

## INSULIN AND CARDIAZOL : EXPERIENCES OF THE COMBINED METHOD.\*

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IN 1933 Sakel described the induction of epileptiform convulsions during hypoglycæmia, using camphor and cardiazol. This was not, to my knowledge, followed up systematically until Georgi's work, which started in 1934.

### REASONS FOR COMBINED THERAPY.

Georgi summarizes his work in a paper published in 1937. He reports cases showing improvement following cessation of insulin treatment, and gives figures which show that, in cases not already much improved by insulin, there is a greater chance of improvement when a subsequent course of cardiazol is given.

Many workers must have been struck by the similarity between the twitchings, spasms and fits seen during hypoglycæmia and those seen in cardiazol therapy, so it is hardly unexpected that similar biochemical changes should be seen. Georgi and Strauss carried out many investigations to establish this similarity, which is seen during the first two hours of hypoglycæmia and in the interval between the injection of cardiazol and the fit. Blood potassium content decreases and blood calcium content rises—an interesting similarity to the findings during barbiturate narcosis. There is evidence which points towards an increased permeability of cell membranes. There is also a fall in blood sugar before the cardiazol fit, though not of such magnitude as to suggest that the cardiazol fit is a manifestation of hypoglycæmia.

Having evidence of similar action, Georgi would appear to be justified in using the term "*Summationsverfahren*" or summation therapy for the combined action of insulin and cardiazol, as the two substances are here used as synergists.

It was early pointed out by Sakel that an epileptiform convulsion during hypoglycæmia was often followed by great improvement. This is now a common experience among insulin workers, though there is the contrary impression that too many fits are not beneficial, but rather the reverse. We should therefore, to obtain the best results, be able to control the fits, and the combined therapy allows of this ; the too placid patient is given beneficial fits,

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while the fit-prone patient is given luminal and only allowed fits if it is thought necessary.

During hypoglycæmia the dose of cardiazol needed to produce a fit is reduced, fits being common with 3 c.c. In itself this is not of great importance, except in so far as it helps to render the failed fit less frequent. In plain cardiazol treatment the failure to produce a fit cannot always be avoided and is usually followed by agitation and nervous upset, so that recovering patients may refuse further treatment. In the combined method the failed fit is less common and is also less upsetting, as consciousness is greatly depressed at the time of injection of cardiazol. Lately, also, I have found that subconvulsant doses of cardiazol given during hypoglycæmia produce sudden awakening, unrest and confusion, which appears to be of greater benefit in rousing the stuporose patient than the actual fit.

One of the disadvantages of cardiazol treatment lies in the terror associated with the injection. Those who have suggested that this terror may be the therapeutic agent presumably have never seen a patient, during a quiet talk, thrown into a state of acute alarm by a banging door. Hypnotics are used to overcome this fear and its attendant inconvenience to the medical staff; they possibly overcome the fit also. Insulin, however, gives somnolence and decreased awareness both of injection and fit, so that there is no shrinking from the next injection, no running away and swimming across the adjacent canal; amnesia is absolute, the only difference from an ordinary insulin morning being perhaps a headache or nausea; insulin has also its own therapeutic effect.

#### METHOD.

Georgi's method of combining insulin and cardiazol is fairly well known; cardiazol is given at the "turning point", somewhere in the second hour. Georgi holds that there is a lag in the fall of the sugar content of the brain, so that there is a marked difference between blood and brain sugar about the end of the second hour, producing liability to fits. This liability to twitchings and fits in the second hour is a fact easily observed, but is by no means so constant as to allow of a conception of a fixed "turning-point". In addition to this variability of the time of greatest twitchings, Kerr has advanced experimental proof that, in rabbits, the brain carbohydrates vary with the blood sugar though there is a little delay. It therefore seems that there is no well-defined optimum time for giving cardiazol, but that it is more reasonable to choose the time at which the maximum tendency to fits may be observed; by so doing I find that a patient who, at the end of two hours and therefore presumably at the turning-point, needed 5 c.c. of cardiazol, at the end of three and a half hours of hypoglycæmia was more "jumpy" and had his fit with only 1.5 c.c.

