised to normal limits by the administration of thyroid, the frequency of fits increased. They concluded, therefore, that this was a protective mechanism, and so the lowered basal metabolism which has been found in schizophrenics by many authors (Bowman, Eidson and Burladge (128), Bowman and Grabfield (129), Gibbs and Lemke (130), Farr (131), Hoskins and Sleeper (132), Hoskins and Walsh (133)) would render them less liable to fits than normal people. Lowenbach (134) investigated the response to labyrinthine stimulation in states of catatonic stupor and excitement, and found indications of reduced excitability of the central nervous system. As epilepsy is fairly generally believed to-day to be an irritative rather than a release phenomenon, such reduced excitability will be another factor in the diminution of liability to fits. It appears possible, therefore,

that the psychological and physiological inertia which occurs in some schizophrenics is inimical to the development of convulsions, but it does not follow that convulsions are inimical to the schizophrenic process.

Gruhle (124) has pointed out that the mental changes seen in epileptic psychoses not infrequently resemble closely those of schizophrenia, although attacks of confusion occurring at short intervals have a certain pathoplastic effect. In the 120 epileptic cases at Bexley I was impressed with the frequency of symptoms which could only be regarded as schizophrenic, namely, thought disorder, delusions and hallucinations in the absence of post-epileptic confusion, mannerisms and the striking of bizarre attitudes. At least 5 of these patients presented at times a picture indistinguishable from schizophrenia, and one must draw the conclusions that there is no rigid dividing line between schizophrenia and epileptic insanity and that they have many features in common.

The affective response in both cases is inadequate, producing a curiously childish quality, although the schizophrenic incongruity of affect is usually absent in the epileptic, who attempts characteristically to cover up his deficiency by loud protests of piety and self-righteousness, and the self-centredness and limitation of interest of the epileptic is not far removed from the introversion of the schizophrenic. One is dealing with ill-defined and little understood groups of disease rather than with clear-cut disease entities, so that interpretations based on figures of incidence, even if any of significance could be produced, must be made with great caution.

There is an extensive literature regarding the question of carbohydrate metabolism in both schizophrenia and epilepsy. With regard to the blood sugar in schizophrenics, Wuth (135) found no definite abnormalities, although high values in anxious cases. Newcomen (136) and Weston (137) obtained normal values. Mumford and Parkin (138) found high values in some cases, which they attributed to a high degree of psychomotor activity. Uyematsu and Soda (139) found a raised blood sugar in 47% of 32 catatonic cases 2½ hours after a meal. Roggenbau (140) found variations from normal, but described no characteristic changes, although actually a few high figures are to be seen in his results. Reiter (141) found hyperglycæmia in some cases and renal glycosuria in others.

The glucose tolerance test of Janney and Isaacson (142), or blood-sugar curve, has attracted many workers. Kooy (143) found some abnormally high curves, but believed that these only occurred in depressed or anxious cases. Bowman, Eidson and Burladge (128) found abnormally sustained curves appearing in their cases in an inconstant manner. Raphael and Parsons (144) found in an investigation of 11 cases the fasting level lower than normal, the acme higher and the return to the initial level unduly delayed, namely for longer than 2 hours. Lorenz (145) found high, sustained curves in catatonic cases, but very low flat curves in simple deteriorating cases.

Schwab (146) finds an initial rise far beyond the normal and delayed return to normal in some cases. Henry and Mangam (147) also found high, sustained curves, which they attributed to retardation of the functions of the autonomic nervous system. Schryver (148) found low fasting values and high, sustained curves in some cases. Barrett and Serre (149) found in 30 cases marked variations in the same individual at different times. Drury and Farran-Ridge (150), in an investigation of 18 cases, found very high and rather broad curves in acute cases, higher in female subjects than in males, and small low curves in chronic cases, lower in males than in females. Mann (151) found unduly sustained curves in cases of stupor; Kasanin (152) examined 40 cases and collected a further 154 from the literature, believing as a result that no characteristic curve occurred in dementia præcox, but that individual curves varied greatly from the normal, being sometimes too high, sometimes too low and sometimes too sustained. Smith and Hill (153), in an investigation of 10 cases, found low curves which were raised by the administration of thyroid and pituitary extracts. Roggenbau (140) finds no characteristic, but many abnormal curves, as also does di Mauro (154).

The blood-sugar curve following the injection of adrenaline has interested several investigators. Raphael and Parsons (155) found that, following the rise, the curve fell below the fasting level, as in normals, but stayed at the low level for a much longer time than in normal cases. Gordon, Ostrander and Counsell (156) found a high, sustained "plateau" curve in schizophrenia in contrast to a rapidly rising and falling "peak" curve in manic-depressive cases. Appel and Palmer (157), using ephedrine, obtain a rapid rise, reaching a maximum at 15 minutes, and taking longer to return to the previous level than normal. They compare this to the curve obtained in cases of endocrine imbalance, namely pituitary, hypo-thyroid and mild diabetic, and regard it as evidence of a relatively inert sympathetic system. Schultze-Bunte (158) finds that the blood sugar rises higher and takes longer to return to fasting level than in normal people, and believes this to be due to hyper-excitability of the vegetative nervous system.

