Response of Diabetic Coma to Various Insulin Dosages

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Over the years the treatment of diabetic acidosis and coma has presented a vexing problem to the physician and has often meant an unfortunate outcome for the patient. Although coma is admittedly an unnecessary and preventable complication of diabetes mellitus, its frequency remains high; at the Los Angeles County Hospital it accounts for approximately 5 per cent of the admissions to the Diabetic Service.

While the reports in the literature are in general agreement on the main principles of treatment, namely, the administration of adequate amounts of insulin and adequate hydration in conjunction with other supportive measures that may be required by the individual patient, there is still considerable disagreement as to what constitutes adequacy, and also as to the rate at which insulin and fluid should be given. Insulin dosages in the first twenty-four hours have varied from as little as 60 units, as reported by Crampton, Mellinger and Palmer,[1] to as much as several thousand units, as noted by Harwood.[2] The dosage schedule also varies widely, ranging from 20 to 50 units given hypodermically every 30 minutes to an amount equivalent to one-half of the blood sugar level or more.

The mortality from diabetic coma likewise has a wide range. McCullagh[3] has stated that a 10 per cent mortality of cases in actual coma is probably attained by few and that rates as high as 25 to 40 per cent still exist. Harwood[2] in 1951 reported that the mortality figures in various parts of the country varied from 2.4 to 43.7 per cent.

METHODS

It was our belief that the Diabetic Service of the University of Southern California Medical School at the Los Angeles County Hospital presented a sufficient variety and number of diabetic coma patients susceptible to sufficient control to permit comparison of the therapeutic effect of differing insulin dosages. The resident staff of this service consists of one resident physician who serves for three months and three interns who serve for one month. Every three days each intern admits and cares for patients for a 24-hour period.

During the period of this study, from May 6, 1952, to May 16, 1953, each intern on the Diabetic Service was assigned one of three specific insulin schedules for all of his patients with diabetic coma. The first schedule consisted of 80 units, the second of 160 units, and the third of 240 units. All insulin was administered intravenously at approximately two-hour intervals until the blood sugar was 300 mg. per 100 cc. or less.

Table 1 shows the method used for reducing the insulin dosage in accordance with changes in the blood-sugar level during the course of treatment. Such a procedure was believed necessary in order to prevent sudden and severe hypoglycemia in patients particularly sensitive to insulin. The interval between injections was kept as close to 2 hours as possible, but the difficulty of caring for acutely ill patients on a hospital ward service resulted in some variation in individual cases. The average minimum time between insulin doses in the 80-unit group was 100 minutes, in the 160-unit group 108 minutes, and in the 240-unit group 103 minutes. The average maximum time between doses in the 80-unit group was 160 minutes, in the 160-unit group 171 minutes, and in the 240-unit group 155 minutes.

TABLE 1

Insulin schedule: initial and subsequent 2-hour doses*

Reduction in Blood-Sugar Level	Urine Test (2-hr. Intervals)	Initial Dose 80 units	160 units	240 units
		Subsequent Dose		
Less than 20%	4+	80	160	240
20–30%	–	40	80	120
30–50%	3+	20	40	80
50–75%	2+	10	20	40
75–100%	1+	0	10	20

*Glucose is to be added when the blood-sugar level falls to 250 mg. per 100 cc. or less.

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The first 4 liters of fluid during the first 48 weeks consisted of 1000 cc. of 0.9 per cent saline solution, 1000 cc. of 1/6-molar sodium lactate, 1000 cc. of 0.9 per cent saline, and 1000 cc. of 1/6-molar sodium lactate, given in this order. During the last five weeks it consisted of 2000 cc. of 1/6-molar sodium lactate followed by 2000 cc. of 0.9 per cent saline. No glucose-containing fluids were administered until the blood-sugar level was 300 mg. per 100 cc. or less.

Therapy other than the above consisted of plasma, whole blood, and vasopressor drugs, usually norepinephrine, vasoxyl, or neosynephrine or all three, when the degree of hypotension warranted. Our definition of hypotensive shock was a systolic blood pressure of 90 mm. of mercury or less, or a diastolic blood pressure of 60 mm. of mercury or less.

The serum bicarbonate levels were determined by the Van Slyke titration method.[4] Blood sugar determinations were done by a modification of the Benedict method.

CASE MATERIAL

While the term "diabetic coma" has been used over the years to describe the condition of diabetic patients with varying degrees of impairment of consciousness and varying degrees of acidosis, we selected for our study only those in whom the serum bicarbonate level was 9.1 mEq/L. or less, not associated with other disease which could account for a depression of the bicarbonate level of this magnitude.

