MEASUREMENTS OF EFFECTS OF HYALURONIDASE IN INSULIN COMA TREATMENT

By

K. E. SCHMIDT, M.D., M.R.C.S., L.R.C.P., D.P.M.

Assistant Psychiatrist, Hill End Hospital, St. Albans, Herts.

in collaboration with

J. TONG

Senior Clinical Psychologist
Rampton Hospital, Retford, Notts.

Introduction

Hyaluronidase, the "spreading factor" is widely used today to aid the distribution and absorption of fluids injected at various sites into body tissues. It is derived from the head of the male sperm cell which by its action dissolves hyaluronic acid in the "shell" surrounding the female egg cell and thereby allows spermal penetration and conception; generally speaking it dissolves the ground substance between cells. The most remarkable usage is in paediatrics where it allows for quick replacement of lost fluid and salt in gastro-enteritis, obviating the need to find veins, and thereby saving practically all cases from death by dehydration. There are many other uses.

Hyaluronidase once injected into body tissue is quickly absorbed into the blood-stream and inactivated by anti-hyaluronidase. These effects have been summarized by Wyburn and Bacsich (1950).

It was hoped that this substance might help to make the deep insulin coma treatment of schizophrenia more predictable and less hazardous, and also that it would assure the complete absorption of the injected insulin at whatever tissue plane, thereby abolishing or markedly reducing the after-shocks numerically.

Review of Literature

Demay *et al.* (1953) examined the effect of hyaluronidase on 6 patients—reduction of dosage, quicker and deeper coma, more rapid waking and absence of after-shock are claimed. Unfortunately no statistical data are given, no control cases are employed and no measurements *re* waking-up times are quoted.

Blandin *et al.* (1955) in a series of 25 cases make similar claims. If one takes the averages of the first and last coma-doses, the hyaluronidase cases appear to require less insulin. (In general the dosages of insulin administered by these authors are remarkably low.) No criteria are given as to which features determine the onset of coma.

Gysin and Wilson (1954) added hyaluronidase to insulin after approximately 10 comas and then reduced the insulin dosage. There is no indication in their report that the insulin dose had already been reduced to a lower level as is usually possible at this stage of the course. The number of i.v.-glucose

interruptions necessary in their unit appear rather high. No figures are given for the claim of a shortened sopor but clinical impressions are included.

Holden and McGuinness (1957) use each patient as his own control in a similar way to Gysin and Wilson. Their numerical data suggest that nothing much was gained by the addition of hyaluronidase but the "clinical impressions" are favourably inclined.

Tyndel (1956) claims reduction of pre-coma time by one-third (presumably this means the time between injection and coma), although some of the other statements are difficult to follow, e.g. "the average duration of therapy was reduced from 61 to 55½ days". Almost all authors claim a reduction in "restlessness" during treatment.

Technical Problems

It is quite obvious that it is very difficult to measure and compare all the factors mentioned in these reports, especially "restlessness". From our observations three different types of "restlessness" may occur either in the soporphase or during the waking-up period: (*a*) twitching of the limbs similar to the clonic stage of an epileptic fit but without proper rhythm—i.e. jactitations, (*b*) what may be described as large-scale writhings and contortions of the whole body, and (*c*) hyper-extension rigidity.

We would suggest that (*a*) is due to cortical/subcortical activity, (*b*) is due to mid-brain activity (righting reflex type of movement) and (*c*) due to medullary and spinal activity (stretch reflex type). Unless one goes very much into details and measures amplitudes of movement or durations of the various types of motor activity it is probably wise to abstain from categorical statements about the hyaluronidase effects on these. From the data given it appears that this has not been done by the various authors. For reference as to criteria see the excellent and detailed study by Frostig (1940) and also by Kueppers (1937). Our staffing facilities did not permit such measurements in all cases. In the current study impressions are given below (see under Restlessness).

Technique

The insulin injection was given at 7.30 a.m. with the object of inducing a coma at 10 a.m., i.e. after 150 minutes. (This may explain to some degree our relatively high doses, since Frostig and others aim for the coma to appear approximately 270 minutes after the insulin injection "in the 2nd half of the 5th hour".)

Again differing from Frostig, our patients remained in the state of "complete" coma for 30 minutes before being interrupted in the usual way by tube-feeding, instead of being fed at the onset of this stage.

To assess some of the effects of hyaluronidase we measured its influence on:

(*a*) Length of sopor.

(*b*) Time of onset of coma.

(*c*) Stability of onset, i.e. the measurement of the intervals of onset of coma from day to day.

(*d*) Waking duration, i.e. time between tube-feeding and the patient being fully awake (even if still slightly disorientated).

(*e*) Number of intravenous interruptions of coma necessary.

(*f*) Number of epileptiform fits.

(*g*) Number of after-shocks—here are included not only intravenous glucose medications which become necessary, but slight reactions such as sweating, excessive hunger and light headedness have been counted.