Work has also been done on sugar tolerance, or the amount when taken by mouth necessary to produce sugar in the urine. Claude, Santenoise and Targowla (159) found low carbohydrate tolerance with occasional glycosuria. Hoskins and Sleeper (160), using galactose and the technique described by Rowe (161), investigated 135 cases and found a tendency to lowered tolerance, indicating in their opinion a depression of functions under endocrine or autonomic control.

Passing to similar investigations in epileptic patients, estimations of the fasting blood sugar have revealed normal values to the majority of observers (Wuth (135), Weston (137), Mumford and Parkin (138)). Nielson (162) and Lennox, O'Connor and Bellinger (163), however, find periodic or constant low values. Lennox and Bellinger (164) investigated the blood-sugar curves in

140 cases, finding 24% abnormally high, 6% abnormally low and 70% within normal range, also marked fluctuations in the form of the curve and in the renal threshold for sugar. Münch-Petersen and Schon's (165) results are similar. They also studied the blood-sugar curve following adrenaline injection. Minchin (166), in a series of 66 cases, and Drewry (167), in a series of 200 cases, report a very high percentage of abnormally low curves.

It will be seen that no consistent results and many anomalies and exceptions have been reported, but one can discern a general tendency for high blood sugars and high, sustained curves to occur more frequently in schizophrenics, and for low blood sugars and low short curves to occur more frequently in epileptics. In other words, there is a suggestion that the mechanism by which glucose is removed from the blood and stored tends to be more active than normal in epilepsy and less active than normal in schizophrenia, which is probably to what Meduna referred.

I have investigated the effects of the treatment on the blood-sugar curve in 15 cases, with the following results:

Blood-sugar Curves Following Ingestion of Glucose.

Patient.	Before treatment.	After treatment.	Number of fits intervening.
A. J. H—	96.124.173.219.145	96.162.174.132.99	16
J. E. H—	109.164.205.168.96	86.124.134.120.101	16
S. S—	88.156.189.214.203	102.142.173.194.143	14
H. L. A—	111.156.173.152.148	90.175.162.150.123	5
R. M. C—	114.223.265.187.126	104.168.247.112.102	14
E. F—	118.262.270.261.206	100.237.242.268.233	16
W. E. M—	105.201.276.230.141	100.142.173.155.120	16
G. F—	98.155.185.141.96	87.162.168.116.89	12
E. P—	90.143.163.134.107	103.177.154.121.120	15
H. W. J—	92.150.175.150.95	95.186.203.142.114	15
D. A. K—	88.124.137.118.100	90.136.154.100.85	10
L. A. S—	85.126.100.74.89	91.102.141.98.98	16
E. J. B—	88.146.126.116.114	103.157.128.123.124	16
A. B. S—	82.114.136.136.142	105.158.157.144.133	15
D. W—	83.122.184.150.135	110.179.187.139.129	18

The changes in the curves are irregular and without apparent significance, although there are noticeably fewer abnormal curves in the post-treatment than in the pre-treatment group. Correction of abnormal types of curve occurred in cases whose mental condition did not respond in any way to the treatment, and a normal pre-treatment curve was not of favourable prognostic import. The investigation yielded no information of value, and gave no support to Meduna's hypothesis.

I also investigated the galactose tolerance in 8 of these cases, using the procedure and all the precautions advocated by Rowe (161), but found many inconsistencies and anomalies, including the appearance of sugar in the control specimens, and eventually discarded the results as useless, probably owing to the unstable affective state of the patients.

As a result of these considerations it will be seen that Meduna's hypothesis does not fit in well with the facts and must be discarded.

Alternative Hypotheses.