The time for cardiazol administration relative to the general course of hypoglycæmia is also of importance and has had little discussion. The usual plan

has been to give cardiazol as a last hope to cases showing no improvement after six or eight weeks of insulin treatment. Yet Sakel observed long ago that the fit occurring early in treatment was of greater therapeutic value than that occurring later, and others have noticed this. So why not give cardiazol from the start of treatment? When I have done this results have been good. The usual dramatic improvement associated with cardiazol occurs and persists, so that both the total number of convulsions and the number of comas is lessened. Very often after a few convulsions improvement is sufficient to allow cessation of combination therapy, and the subsequent course of hypoglycæmia for stabilization is shorter and need not be so intensive. This conclusion, that it is better to start combining the two methods early, will appear to be impressionistic when the few results I have to show are analysed, and I trust it will be remembered that these figures were not collected in order to demonstrate that early combination therapy has advantages, but that early combination was persisted in because the results appeared to be better.

The method at present used at St. Bernard's is to attain the coma dose of insulin first, as in Sakel's method. In this phase the patient's confidence is being gained and fears allayed, so no cardiazol is given. The first coma is terminated immediately, and thereafter the coma dose is given daily, with injections of cardiazol twice weekly, in addition, at the time of maximum spasms or just before the onset of coma in patients who do not have spasms. The intermediate comas are allowed to become deep or are kept light according to the type of case, as in straightforward insulin treatment. I have had difficulty in getting patients to drink after the fit, so I now pass a nasal tube immediately and give glucose when the patient begins to rouse, or at any rate within the half hour. When good improvement is shown, cardiazol is discontinued and a stabilizing insulin treatment follows.

#### DIFFICULTIES AND DANGERS.

These are seldom of a serious nature. In a letter to Dr. Freudenberg, Georgi writes that he has had no serious complications at all. I have had one case in which sugar was delayed, by a mistake, until two hours after the fit; coma was prolonged, lasting until 4 p.m., but there was no ultimate harm done. Dr. Larkin tells me of a case of his in which laryngeal spasm and collapse occurred after the fit, needing artificial respiration and intracardiac glucose; I believe that similar collapses have occurred with plain cardiazol. Larkin now gives a few c.c. of glucose solution intravenously after the cardiazol to prevent trouble.

Vomiting after the fit is an annoying complication. The vomiters are often helped by an injection of atropine about an hour before the cardiazol is due. I also take care to drain the stomach before giving glucose to these cases—a further point in favour of using the nasal tube as a routine. Reducing the cardiazol dose to the minimum needed for a convulsion also seems to reduce the incidence of vomiting; this also seems to be the case with plain cardiazol. If vomiting

does occur, the hypoglycæmic patient usually returns to coma, in which case intravenous sugar is safest, as the stomach often seems to make a habit of vomiting.

From the results at my disposal I have been unable to formulate indications for combined therapy. The indication previously held has been that cases showing no improvement on insulin alone should have combined treatment. Stuporose cases have been regarded as particularly benefiting, and so constitute the greater number of cases in my results. Excited catatonics have done well, however, and paranoid schizophrenics have also benefited. I understand that Georgi will shortly be publishing results of combination therapy, which should clear up these points; at present I know of no published results, apart from those mentioned here and there in the results of insulin therapy.

## RESULTS.

## Summation therapy started early (during first month).

Case.	Type.	Duration (years).	Combination treatments.	Result.
1	Paranoid	1	II	+
2	"	2	3; 7 sp. ep.	-
3	Stuporose	3	12	+
4	"	$\frac{9}{12}$	6	+++
5	"	3	15	++
6	"	2	4	++
7	"	1	3	++
8	Excited	$\frac{6}{12}$	2	+
9	"	$\frac{6}{12}$	2	+++
10	"	$\frac{6}{12}$	15	-
11	Alternating	3	22	-
12	Hysterical	1	7	+
13	Stuporose	$1\frac{1}{2}$	2	+++

## Summation therapy started late.

14	Paranoid	4	10	+
15	"	2	2	++
16	Stuporose	12	19	-
17	"	3	5	++
18	"	$1\frac{1}{2}$	9	++
19	"	8	21	-
20	"	5	..	-
21	"	7	4	-
22	"	5	13	+
23	Excited	4	10	-
24	Hebephrenic	2	18	-

+++ Full remission. ++ Partial remission (one symptom persists). + Fit for discharge.

## SUMMARY.

Combination therapy possesses advantages over both insulin and cardiazol used separately ; where combination is used from the beginning the benefits are greater ; other cases besides stuporose catatonics are benefited by the combined method.

I am indebted to Drs. James and Freudenberg, of Moorcroft, Hillingdon, for permission to use their results, and to Dr. Lewis, Medical Superintendent of St. Bernard's Hospital, for permission to publish my own.

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