(*h*) As the aim in the unit was to induce the onset of coma at 10 a.m. dosage was altered mainly according to this requirement. We have therefore also compared the average insulin dosages of those days when hyaluronidase was administered (H days) with those days when hyaluronidase was not used (non-H days), for each patient and constructed average insulin dosage curves for the H days and non-H days. These two curves are opposed to the average dosage curve of 30 control cases, matched approximately as to sex, age, body build, previous personality and body weight, mode of onset, duration and type of psychosis.

Thirty-two schizophrenic patients received hyaluronidase 500 I.U. together with insulin in one injection (deep intra-muscularly, changing the site daily). The patients were classified as follows:

1. *Pilot Group.* Eight patients served as a pilot group and received the additional drug at various stages during the course, for a few days only, varying from 4–19 days at the most.

2. *Alternate Days Group.* Eight patients received hyaluronidase from the first injection onwards every second day. (Since it is known that the action of hyaluronidase is utilized at the site of the injection, there is no overlap from one day to the other. Our observations tend to confirm this.)

3. *Alternate Weeks Group.* Eight patients received the additional drug from Monday to Saturday of one week (Sunday being a rest day) followed by a week with insulin alone, and so on alternately.

4. *Sixteenth to Thirtieth Coma Group.* Eight patients received the hyaluronidase from their 16th to their 30th coma only; on both parts of the course before and after these 15 days insulin alone was given.

For each of the 32 patients the following curves were constructed:

(*a*) Dosage curve.

(*b*) Onset of twitching.

(*c*) Onset of sopor.

(*d*) Onset of coma.

(*e*) Feeding.

(*f*) Waking up.

Entries in the daily sheet, from which the curves were constructed, were made to the nearest 5 minutes. The curves therefore also express 5-minute intervals. One would expect that, if the claims for hyaluronidase were valid, there would be definite breaks in these curves, depending on the administration or discontinuation of the drug.

Altogether 630 injections of hyaluronidase were given. The above 8 measurements were compared for the total, and also for each group separately. The groups were well matched as to the criteria quoted for the 30 control cases.

Hypotheses and Data

Hypothesis I

Duration of Sopor

The duration of sopor, i.e. the interval between the onset of sopor and coma, is not significantly influenced by the addition of 500 U. of hyaluronidase to the daily intramuscular injection of the coma-producing dose of insulin.

Definition of Onset of Sopor

(*a*) Patient is unconscious but at such a shallow level that he still responds to certain tactile stimuli, but not to auditory stimuli and cannot be properly roused.

(*b*) He is usually sweating, restless and twitching. His muscles are hypertonic.

(*c*) He is amnesic.

Criteria for Onset of Coma

(*a*) Patient is unconscious.

(*b*) He does not react to stimuli; (glabellar, tapping, visual, tactile, etc.).

(*c*) Muscles are mainly flaccid.

(*d*) Tendon reflexes weak or absent.

(*e*) Plantar reflexes absent or extensor.

For each of the 32 patients the length of sopor during the "H days" was compared with that for the "non-H days" and analysed for statistical significance with the usual formula.

From Table I it can be seen that the length of sopor was shortened (calculating averages for each case and comparing an equal number of H days with non-H days) in 17 out of 32 cases, lengthened in 13 and no difference in 2. Even if there is a preponderance of the shortened cases and even if this were statistically significant it would obviously be of only limited clinical importance.

For three individual patients the mean duration of sopor was ten minutes shorter under hyaluronidase than when the same patients were not under the additional drug. This difference was significant at the $P=0{\cdot}05$ level. However, for two other patients (II/5, III/8) the effect of hyaluronidase was to significantly *increase* the mean duration of sopor by 11 and 10 minutes, respectively. In no other case was the mean sopor duration significantly changed by the additional drug.

Taken as a whole the mean sopor duration times under hyaluronidase did not differ significantly from the sopor duration times of non-hyaluronidase days. This appears from the following table, for which χ^2 is obviously not significant:

	<40	>39	
H. Group	15	17	32
N.H. Group	15	17	32
	30	34	64

HYPOTHESIS II

Time of Onset of Coma

The time of onset of the insulin coma is not significantly expedited by the addition of hyaluronidase (the injections were given at 7.30 a.m.).

Method

Averages of onset were arrived at comparing equal numbers of H and non-H days.