Insulin Dose, Age, and Sex (*Table 2*):

Forty-three patients with diabetic coma of this type were admitted during the fifty-three week period of the study. Twelve were treated on the 80-unit schedule, 18 on the 160-unit, and 13 on the 240-unit. The average ages for the three groups were 34.6, 48.7, and 45.3 years, respectively. The age ranges were similar for all three groups. As is true of our diabetic hospital patients as a whole, females predominated.

Admission Blood-Sugar, Serum Bicarbonate, Serum Potassium, and NPN Levels (*Table 3*):

The blood-sugar levels at the time of admission for all three groups were between 380 and 1230 mg. per 100 cc., with both extremes in the 80-unit group. The average levels were 688, 755, and 820 mg. respectively for the 80, 160 and 240 unit groups.

The range of bicarbonate levels on admission was restricted by design and was 3 to 10 mEq/L., as shown in Table 3, only two cases having a level higher than 9.1 mEq/L. The averages for the three groups were 6.4, 5.4, and 7.0 mEq/L.

TABLE 2
Number and age of patients by dosage schedule groups

	80-Unit Schedule	160-Unit Schedule	240-Unit Schedule
Number of patients	12	18	13
Age range (years)	16-70	17-83	21-76
Average (mean) age (years)	34.6	48.7	45.3
Per cent female	100.0	84.0	69.0

TABLE 3
Electrolyte and NPN levels on admission

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
	mg./100 cc.		mg./100 cc.		mg./100 cc.	
Blood Sugar	380-1230	688	440-1150	755	470-1120	820
	mEq/L.		mEq/L.		mEq/L.	
Serum bicarbonate	3-9	6.4	4-10	5.4	4.9-9.5	7
Serum potassium	3.8-7.9	5.4	3.9-5.2	4.5	3.3-7.4	4.7
	mg./100 cc.		mg./100 cc.		mg./100 cc.	
Nonprotein nitrogen	25-103	53	34-114	70	47-112	76

Seventeen of the 43 patients had serum potassium determinations at the time of hospital entry. These ranged from 3.3 to 7.9 mEq/L. with averages of 5.4, 4.5, and 4.7 mEq/L. Electrocardiograms were made on admission in many of the other cases; we believe this is usually a rapid and rather accurate means for the diagnosis of hypopotassemia and hyperpotassemia.

The values for nonprotein nitrogen of the blood on admission averaged well above the upper limits of normal, being 53 mg., 70 mg., and 76 mg. per 100 cc. for the 80-unit, 160-unit and 240-unit groups, respectively. All the admission levels were above normal in the 240-unit group (from 47 to 112 mg.). In the 80-unit group they ranged from 25 to 103 mg. and in the 160-unit group from 39 to 114 mg.

THERAPY

Fluid and Electrolytes (*Table 4*):

The rate of flow of intravenous fluid was ordinarily as fast as the solutions would run by gravity. It averaged 630, 780, and 560 cc. per hour for the entire period of coma for the 80-, 160-, and 240-unit groups, but approached 1000 cc. per hour during the first two to three hours. The total volume averaged 4880 cc. for the 80-unit group, 6535 cc. for the 160-unit group, and 4460 cc. for the 240-unit group.

TABLE 4
Fluid and electrolytes during coma treatment

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
	vols./cc.		vols./cc.		vols./cc.	
Fluid	1900-7800	4800	2550-8500	6535	2350-7000	4460
	gm.		gm.		gm.	
Sodium (i.v.)	5.7-21.5	15.9	7.4-27.7	16.9	8.4-24.7	15.4
Potassium						
i.v.	0-7.0	3.8	0-5.5	2.8	0-4.8	2.2
Oral	0-6.0	2.4	0-3.5	2.6	0-7.0	—*

*3 cases only.

The amount of sodium administered in the above fluids averaged 15.9 gm. or 692 mEq. for the 80-unit group, 16.9 gm., or 735 mEq. for the 160-unit group, and 15.4 gm., or 670 mEq. for the 240-unit group.

The end point in measuring the fluid volumes and sodium quantities was the same as for insulin, namely, the termination of clinical evidence of coma or the fall in the blood-sugar level to 300 mg. per 100 cc., whichever was earlier.

The data on potassium therapy are disappointing. Despite our long-held beliefs, written directions, and repeated conferences with the attending and resident staff personnel, there remains an obvious reluctance on the part of interns to administer potassium salts parenterally in amounts that we believe advisable in the treatment of diabetic coma. Part of our coma regimen calls for 1.0 gm. of potassium chloride in each liter of intravenous fluid as a minimum, if urinary output is satisfactory, and 2.0 gm. orally or by stomach tube every four hours for the first twenty-four hours.