These must depend on current hypotheses concerning the nature of the physiological disturbance in schizophrenia. One of the most widely held postulates some disturbance of oxidative processes. Golla, Mann and Marsh (168, 169) found that the excitability of the respiratory centre was diminished, with consequent accumulation of carbon dioxide and acidosis. Mann (170) found in schizophrenics an increase in the amount of neutral sulphur in the urine following the ingestion of 5 grm. of sodium thiosulphate, indicating diminished oxidation of the latter. This increase was not, however, very marked. Loewenhardt, Lorenz and Waters (171) found that it was possible to interrupt a catatonic stupor for about 20 minutes by stimulating the respiratory centre with a carbon dioxide mixture, and Loewenhardt, Lorenz and Malone (172) found that stimulation of the respiratory centre by means of sodium cyanide injections was also beneficial. Even during this so-called lucid period, however, their patients seemed to exhibit marked thought-disorder. Looney and Childs (173) observed high blood lactic acid values in schizophrenics, and believed that these must be ascribed to some local action which interferes with oxidation. On the other hand, Hoskins (174) finds normal mean levels for lactic acid and glutathione, but that these two levels are unduly closely related, indicating that the schizophrenic is forced even during rest to use an accessory mechanism of oxidation on which the normal subject is not dependent. McFarland (175) has shown that the mental manifestations of oxygen-lack resemble closely those of schizophrenia. I have already referred to the literature on the basal oxygen consumption in schizophrenia, a majority of workers finding a tendency to lowered values. This hypothesis is attractive from our point of view, since Jowett and Quastel (176) have demonstrated that narcotics decrease the respiration of nervous tissue, and cardiazol, being pharmacologically antagonistic to them, might be supposed to increase it, in addition to its well-proved effect on the respiratory centre. Against it are the estimations of the oxygen content of the carotid and jugular blood of schizophrenics made by Thompson, Corwin and Aste-Salazar (177), which do not reveal any abnormality in the oxygen consumption of the brain, and the probability that all the above findings are only secondary to reduced cerebral activity.

I have endeavoured to investigate the basal oxygen consumption in the patients undergoing the treatment, using a Benedict-Roth apparatus with nosepiece. A high proportion of the patients would not tolerate the apparatus, and the results in the remainder were erratic and valueless. I can heartily concur with Hoskins's statement that "to obtain a true basal rate in most schizophrenic persons is difficult if not impossible". Not only is there the difficulty of keeping them still, but I found that in the majority of cases the apparatus aroused the most acute anxiety, which it was impossible to allay, even after half a dozen attempts. In consequence, the breathing was so irregular that most of the tracings were unreadable, and in the remainder high values, up to +80 in one or two cases, were obtained. It is possible that an examination of the changes in blood lactic acid and blood glutathione in patients under treatment would yield information of value.

Efforts have been made to prove that schizophrenia is due mainly or entirely to circulatory disturbances. Freeman (178) found marked slowing of the circulation in schizophrenic subjects, but Finesinger, Cohen and Thompson (179) failed to confirm his results, as also did some earlier work by Loewenhart, Lorenz, Martin and Malone (172). Pickworth (180) advances some histological evidence in favour of inequality of blood-supply in different areas of the brain, but his work awaits confirmation. Hallay (181) has obtained lucid intervals in catatonics by intermittent pressure on the jugular veins. This phenomenon is of doubtful significance, as so many possible factors are involved. Several observers have described a slight tendency to decreased permeability of the hæmato-encephalic barrier in schizophrenia (Katzenelbogen and Goldsmith (182, 183), Hauptman (184), Malamud, Fuchs and Malamud (185), Malamud and Rothschild (186), which may indicate some circulatory disturbance in the small proportion of cases in which it occurs. In view of Prados y Such's work, it is worthy of mention. The most satisfactory method of measuring decreases in permeability involves the administration of bromide, which of course is contra-indicated during the cardiazol treatment. Nevertheless, in spite of the unsatisfactory state of our knowledge, Stief (187) believes that the effect on the cerebral circulation is the important factor in this treatment, and that the therapeutic agent is vaso-spasm, which may act either by killing off redundant nerve-cells, or by subsequent vasodilatation and improved cerebral circulation. There is no real evidence in favour of this hypothesis, and Gibbs, Lennox and Gibbs's (79) findings are against it.

Anomalies in the autonomic nervous system have been observed by many workers, the implication being that the main site of disturbance is in the region of the hypothalamus, and Pfister (188) believes that the mechanism of the treatment is to be found here. The most commonly described abnormality is a hyposensitivity to adrenaline (Schmidt (189), Schultz (190), Claude, Santenoise and Targowla (159), Dawson (191), Kanner (192), Appel and Palmer (157), Freeman and Carmichael (193)), but many observers fail to find this (Biller (194),

Severin (195), Newcomen (136), Sierra (196), Lowry and Wright (197), Northcote (198)). The extreme variability and inconsistency of most of the results is striking, and one is left with the impression that the attempts to prove that schizophrenia is characterized by a state of vagotonia or by any definite picture of autonomic imbalance are artificial and have little factual basis. Freeman and Carmichael's results are carefully controlled, but all they show is that the rise of blood-pressure following adrenaline injection tends to be less in schizophrenic than in normal subjects. This is not, however, proof of specific autonomic abnormality, as Gillespie (199) has shown that the blood-pressure of schizophrenics is more constant than that of normals, and does not so readily respond to stimuli. Gillespie's results agree well with modern work pointing towards depression of the physiological mechanisms in schizophrenia, so that the organism adapts itself less well to the environment (Hoskins and Sleeper (200), Gottlieb and Linder (201, 202), Finkleman and Stephens (203), Katzenelbogen (204), Thomson, Corwin and Aste-Salazar (177)).