TABLE I

Average Measurements on 32 Patients Undergoing Insulin Coma Treatment

1 Patient No.	2 N	3 Sopor Duration H.	3 NH.	3 Diff.	4 Onset of Coma H.	4 NH.	4 Diff.	5 Stability of Onset H.	5 NH.	5 Diff.	6 Waking Duration H.	6 NH.	6 Diff.	7 Intravenous Glucose H.	7 NH.	7 Diff.	8 Epileptiform Fits H.	8 NH.	8 Diff.	9 After Shocks H.	9 NH.	9 Diff.
I. Pilot Group:																						
1	6	*−33	23	−10	10·37	10·37	0	*+21	43	+22	10	9	−1	0	1	+1	0	0	0	0	0	0
2	7	38	38	0	9·33	9·43	+10	10	18	+8	7	11	+4	0	0	0	0	0	0	0	0	0
3	11	38	33	−5	* +9·79	10·04	+15	7	7	0	13	11	−2	0	0	0	0	0	0	0	0	0
4	9	40	37	−3	10·04	10·11	+7	23	23	0	17	19	+2	0	0	0	4	3	−1	0	0	0
5	9	31	36	+5	*+9·58	10·28	+30	33	35	+2	28	22	−6	1	3	+2	5	0	−5	0	0	0
6	17	37	30	−7	*−10·42	10·23	−19	17	12	−5	6	6	0	0	0	0	0	1	+1	0	0	0
7	19	47	42	+5	9·47	9·54	+7	16	13	−3	7	7	0	0	0	0	0	1	+1	1	1	0
8	17	50	41	−9	10·06	10·05	−1	16	15	−1	18	17	−1	13	12	−1	6	7	+1	0	0	0
II. Alternate Days Group:																						
1	25	40	47	+7	*+9·57	10·12	+16	*+14	32	+18	10	11	+1	2	1	−1	2	1	−1	0	0	0
2	24	50	52	+2	10·24	10·30	+6	20	15	−5	13	14	+1	0	0	0	0	0	0	2	0	−2
3	23	32	28	−4	9·53	10·06	+13	*+18	34	+16	14	16	+2	3	2	−1	0	0	0	0	0	0
4	24	34	37	+3	9·45	9·51	+6	17	19	+2	11	11	0	2	0	−2	0	0	0	0	0	0
5	24	*+31	42	+11	10·47	10·55	+8	14	16	+2	11	11	0	1	0	−1	0	0	0	0	0	0
6	23	35	36	+1	10·20	10·25	+5	23	35	+12	23	25	+2	3	1	−2	4	3	−1	0	0	0
7	22	*−57	47	−10	9·33	9·36	+3	21	24	+3	*+13	20	+7	3	4	+1	0	0	0	0	0	0
8	25	55	63	+8	10·40	10·50	+10	20	19	−1	21	21	0	0	1	+1	1	1	0	0	0	0
III. Alternate Weeks Group:																						
1	24	45	45	0	9·53	10·06	+13	12	19	+7	21	20	−1	4	4	0	0	0	0	0	0	0
2	24	36	40	+4	10·12	10·18	+6	14	15	+1	19	18	−1	0	0	0	0	0	0	0	0	0
3	23	45	46	+1	9·31	9·40	+9	11	11	0	20	21	+1	5	6	+1	0	1	+1	1	0	−1
4	21	40	36	−4	10·16	10·29	+13	16	20	+4	13	16	+3	0	1	+1	2	0	−2	2	0	−2
5	24	48	55	+7	10·06	10·05	−1	17	10	−7	15	13	−2	0	0	0	0	0	0	1	1	0
6	27	31	37	+6	9·50	9·43	−7	16	13	−3	19	20	+1	1	0	−1	0	2	+2	0	0	0
7	21	37	32	−5	9·55	10·05	+10	12	16	+4	20	17	−3	2	0	−2	3	4	+1	3	3	0
8	24	*+41	51	+10	9·33	9·40	+7	7	10	+3	17	14	−3	1	1	0	1	2	+1	0	0	0
IV. 16th–30th Coma Group:																						
1	15	54	50	−4	9·59	9·49	−10	22	19	−3	7	8	+1	0	0	0	0	2	+2	0	0	0
2	15	48	50	+2	10·27	10·25	−2	*+9	23	+14	10	21	+1	0	0	0	8	7	−1	0	0	0
3	15	33	26	−7	9·54	10·04	+10	24	31	+7	14	18	+4	0	0	0	5	11	+6	0	0	0
4	15	*−49	39	−10	10·21	10·25	+4	*−18	7	−11	13	14	+1	0	0	0	5	1	−4	0	0	0
5	15	61	63	+2	9·58	10·05	+7	21	26	+5	*+12	16	+4	1	0	−1	0	0	0	0	0	0
6	15	38	31	+7	10·13	10·19	+6	10	12	+2	18	22	+4	1	0	−1	4	5	+1	0	0	0
7	15	54	61	+7	10·10	10·17	+7	17	25	+8	20	19	−1	0	1	+1	0	0	0	0	0	0
8	15	66	63	−3	9·57	10·04	+7	27	23	−4	23	25	+2	2	0	−2	4	8	+4	0	0	0
														45	38	−7	54	60	+6	10	5	−5