Six of the 43 patients in the series received no potassium parenterally; one of them died. Three patients received less than 0.75 gm. The average amount given was 3.8 gm. for the 80-unit group, 2.8 gm. for 160-unit groups and 2.2 gm. for the 240-unit group. While 5 patients survived without benefit of potassium therapy, a study of the deaths in this series clearly indicates that potassium is a part of the therapy of coma that cannot be left to chance with impunity.

Insulin Therapy:

As would be expected with these schedules, more insulin on the average was administered in the 240-unit group than in the other two groups to end the coma. In determining the effectiveness of insulin therapy we believe that the essential points to be considered are: (1) the time required for clinical recovery from coma, (2) the time required to lower the blood-sugar level to 300 mg. per 100 cc. or less, and (3) the time required to elevate the bicarbonate level to 20 mEq/L. or more (Table 5). When the end point of the coma was taken to be the clinical appearance of the patient, a blood-sugar level of 300 mg. or less, or death, whichever came first, the insulin dosage for the 80-unit group averaged 271 units for the living cases and 393 units for all cases, the 160-unit group averaged 405 units for the living cases and 530 units for all cases, and the 240-unit group averaged 805 units for the living cases and 836 units for all cases. (See Figure 1.)

TABLE 5
Time required for recovery from clinical and chemical coma

	80-Unit Schedule		160-Unit Schedule		240-Unit Schedule	
	Range	Mean	Range	Mean	Range	Mean
Hours to end of clinical coma	4.5-18	9.2	2.5-17	8.8	4-12	7.4
Hours before blood sugar 300 mg./100 cc. or less	4-12	5.9	3.5-16	5.9	4-21.5	6.1
Hours before serum bicarbonate 20 millequiv. per liter or more	4-12	8.0	5.8-16	8.0	4-13.5	5.2

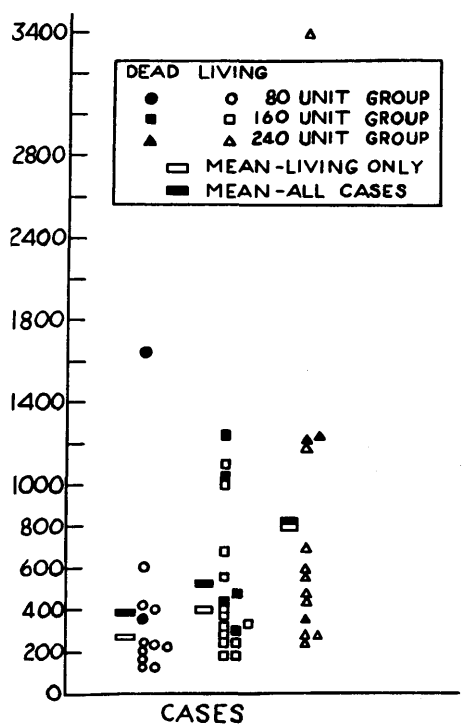

FIGURE 1. Total units of insulin received by each patient from admission to end of clinical coma, a blood-sugar level of 300 mg. per 100 cc., or less, or death, whichever came first.

Figure 2 is a graphic comparison on an arithmetic and geometric scale of the time required to end clinical coma and to reach a blood-sugar level of 300 mg. or less in the 160-unit group. The abscissa for the arithmetic scale is minutes and for the geometric scale is log of minutes, and the ordinate for both is the probability or normal equivalent deviate scale. The measurements for each case are plotted in their order of magnitude. The curved and straight lines are those derived by calculation. It is seen that the cases have nonlinear distribution on the arithmetic scale and a linear distribution on the geometric scale, with the observed points departing in random fashion from a straight line. The subsequent graphs are based on this geometric relation, in which a geometric change in effect (time) is produced by an arithmetic change in cause (dosage).

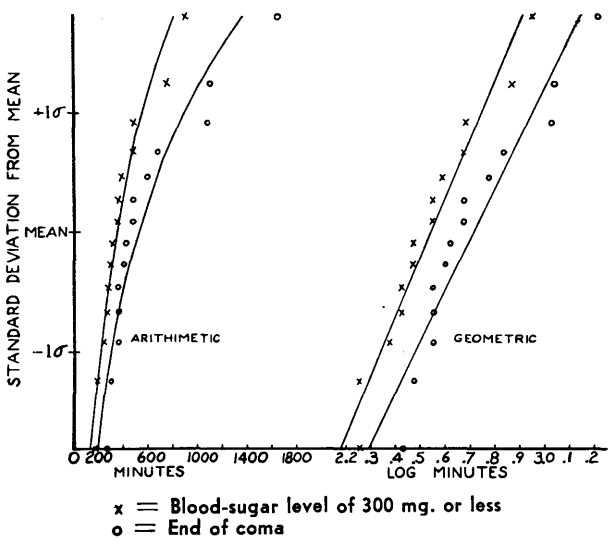

FIGURE 2. A comparison of graph types developed on an arithmetic and geometric scale of the time required to end clinical coma and to reach a blood-sugar level of 300 mg. per 100 cc., or less in the 160-unit group.