As some indication that vagotonia is not a characteristic of schizophrenia I may cite Monnier (205), who describes patients who are obviously anxious and sympatheticotonic as particularly suitable for treatment by prolonged narcosis; McCowan (206), who finds increased psychogalvanic reflexes in hebephrenics, and Sakel (207), who believes that the success of his hypoglycæmic shock treatment of schizophrenia depends on the correction of excessive adrenaline secretion. From my own experience of these cases before treatment, I have no doubt that it is possible to arouse in them the most acute anxiety, shown by tachycardia, sweating and dilatation of the pupil, but that the necessary stimulus is quite different from that which would be effective in normal people.

I investigated the response of the blood-pressure and pulse-rate to the subcutaneous injection of 1 c.c. of 1/1000 adrenaline solution in four patients prior to their treatment, but found considerable variations in response on different occasions in spite of rigid standardization of conditions. The injection was always given over about the mid-point of the deltoid muscle with the patient in bed at approximately the same hour of the morning. In these circumstances I decided that further injections during the course of treatment would not yield results of any value. It is probable that intravenous injection would have been more satisfactory, but it was felt that, as the successful execution of the treatment depended largely on the persistence of veins suitable for injection, it would be unwarrantable to give an additional course of intravenous injections.

Allied to autonomic disturbances are anomalies in the endocrine system. There is an enormous literature on this subject, and no direct causal relationship between any well-recognized endocrine disturbance and schizophrenia has yet been established. Hoskins and his co-workers have recently advanced some evidence in favour of an adrenal cortical deficiency in schizophrenia, but their

patients appear to be a carefully selected group with low blood-pressure and body-weight as two of its chief characteristics (Hoskins and Sleeper (208), Hoskins and Freeman (209, 210, 211), Freeman, Linder and Hoskins (212)). Kennedy (89) believes that patients who improve under this treatment show a rise in blood-pressure corresponding to the change in their mental state. I have observed the effect of the treatment on the blood-pressure in 21 cases, with the following results :

Blood-pressure Readings. Pulse-rates italicized.

Patient.	Before treatment.		After treatment.		Number of fits intervening.
K. H—	100/70	*60*	135/85	*70*	18
G. W—	120/90	*80*	115/75	*80*	20
A. G—	110/70	*70*	130/80	*70*	20
L. J. S—	110/70	*70*	170/100	*90*	10
A. J. H—	120/80	*70*	150/90	*90*	16
J. E. H—	110/85	*70*	130/90	*70*	16
S. S—	150/100	*85*	145/85	*100*	14
H. L. A—	140/85	*90*	140/80	*90*	5
I. G—	135/95	*80*	140/85	*80*	17
J. S. F—	120/70	*80*	140/80	*70*	20
R. M. C—	170/110	*80*	160/90	*70*	22
E. F— .	140/90	*90*	180/110	*90*	14
W. E. M—	140/90	*112*	160/100	*100*	16
G. F—	140/80	*100*	140/80	*100*	12
E. P—	130/80	*70*	130/80	*90*	15
H. W. J—	120/80	*70*	160/100	*80*	13
G. A. K—	110/70	*80*	180/120	*90*	10
L. A. S—	120/70	*70*	120/70	*70*	18
E. J. B—	110/70	*70*	120/75	*90*	18
A. B. S—	130/80	*80*	120/70	*80*	14
D. I. W—	120/80	*80*	125/80	*80*	20

All blood-pressures were taken early in the morning with the patient resting in bed. Every effort was made to allay anxiety, and frequently as many as 20 estimations were made in an effort to accustom the patient to the procedure. Nevertheless it will be seen by the accompanying pulse-rates that this aim was not always achieved. The results are inconstant, but in a few cases a definite hyperpiesis appeared, and in some cases was still present several weeks later. It is hard to believe that it was really persistent, as there were no signs of cardiac distress or enlargement. There was no abnormality in the urine of these cases and the blood urea fell within normal limits. The hyperpiesis was very

marked in some cases whose mental condition showed no change, and the changes in blood-pressure appeared to be quite unrelated to the mental state.