REMARKS

Column 1 contains the four groups of 8 patients each, the name given to each group indicating in which manner the patients received the hyaluronidase in addition to the insulin. 2: "N" gives the actual number of "hyaluronidase days" for each patient, and also the number of non-hyaluronidase days with which they have been compared. 3: "Sopor" is taken from the beginning of sopor to the onset of coma (both as defined in the article). The figures mean minutes and are averages. 4: "Onset" means time of onset of coma, again in averages. 5: "Stability" means the average for each patient of the difference from H. day to H. day (and non-H. day to non-H. day respectively), i.e. a measure of the predictability of the time of onset. (Theoretically one would expect these figures, in minutes, to be smaller on the H days, which in fact they are.) 6: "Waking Duration", means the averages in minutes from time of nasal feed to rational waking state, for each patient. 7: "Intravenous Glucose" i.e. those days on which i.v. glucose was needed to either aid wakening (usually given if patient is not awake 20 minutes after nasal interruption of coma) or to terminate distress. 8: "Fits" means epileptiform fits occurring during the days under consideration. 9: "After shocks" relates to the minor symptoms of hypoglycaemia which occurred in the afternoons. Again equal numbers of "H" and "non-H" days have been compared for each patient. "H" and "NH" in columns 3–9 indicate the averages for the days of comparison, i.e. total divided by N on each side (in group IV [16th–30th coma] the 7 comata before coma 16 plus the 8 comata after coma 30 have been compared with the "Hyalase"—comata 16–30, i.e. the same number—15).

* Significant difference (P approaches or is greater than 0·05). Direction change in the expected direction indicated by +; change in the opposing direction indicated by −.

Result

From the table it can be seen that in 25 out of the 32 cases such a precipitation of onset in fact took place, in 6 cases a postponement and in one there was no change. If one takes the average of the averages—a questionable method—one would arrive at a mean precipitation of coma for each of the 630 H days by 6 minutes. Whilst there is undoubtedly a change produced by the hyaluronidase in the desired direction it is not of great clinical importance.

For two individual patients the mean time of onset of coma under hyaluronidase was significantly less than the mean time of onset for the same patients when not under the additional drug (Cases I/3 and II/1, Table I). In one other case (I/5) the mean reduction is sufficiently marked to approach statistical significance and in one case (I/6) the effect of the drug is markedly to increase the time of onset to a degree that also approaches significance.

Statistical tests applied to individual scores of the remaining 28 patients failed to indicate any individually significant change. We have noted that the injection was given at 7.30 a.m. on each occasion with the object of inducing a coma at about 10 a.m. If the average coma time for the H days and the N.H. days are considered then the mean Coma Time for the H. group occurs before 10 a.m. more frequently than is the case for the N.H. groups ($\chi^2=5\cdot32$, significant at $P=0\cdot05$ level). The actual table is as follows:

	Mean Coma Time		
	Before 10 a.m.	After 10 a.m.	
H. Group	17	15	32
N.H. Group	8	24	32
	25	39	64

HYPOTHESIS III

Stability of Onset of Coma

The addition of hyaluronidase has no stabilizing effect on the onset of coma, i.e. if hyaluronidase has a positive effect then the coma would occur more frequently at about the same time than when hyaluronidase is not given, diminishing the amplitude between the times of onset and therefore aiding predictability.

Averages were calculated for the differences in minutes of the onset on the H days and compared with the average differences between an equal number of non-H days. It was found that in 19 patients a diminution of the amplitude occurred, in 3 it was unchanged and in 10 it was increased. It appears that hyaluronidase has a favourable effect, even if it might not be of great clinical significance. The calculated value of χ^2 for these data does not reach statistical significance although the trend is apparent.

For four individual patients the mean rating of stability of onset was significantly increased by the addition of hyaluronidase (Cases I/1, II/1, II/3 and IV/2). In one other case (IV/4) however, the effect of hyaluronidase was to reduce significantly the mean rating of onset of stability. Statistical tests applied to the remaining 27 patients failed to indicate any individually significant change.

HYPOTHESIS IV

Waking Time

The time taken between nasal interruption of the coma and awakening of the patient is not significantly shortened.

Again averages of waking time were calculated in minutes and it was found that these were shorter in 17 cases, unchanged in 5 cases and lengthened in 10 cases (see column 6 of Table I).

For two individual patients only (Cases II/7 and IV/5) the addition of hyaluronidase to the injection reduced the average waking duration by 7 minutes—a difference that is significant at the 0·05 level of P.

Miscellaneous Points

From the table it will be seen that the necessity for intravenous interruption of coma did not arise in 12 cases, either when hyaluronidase was administered or when not. In the remaining 20 cases, the necessity arose more frequently with hyaluronidase in 11 cases, was diminished in 7 cases and equal in 2 cases. During the 630 H days a total of 45 i.v. glucose interruptions were necessary as opposed to only 38 during the same number of non-H days. In this respect in our trial, hyaluronidase appears slightly disadvantageous. A statistical analysis is obviously unwarranted.