The similarity among each of the other groups in each of the three time intervals studied is shown in Table 5, in which the average time from the onset of treatment to the clinical end of coma was 9.2 hours in the 80-unit group, 8.8 hours in the 160-unit group, and 7.4 hours in the 240-unit group. While superficial inspection of these means suggests that larger dosages progressively shorten the duration of coma, the differences between pairs of these means carry probability values of 0.4 to 0.8 and are clearly not significant, and the 0.98 confidence limits of the population mean of the 34 cases combined as one group are 6.7 and 10.7 hours. Figure 3 is a graphic demonstration that the 34 patients who recovered from clinical coma in the three groups may be considered as one group normally distributed in a population of cases of diabetic coma. From the random distribution of the cases along the line, irrespective of insulin dosage, it is apparent that the duration of coma was not affected by different insulin dosages in the ranges studied.

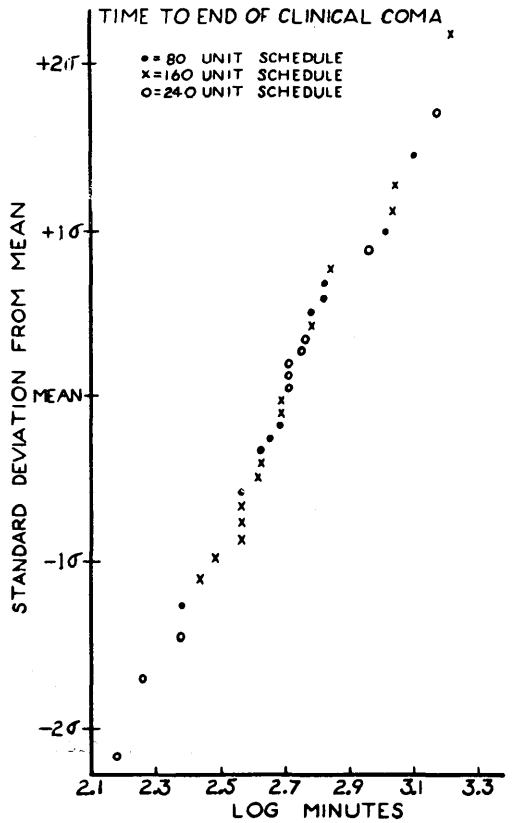

FIGURE 3. Distribution of cases in all three groups as to time to end of clinical coma.

The time required to reach a blood-sugar level of 300 mg. or less averaged 5.9 hours for the 80- and 160-unit groups and 6.1 hours for the 240-unit group. The differences between these means carry probabilities of 0.9 or more that they could have been due to chance rather than to differences in the amounts of insulin used. For the entire group of 34 cases in which the blood sugar reached 300 mg., the 0.98 confidence limits of the population mean are 4.8 and 7.3 hours. Figure 4 is a graphic presentation of the homogeneity of the cases when treated as one group.

Several limitations, however, are present in these statistics. One is that eight patients received some glucose intravenously or oral feedings before the blood-sugar level reached 300 mg., which should prolong the

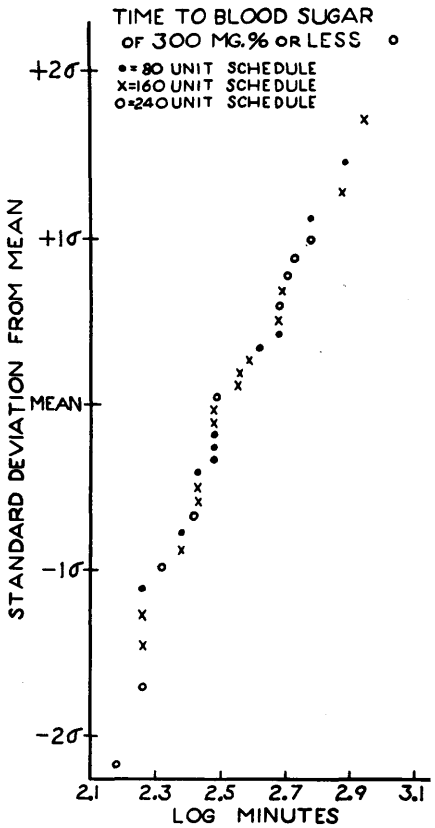

FIGURE 4. Distribution of cases in all three groups as to time required to lower blood sugar to 300 mg. per 100 cc. or less.