The effect on the weight in 49 cases was as follows:

Patient.	Number of fits given.	Result of treatment.	Effect on weight.	
			Gain.	Loss.
R. R—	23	R.	4 lb.	..
E. A. H—	25	I.	2 ,,	..
G. T. H—	14	N.I.	12 ,,	..
A. E. O—	11	I.	14 ,,	..
E. J. E—	16	R.	6 ,,	..
H. C. G—	18	N.I.	..	1 lb.
E. J. H. B—	24	N.I.	2 lb.	..
C. K. J. F—	24	I.	9 ,,	..
P. L—	9	N.I.	6 ,,	..
F. G. P—	17	N.I.	8 ,,	..
J. D—	16	R.	8 ,,	..
O. H. D—	20	R.	..	..
G. S. T—	12	R.	8 lb.	..
R. M. M—	20	I.	12 ,,	..
J. D. W—	20	N.I.	..	2 lb.
H. B—	5	R.	11 lb.	..
H. D—	20	R.	16 ,,	..
L. T. W—	20	I.	8 ,,	..
S. E. S—	20	N.I.	19 ,,	..
A. C. G—	20	N.I.	2 ,,	..
A. J. H—	20	N.I.	7 ,,	..
J. E. H—	20	N.I.	..	5 lb.
S. J. A—	20	N.I.	2 lb.	..
W. M—	20	N.I.	1 ,,	..
S. S—	20	I.	..	3 lb.
W. E. M—	20	I.	18 lb.	..
G. F—	20	N.I.	..	5 lb.
E. P—	20	N.I.	1 lb.	..
D. A. K—	21	N.I.	..	9 lb.
K. A. H—	20	I.	2 lb.	..
C. N. S—	20	R.	..	16 lb.
F. J. L—	20	N.I.	9 lb.	..
J. S. F—	20	N.I.	10 ,,	..
W. H—	7	N.I.	..	3 lb.
W. C—	20	N.I.	2 lb.	..

Patient.	Number of fits given.	Result of treatment.	Effect on weight. Gain.	Effect on weight. Loss.
A. J. S—	20	N.I.	19 ,,	..
W. E. P—	20	N.I.	19 ,,	..
E. J. B—	20	I.	..	3 lb.
L. A. S—	20	R.	..	6 ,,
F. T—	20	I.	13 lb.	..
C. B. S—	20	N.I.	4 ,,	..
G. W. A—	20	N.I.	4 ,,	..
F. A—	14	N.I.	..	6 lb.
H. D—	20	R.	6 lb.	..
S—	..	R.	9 ,,	..
D. J. C—	20	N.I.	4 ,,	..
C. G—	10	N.I.	..	5 lb.
A. L. R—	20	N.I.	15 lb.	..
W. R. R—	20	N.I.	3 ,,	..

I. = Improved.
N.I. = No improvement.
R. = Recovered.

It will be seen that the majority of the patients gained weight, and the treatment undoubtedly improves appetite in many cases. This was, however, obviously independent of the mental changes, and in some cases who made a good recovery the weight remained stationary or even decreased. On the other hand, patients who showed no mental improvement registered a marked increase. It is evident that the adrenal cortex plays no part in the mechanism of this treatment, if Hoskins and Freeman's view that low blood-pressure and body-weight are the chief signs of adrenal cortical deficiency be correct.

Humbert and Friedemann (213) stress the life-death antagonisms which are aroused, in other words the revival of strong primitive normal responses and the elimination of recent abnormal ones—a conception also advanced by Sakel in connection with his treatment by hypoglycæmic shock. Gillies (214) believes in the non-specific stimulation of cerebral cells that had become functionally inactive. The pharmacological action of cardiazol lends some support to this view, as also does Boss's (215) conception of schizophrenia as a condition in which the ego as a functional psychic organ has failed.

None of these hypotheses has any body of fact behind it, and we must admit that the treatment is quite empirical. Loss of contact with the environment is the chief feature of schizophrenia, and any strong stimulation will tend to jolt the patient out of his inner world of phantasy to a realization of his surroundings. To put it more physiologically, an abnormal strain is put on the

various sluggish adaptive mechanisms which arouses them to activity. In the present state of our knowledge this is as far as we can go in hypothesis construction.

Results.

Meduna distinguishes between symptomatic and endogenous schizophrenia, regarding the latter as of hopeless prognosis, whether treated or untreated. It appears roughly to consist of cases of slow, gradual onset with poor pre-psychotic personality in which the outlook is universally regarded as bad. He regards low intelligence or actual mental defect as also a bad prognostic sign. In the symptomatic cases the success of the treatment will depend chiefly on the duration of the illness, roughly 70 to 80% remitting if treated during the first year and about 50% if treated during the second year, but subsequently only an insignificant proportion of cases. Angyal and Gyarfas (216) obtained in a series of 45 cases 44·4% of remissions, but 4 of these subsequently relapsed. They concluded that stupors react best to cardiazol, but that in paranoid cases insulin shock is preferable. Wahlman (217) treated 21 cases but obtained no complete remissions, and 11 of his cases were quite uninfluenced. Nevertheless he feels that his results are promising. Gulotta (218) gave 10 patients 8 fits each and observed no change in their condition whatsoever. Briner (117) gives the results of treatment of 111 cases as follows :