As regards epileptiform fits it will be seen from Table I that in the 32 cases, during the days under consideration fits occurred in 19 of the patients. In 11 cases there were fewer fits on H days, in 1 case there was no difference and in 7 cases there occurred more fits on H days. Altogether 114 fits occurred during the time under consideration for the 32 patients.

This situation appears slightly in favour of hyaluronidase addition to the insulin dose, although the distribution is obviously insignificant.

After-shocks were very rarely seen throughout. In view of the very high incidence reported from other units we may be allowed to attribute this favourable picture of our unit to the excellent nursing care. During 1,260 coma days (630×2) altogether 15 after-shocks occurred, 10 during H days and 5 during N.H. days. In view of the small overall incidence no comment is justified.

One patient from group IV (who had hyaluronidase added from the 16th to the 30th coma) had to be re-admitted in another psychotic phase (patient IV/4). This time she had hyaluronidase from the first to the last day of the course. Her average dose was 296 units (264 units), the average duration of sopor 45 minutes (44 minutes), average time of onset 10.29 a.m. (10.27 a.m.), stability of onset (as defined above) 12 minutes (13 minutes) waking duration 19 minutes (13 minutes); she had 11 epileptic fits (6) and once needed intravenous glucose interruption of the coma (zero). The figures in brackets are the figures relating to the first course. It is only fair to say, however, that she was the one patient who had already reacted unfavourably to hyaluronidase during the previous course (see Table I, patient IV/4).

We are unable, with our criteria for the reduction of the dose of insulin during the course of treatment (that is with an aim to achieve the onset of coma at 10 a.m.), to support the claims of other authors in this respect. Had we chosen different criteria the picture *might* have been different also, but in view of the lack of information and detailed measurements provided in other accounts, we are unable to comment on this discrepancy. The three curves in Figure 1 show that there was no difference between the H days and N.H. days or the control group as regards dosage. Minor reductions might have been possible. We would like to add that the "average coma dose" has been arrived at by adding all the insulin doses given during the whole of the course, that is including the introductory stepping up of the dosage until coma was reached, and this figure has then been divided by 50. This in part explains the relatively high figures.

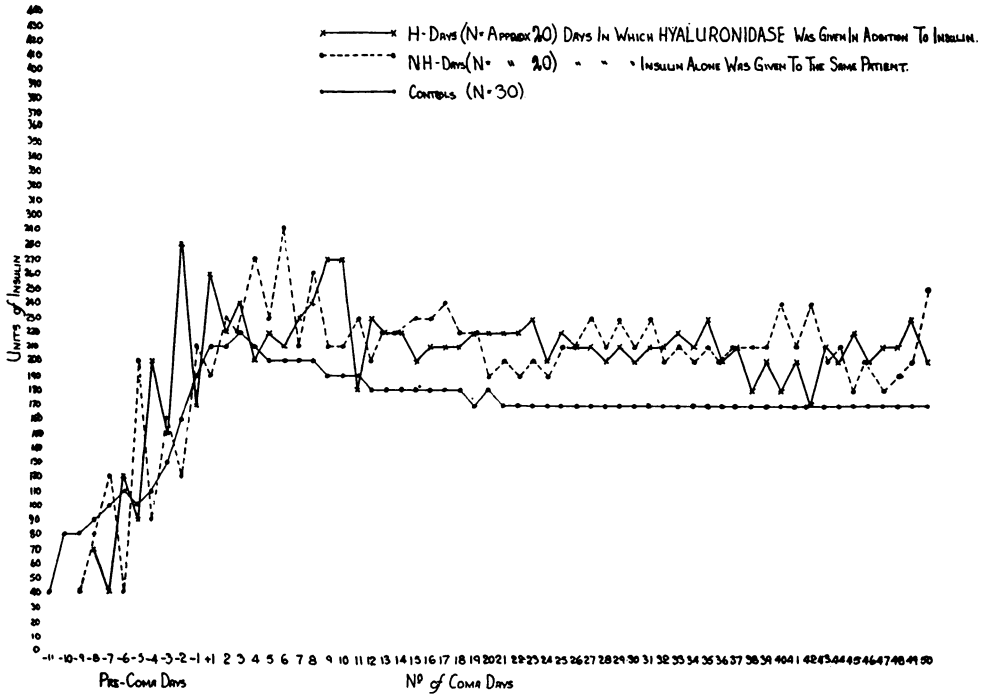

FIG. 1.