Duration of illness.	Less than 1 year.	1 to 5 years.	Over 5 years.
Social cure (complete remission) . . .	17–50% .	3–13% .	3–5%
Discharged improved .	3–9% .	0 .	2–4%
Improved . . .	8–24% .	16–65% .	28–52%
Unchanged . . .	6–17% .	5–22% .	21–39%

The best results were seen in catatonics, and depressed anxious cases also did well, but profound stupors did badly. Finiefs (219) states that he cannot produce any imposing figures of recoveries, but that the method appears beneficial in early psychoses, especially the stuporose and catatonic. Scheuhammer and Wisgott (220) obtained 13 complete remissions out of a total of 30 cases treated. Dhunjibhoy (221) treated 12 cases, of which 3 recovered and were discharged, 4 were greatly improved and converted into working patients, and 5 remained unimproved. Pullar Strecker (222) compared Meduna's, Briner's and Angyal and Gyarfas's results with the spontaneous remission figures in a group of untreated cases, finding a remission rate of 37·4% in the former and of 23·6% in the latter.

Case Material.

I have taken as the material for an inquiry into the effects of this treatment the first hundred cases of schizophrenia to which it was applied at Bexley.

It is a commonplace that the four different groups into which cases of schizophrenia are classified are ill-defined, and that patients frequently alternate between two or even three of them. Thus many of the catatonic patients had long periods in which they presented a hebephrenic picture, and some passed over to a comparatively alert paranoid state. With these reservations, and using the condition at the time of commencing treatment as the basis of classification, the cases could be divided into 33 catatonics, 46 hebephrenics, 20 paranoids and 1 simplex.

Using the criteria described at the beginning of this paper, the prognosis in 53 of the cases was to be regarded as fair and in 47 of the cases as poor. No account is taken of the duration of the illness in this estimate, as that factor is considered separately. Low intelligence or even actual mental defect is not necessarily regarded as a bad prognostic sign, in spite of Meduna's opinion of it, since it is not so regarded by the majority of authorities, and many take the contrary view. For example Henderson and Gillespie (223) state that the defective "is more easily plunged into a psychosis than the latter (normal individual) and recovers also with a corresponding facility", and Mapother and Lewis also describe defectives as liable to short schizophrenic episodes. The group with poor prognosis consists of the classical dementia præcox type, with insidious onset and poor pre-psychotic personality.

The determination of the duration of the illness is by no means straightforward, especially in the cases with gradual onset. I have taken the first definitely and grossly abnormal piece of behaviour as the commencement of the illness and have ignored any previous attacks. That is, in those cases, 12 in number, who have had complete remissions I have taken the end of the last remission as the onset of the present illness. In other words, the shortest possible estimate was made. Using this method of computation the duration of the illness was under 6 months in 21 cases, between 6 and 12 months in 12 cases, between 1 and 2 years in 28 cases and over 2 years in 39 cases.

Forty-five of the patients were females and 55 were males. With regard to their age at the time of onset of their illness, 65 fell into the group 15 years to 25 years, 33 in the group 25 to 35 years, and 2 in the group 35 to 45 years.

Meduna believes that the convulsant dose is smaller in those cases which are going to react well to the treatment, as the schizophrenic and anticonvulsant diathesis has not got such a firm grip on them. Georgi and Strauss hold the opinion that the true explanation of this phenomenon is that an unsuccessful injection is harmful to the patient, and militates against the success of the treatment. An investigation into the average convulsant dose and number of unsuccessful injections in 35 cases selected at random showed

that these views are fallacious, since on the whole the cases who recovered needed a larger dose than those who did not, and several of the former had a large number of unsuccessful injections. The figures were as follows:

Patient.	Result.	Average fit-producing dose in grammes.	Number of successful injections.	Number of unsuccessful injections.
D. R. C—	N.I.	0·70	20	6
J. C—	N.I.	0·53	20	0
A. L. R—	N.I.	0·92	20	6
C. G—	N.I.	0·64	11	3
J. D. W—	N.I.	0·80	20	5
A. C. G—	N.I.	0·67	20	4
A. J. H—	N.I.	0·73	20	6
J. E. H—	N.I.	0·66	20	3
S. J. A—	N.I.	0·66	20	4
W. M—	N.I.	0·56	20	4
G. F—	N.I.	1·22	20	12
E. P—	N.I.	0·65	20	2
D. A. K—	N.I.	0·61	20	6
H. W. J—	N.I.	0·77	20	4
G. T. H—	N.I.	0·88	14	7
E. H. J. B—	N.I.	1·01	22	10
W. F. R—	I.	0·81	20	4
L. T. W—	I.	0·77	20	5
S. E. S—	I.	0·75	20	7
R. A. M—	I.	0·79	9	5
S. S—	I.	1·03	20	10
W. E. M—	I.	0·60	20	2
A. T. E—	I.	0·61	20	2
E. A. H—	I.	0·89	25	6
A. E. O—	I.	0·87	11	8
C. J. K. F—	I.	0·87	24	7
H. B—	R.	0·67	5	5
R. R—	R.	0·86	23	6
E. J. E—	R.	1·02	18	11
J. D—	R.	0·76	16	4
O. H. D—	R.	1·27	20	10
G. S. T—	R.	0·78	9	6
C. N. S—	R.	1·07	19	8
H. D—	T.R.	1·0	20	8
H. C. G—	T.R.	0·95	18	13