RESTLESSNESS

We are unable to be definite about the effect of hyaluronidase in this respect. The reasons have already been given, i.e. that there are at least three different types of restlessness and each would have to be measured separately; also, there are patients who go into coma smoothly without exhibiting any of the forms, and thirdly, "restlessness" may occur at all stages and would have to be assessed separately for its occurrence and modification by hyaluronidase during the pre-sopor stage, during sopor, coma, and during the waking-up period. The writer is unable to give even an impression concerning restlessness, but two of the nurses in charge of the insulin unit reported that there was no change and one (A.E.) was quite definite that a favourable change took place on hyaluronidase days. He quotes three cases (only one of them in the group of the 32 cases under consideration). Without detailed measurements the report is that the sopor time was shortened by approximately 20 minutes by hyaluronidase and "that during those days there was less restlessness" (43rd=52nd coma). In another case he states that "the patient did not become so distressed after nasal feed and usually woke up more easily". For the third case (second case of group IV) he states that the restlessness changed somewhat in character, as if "the punch had gone out of him". The amplitude of the excursions of the limbs appeared to be somewhat reduced.

In 9 of the 32 patients no restlessness was observed. In 11 cases there was a moderate amount of restlessness present, but no noticeable difference between the H and non-H days. In 12 cases restlessness was marked and measured in minutes (taken as all measurements to the nearest 5 minutes). If one differenti-

https://doi.org/10.1192/bjp.104.437.1136 Published online by Cambridge University Press

TABLE II

Clinical Features of 32 Patients

	1 Patient No.	2 Sex	3 Age (in years)	4 Duration of Psychosis (in months)	5 Mode of Onset	6 Type of Schizophrenia	7 Weight on Admission (in lbs.)	8 Gain in Weight (in lbs.)	9 Body-Build	10 Previous Personality	11 Dosage (Average Coma Dose)
I:											
	+1	F	28	3	S	H	128	10	L	AN	340
	2	M	44	1	S	P	111	36	L	AN	169
	+3	F	32	1	S	H	100	15	L	SC	246
	4	M	24	3	S	P	184	21	A	CY	264
	5	M	33	6	S	P	198	3	A	SE	178
	6	M	22	12	G	H	121	20	L	HY	248
	7	M	36	6	S	P	126	13	L	SE	256
	8	M	32	36	S	H	139	9	L	PS	239
II:											
	+1	F	30	1	S	H	106	14	A	CY	299
	2	M	18	12	G	S	124	22	L	SC	460
	+3	M	40	1	S	H	131	21	A	AN	88
	4	M	33	1	S	P	112	13	L	SE	88
	+5	M	23	4	G	H	130	20	L	SC	506
	6	M	18	1	S	H	113	9	L	SC	188
	+7	M	46	8	S	P	167	7	A	AN	214
	8	F	25	6	G	C	125	9	L	SE	327
III:											
	1	F	33	1	S	P	101	26	L	SE	212
	2	M	28	36	G	P	113	9	L	SC	192
	3	F	36	1	S	P	129	11	A	AN	134
	4	F	37	1	S	P	118	1	L	AN	200
	5	F	21	2	G	H	122	17	P	SE	178
	6	M	27	24	G	S	113	9	L	SC	132
	7	M	29	24	G	P	152	23	A	SE	301
	+8	M	39	18	G	H	125	17	L	SC	130
IV:											
	1	M	36	6	G	P	117	18	A	SE	218
	+2	M	19	1	S	H	137	6	P	AN	341
	3	M	23	3	G	H	140	19	A	SC	112
	4	F	21	12	G	C	109	17	L	SC	264
	+5	F	18	1	S	P	106	17	L	SE	144
	6	M	24	18	G	S	163	22	A	SC	439
	7	F	24	3	S	H	119	11	A	SC	317
	8	M	23	1	S	H	148	15	L	SC	216

REMARKS

Column 4: Duration of psychosis in months; if "1" this means one month or less, possibly only a few days. 5: Mode of onset; Sudden (over days)=S Gradual (over months)=G. 6: Type of Schizophrenia (predominantly); H=hebephrenic; S=simple schizophrenia; P=paranoid; C=catatonia. 9: Body-build; A=athletic; L=leptosome asthenic; P=pyknic. 10: Previous personality; PS=psychopathic; SC=schizoid; AN=anankastic; SE=sensitive; CY=cyclothyme; HY=hysterical. + before the patients number=statistically significant changes occurred during hyaluronidase days in one or several respects.

ates between (1) excessive twitching in pre-sopor and early sopor, (2) writhing movements, contortions and hyper-extension in sopor, (3) hyper-extension and whole body contortions in coma and (4) contortions, hyper-extension spasm and writhing movements during the waking time, the following table gives some indication of the distribution.

Patient	I/2	I/4	I/5	I/6	I/8	II/2	II/7	III/1	III/3	III/4	III/7	IV/2
Type of Restlessness	2/3	1 1/3	1	2	2	2	1/2/3	1	3	2	2/3/4	1/2/3/4

In patient I/6 a diminution of the duration of restlessness occurred by two minutes (average), patient II/7 however, was "if anything a little worse during the H days". In patient III/3 the amount of respiratory distress which soon set in after the onset of coma (only allowing for comata of 5 minutes duration), was unchanged under hyaluronidase medication. The favourable effect of hyaluronidase in patient IV/2 has already been mentioned above. In the remainder of the patients the final comment has always been: "no difference as to duration and intensity of the various forms of restlessness."

Clinical Correlations

We will now try to answer the question whether relationships can be established between (*a*) those cases in which hyaluronidase produced very definite favourable changes and (*b*) features which these patients might otherwise share; e.g. 1. Sex. 2. Age. 3. Duration of psychosis. 4. Mode of onset. 5. Type of psychosis. 6. Weight on admission. 7. Gain in weight, during the insulin course. 8. Body build. 9. Pre-psychotic personality. 10. Average coma dosage of insulin required. These features are given in Table III. No attempt is made to interpret them but they are worth recording in case of future research. The table lists only those features which are significantly changed during the days of hyaluronidase addition to the insulin dosage.

Discussion and Conclusion

The results of the current investigation are somewhat at variance with other reports. We have tried to cover as many as possible of the aspects mentioned in other papers. Several factors have been assessed which were not considered previously, e.g. "Stability of onset" and the number of epileptiform fits. A curious feature is our generally rather high dosage as compared with other (especially French) workers. Possibly the increase of the dosage by 40 units daily until coma is produced rather than increases by 10 units daily may explain this difference, together with the differences in coma time lag and our method of arriving at the "average coma dose". Unfortunately in the other papers, body weights are not quoted so that comparison in this direction is not possible.

In the preceding results the statistical comments concerning patients of the "Pilot group" should be considered in the light of the limited number of days involved.

Whilst it appears that the addition of hyaluronidase does influence some of the events during the insulin coma treatment of schizophrenia and mostly in a favourable direction, we are unable to confirm the extensive changes claimed by other authors. Our results indicate that definite clear-cut changes only occur in a few patients, and there is a suggestion that these affected features occur in the acute hebephrenic group. A further trial of hyaluronidase in certain "difficult cases" appears worth while. Data are given to help selection of these cases (Table III). Restlessness, whilst possibly being qualitatively influenced, warrants

TABLE III

Common Features Shared by Patients Who are Significantly Affected in One Factor by Hyaluronidase

1	2	3	4	5	6	7	8	9	10	11	12
Factor	Patient	Sex	Age (in years)	Duration of Psychosis (in months)	Mode of Onset	Type of Schizophrenia	Weight on Admission (in lbs.)	Gain in Weight (in lbs.)	Body-Build	Previous Personality	Dosage (average per coma)
Sopor duration	II/5	M			G	H	130	20	L	Schizoid	
	II/8	M			G	H	125	17	L	Schizoid	
Onset of coma	I/3	F	32	1	S	H	100	15			
	II/1	F	30	1	S	H	106	14			
Stability of onset of coma	I/1			3	S	H	128			Anankast	340
	II/1			1	S	H	106			Cyclothyme	299
	II/3			1	S	H	131			Anankast	88
	IV/2			1	S	H	137			Anankast	341
Waking duration	II/7				S	P					
	IV/5				S	P					

Symbols employed in this table as in Table II.

https://doi.org/10.1192/bjp.104.437.1136 Published online by Cambridge University Press

SAMPLE OF RECORDINGS (Condensed from Daily Sheets). Patient II/2.