N.I. = No improvement. R. = Recovered.
I. = Improved. T.R. = Temporary remission.

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Effect on the Mental State.

The changes in the mental state produced by the treatment were marked, and only a small proportion of the cases failed to react in any way. They were, however, extremely varied and irregular, and no cases in which there occurred a definite evolution of the psychosis, such as is described by Kennedy, were seen. The specific and characteristic picture was one of euphoria with mild overactivity, undoubtedly the result of the treatment, since most of the patients had never exhibited it previously. The most profound effect was obtained in cases of catatonic stupor, who passed into a state of catatonic excitement or a hebephrenic condition, if they did not recover completely. Complete recovery with insight occurred with dramatic suddenness in some cases, while in others it followed on slow and gradual improvement. In the latter case it appeared more durable than in the former, although exceptions were noted. The manner in which it occurred showed some correspondence with the manner of onset of the psychosis. For example a patient who made an extremely dramatic recovery following her first fit had fallen ill very suddenly, passing in the course of a few minutes from a condition of which the sole abnormality was insomnia with a mild degree of depression to an acutely confused, hallucinated state. On the other hand, a girl whose illness had started with a gradually increasing depression, culminating in a suicidal attempt, following which she passed in the course of a few weeks from a hebephrenic condition to one of catatonic stupor, made a steady, slow improvement, being sent out of hospital on a month's trial 5 months after the commencement of the treatment. This is only to be expected on general principles, and in all branches of medicine there is a tendency for diseases of sudden, acute onset to heal more rapidly than those of slow, insidious onset.

Minor degrees of improvement were far more common, mute, inaccessible patients beginning to talk, incontinent, helpless patients becoming clean and able to look after themselves, and unoccupied patients starting to work. The change from a state of stupor to a state of excitement cannot be regarded as beneficial, and those patients in whom it occurred were rendered much more difficult to care for and troublesome. Only 24 of the cases showed no improvement, either temporary or permanent, during the course of treatment. The assessment of improvement is a matter of the greatest difficulty, and I have regarded patients as improved when they show some definite change for the better of the type indicated above. Tendency to relapse was marked, and one of the chief advantages of the alterations produced in unrecovered cases was their accessibility to occupational therapy. In the catatonic and hebephrenic type of case this was rendered possible by increased interest in the environment and improved active attention, while in the less deteriorated paraphrenic cases who refused to work because they considered themselves injured, the state of euphoria induced caused them to forget their grievances, at least for a

time. Many cases relapsed in spite of every effort to interest them in some occupation, but some stuporose cases could be kept in an accessible condition by the administration of one or two fits every two or three months. It appears hardly possible to keep up this procedure indefinitely.

It must be remembered that the condition of some of these patients is very variable, and that improvement ascribed to the treatment may really be spontaneous. Theoretically one could compare the extent to which improvement takes place in (*a*) untreated cases and (*b*) treated cases, but the practical difficulties in the way of such a study are great. In the first place few hospitals keep detailed enough records for the week-to-week condition of the patients to be ascertained, and one is obliged to rely on one's clinical judgment. Several of the cases who were definitely improved by the treatment had shown no change for long periods, and their mental processes appeared to be getting fixed at a low level. For example, one girl was in a state of resistive stupor for 2 years, but since the treatment, has been well occupied, although very deluded and irrational, and another fatuous, giggling, incoherent hebephrenic worked for the first time in $2\frac{1}{2}$ years. One feels justified, therefore, in assuming that the improvement, in some cases at any rate, is directly attributable to the treatment.

Concerning the condition of those patients who were discharged, the completeness or incompleteness of a remission is always a matter of opinion, and it cannot be denied that many of them showed marked personality defects. None of them, however, showed definite psychotic features, and all could be said to have insight, in the sense that they realized that they had been ill and had some conception of the nature of their illness. The routine procedure in certified cases was to send them out on a month's trial in the care of their families, and to discharge them at the end of this period if no relapse had occurred. This was done in 12 cases. The thirteenth certified case wished to go to her family overseas, so was kept in hospital for a month after she had completely recovered. A very sensible letter was received from her 2 months after her discharge, saying that she was in the best of health. The status of the one temporary patient was changed to that of voluntary a fortnight before her discharge, and $4\frac{1}{2}$ months later she was visited by the social worker, who reported that she was doing well. The remaining 5 patients were voluntary, and had all been well for at least a month before their discharge.

End-Results.

No figures for the end-results of treatment will be given, as the ultimate fate of many of the patients remains in some doubt. The cases whose illness had lasted less than 12 months showed a much better remission-rate than those whose illness had lasted between one and two years, while few of those with a history of over two years appeared likely to have a complete remission.

There were no striking differences in the quality of the results between the catatonic, paranoid and hebephrenic groups, but in the small group of cases, twelve in number, who had had previous remissions the results were particularly good.

The results in the cases of poor prognosis were definitely bad, only one remitting completely and a large proportion remaining unimproved. It is evident, therefore, that the usual prognostic criteria are of value in assessing the possibilities of benefit from cardiazol. Wortis (224) has made the same observation with regard to treatment by hypoglycæmic shock.

Complications.

The most frequent complication of the treatment encountered was some form of intercurrent infection, which occurred in 10 cases. The types of infection were crops of boils in 4 cases, and in 1 case each, follicular tonsillitis, coryza with pyrexia, an abscess on the face, colitis, intermittent pyrexia of unknown origin and localized consolidation of the lung, followed by formation of a pulmonary abscess. Nine of these cases cleared up satisfactorily and, after an interval, were able to complete their treatment. The tenth is the last case mentioned in the list, and the pulmonary abscess is still present. It seems likely that the treatment diminishes the resistance of the body to bacterial invasion, so that every precaution should be taken to ensure that no infection is present at the commencement of treatment, and to guard the patients against exposure to infection during its course. This danger appears to have been recognized by Finiefs, who ascertains the red-cell sedimentation-rates of his patients, and Kennedy, who advocates the keeping of 4-hourly temperature charts for 2 days prior to the commencement of treatment.

The other complication was dislocation of joints produced by muscular action during the fit, which occurred in 4 cases. In 2 cases dislocation of the shoulder-joint occurred twice in each case, twice on the same side in one case and on opposite sides in the other case. Dislocation of the jaw was seen in 2 cases. In every case reduction was effected with very great ease.

Discussion of Results.

It is quite clear that this treatment exercises in a large majority of cases a definite effect on the clinical picture, which, however, is frequently of short duration. I took as a control group the cases of schizophrenia with a history of less than 12 months admitted to Bexley during the period April, 1934, to April, 1936. These numbered 113, but of these 7 had been lost sight of, owing to their being voluntary patients who had left hospital in an unsatisfactory state, to their discharge in the care of relatives under Section 79 of

the Lunacy Act, or to their transfer to other hospitals. Of the remainder, 35 had made a satisfactory recovery and had been discharged, whereas 71 had not, giving a recovery-rate of 33%. The difference in discharge-rate between the treated and untreated cases appeared unlikely to be sufficiently great to be really conclusive or significant, especially since the treatment was not given to every case of schizophrenia admitted, so that a certain amount of selection was exercised. It must be remembered, however, that in the control group the recoveries were spread over a much longer period than in the treated group, so that their onset appears to have been hastened even if they were not actually induced.

The superiority of the results in the group of cases in which previous remissions have been noted is quite striking, and it appears probable that there exists a disease of the schizophrenic group liable to remit and to relapse which is particularly benefited by this treatment, the psychotic periods being shortened and the onset of remissions hastened. The only advance that has been made in the isolation of such a disease is the work of Gjessing (225), who found fluctuations in the nitrogen excretion in a few patients corresponding to the mental changes. It would be of great interest, therefore, to repeat Gjessing's work on cases undergoing convulsion therapy, although his technique is rather too complicated to be carried out efficiently at the average mental hospital.

The general impression gained is that this treatment exercises no very profound effect on the course of the disease, although it may hasten recovery in cases which are going to remit and do something to arrest its progress and to prevent its worst ravages in cases which are not. In this it is probably no more effective than other types of shock treatment, such as artificial pyrexia and insulin, but it compares very favourably with them as regards ease of administration and freedom from danger. Our therapeutic resources for the combating of schizophrenia are so poor that we cannot afford to neglect any palliative.

Summary and Conclusions.

The technique of Meduna's method of treating schizophrenia and the physiological effects produced are described. Meduna's hypothesis is criticized and possible modes of action are discussed. No consistent effects are found on the blood-pressure, body-weight or blood-sugar curve.

The percentage of recoveries does not appear significantly higher than those in a control group of untreated cases, but there is some evidence that it hastens remissions when these are on the way and shortens psychotic episodes. Of the unrecovered cases, about 40% showed some durable clinical improvement following the treatment. It has, therefore, a definite, although limited value.

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