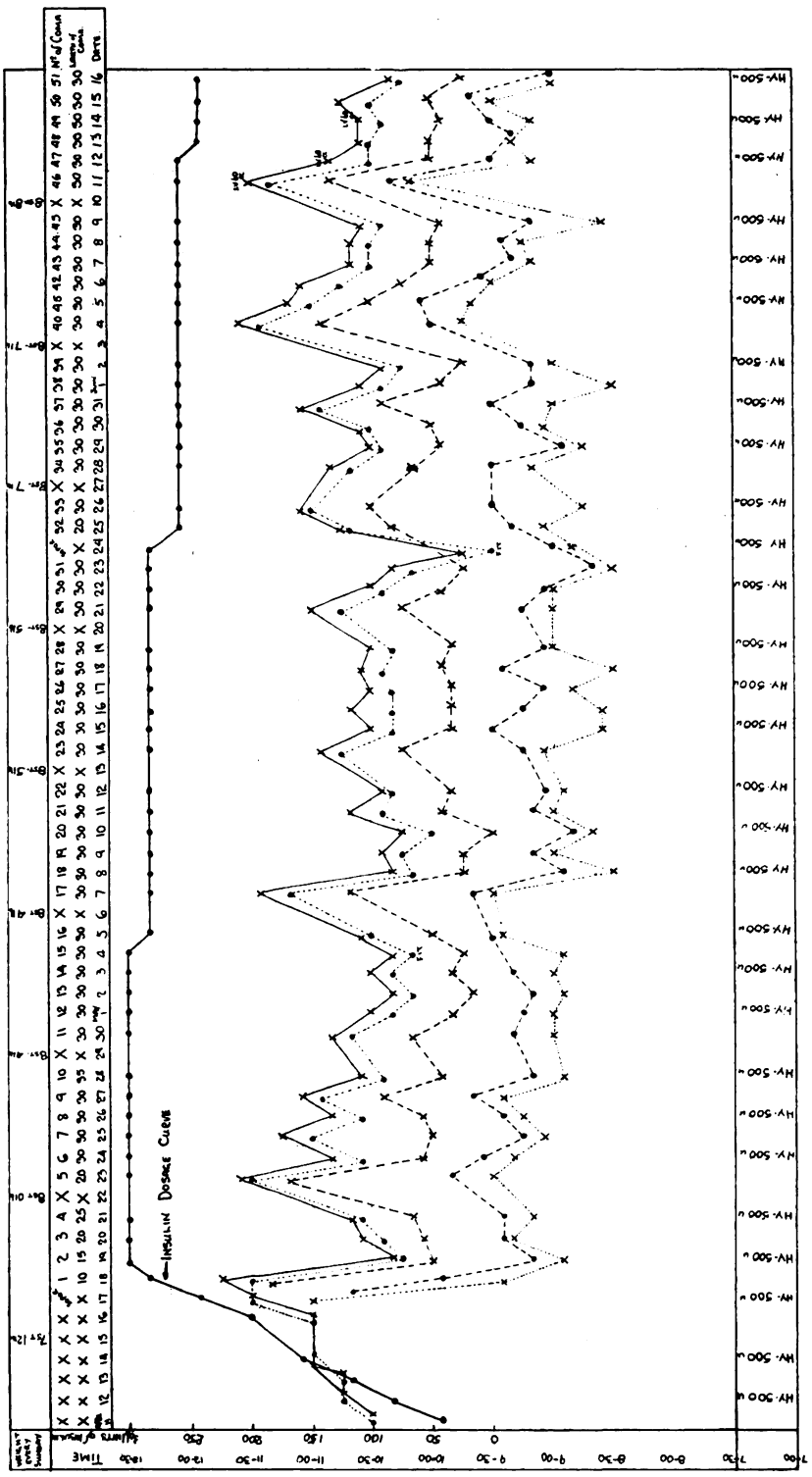

FIG. 2.

https://doi.org/10.1192/bjp.104.437.1136 Published online by Cambridge University Press

a special study with precise measurements and definitions. With the criteria set in *this* trial for the reduction of insulin dosage, no such reduction appeared indicated or possible by the addition of hyaluronidase to the insulin injected.

Summary

A trial has been carried out on 32 schizophrenic patients receiving courses of insulin coma treatment to determine by measurements, whether the various stages of the coma could be favourably influenced by the addition of hyaluronidase to the insulin dosage. The patients were divided into four groups of 8 patients each, who received the hyaluronidase (apart from a pilot-group) on alternate days, alternate weeks, and from the 16th to the 30th coma respectively.

The factors assessed were duration of sopor, onset of coma, stability of onset of coma, waking duration, necessity for intravenous glucose interruption, epileptiform fits, after-shocks and insulin dosage. Most of the factors appeared significantly favourably influenced by the addition of hyaluronidase in a few patients only, except for dosage where no drastic reduction appeared to be indicated or possible in any single case with the criteria adopted.

An attempt is made to correlate these data with characteristics of the patients and the features of their psychosis. The results indicate the possible importance of the acute hebephrenic group.

Acknowledgments

Appreciation is expressed to Dr. Crowe, Medical Superintendent, Parkside Hospital, Macclesfield, Cheshire, for permission to carry out the trial, to Messrs. Davidson (Assistant Chief Male Nurse), Earnshaw, and Assistant Matron Miss Glass (nurses in charge of the insulin unit), for their most willing co-operation and untiring efforts in the detailed recording of the events by the minute, and also to their assistants, to Benger Laboratories Limited for supply of hyaluronidase (Hyalase) as well as for help with the references.

References

1. Blandin, J., Guillon, A., and Racine, Y., *Ann. Méd.-Psychol.*, 1955, **1,** 429.
2. Demay, G., Mises, R., Bories, J., and Chavoit, P., *ibid.*, 1953, **2,** 339.
3. Frostig, J. P., *Amer. J. Psychiat.*, 1940, **96,** 1167.
4. Gysin, W. M., and Wilson, J. L., *Dis. Nerv. Syst.*, 1954, **15,** 138.
5. Holden, J. C., and McGuinness, O. L., *Brit. Med. J.*, 1957, July, 85.
6. Kueppers, E., *Dtsch. Med. Wschr.*, 1937, **63,** 377.
7. Tyndel, M., *J. Amer. Med. Ass.*, 1956, **162,** 32.
8. Wyburn, G. M., and Bacsich, P., *Practitioner*, 1950, **164,** 361.