time required to reach this level. A second is that the first blood-sugar level less than 300 mg. may have been obtained some time after the blood sugar actually passed this level (at least variable times in the different cases). Finally, it might be expected that the higher the starting level of the blood sugar the longer it would require to reach any arbitrary level. None of these, however, is germane to the issue of the response of the blood sugar to insulin. This response can be directly studied since data are available relative to the time interval from each dose of insulin to each blood sugar value. Multiple graphic representations of the blood-sugar values against time were made, and it was found that a plot of the log of the blood-sugar value against the log of the time gave a good approximation of linearity in the great majority of individual cases. A regression was then computed on this linear basis. It is recognized that this might well fail to describe the results very early or very late beyond the limits covered by these data.

A regression coefficient, measuring rate of change of the blood sugar and not dependent in measurement on the initial blood-sugar value, was calculated for each patient prior to the administration of glucose, and the mean and standard deviation of the means of these regression coefficients was found for the various patient groups.

Comparing in this fashion survivors and fatalities, a t value of 0.27 carrying a probability of 0.8 was found. Comparing the mean regression values of the 80- to 160-, 80- to 240- and 160- to 240-unit groups, probabilities of 0.5, 0.15, and 0.2 were obtained. Finally the question as to whether the rate of blood sugar fall was related to blood-sugar level on admission was tested for survivors and deaths, for each treatment group and for all patients, and no correlation was found.

The average times required for the bicarbonate to reach 20 mEq/L. or more were 8.0, 8.0 and 7.4 hours, for the 80-, 160- and 240-unit groups respectively, as shown in Table 5, and although there appears to be some difference in favor of the 240-unit treatment schedule, Figure 5 graphically demonstrates the three dosage groups to be randomly distributed in a linear pattern.

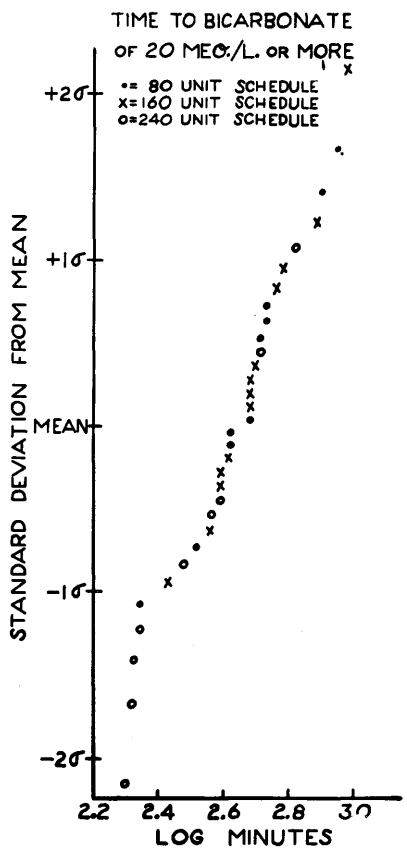

FIGURE 5. Distribution of cases in all three groups as to time to raise serum bicarbonate to 20 milliequiv. or more.

In a manner similar to that used in determining the rate of fall of the blood sugar, a regression study was made in each patient determining the rate of increase in the bicarbonate values. The probabilities attached to the differences between pairs of means for these regression rates for survivors and fatalities were in the 80-unit group 0.01, in the 160-unit group 0.05, in the 240-unit group 0.5, and for all survivors and all fatalities 0.01. In each instance the rate of bicarbonate rise was more rapid in the survivors than in the fatalities, and this difference appeared significant.

The probabilities for the differences between the means of the three treatment groups were from 0.3 to 0.8 for the survivors and from 0.2 to 0.9 for the deaths. For all patients in the several groups the p values were 0.4 to 0.8. These are all probabilities which one would expect to encounter in drawing multiple samples from the same population, and any difference observed could be ascribed to chance alone. No significant correlation was noted between the bicarbonate regression coefficient and the bicarbonate value on admission, or between the bicarbonate and blood-sugar regression coefficients.

One might suspect that increasing insulin dosage, all other factors being similar, would increase speed of recovery from the insulin deficit state of diabetic coma, and this would obviously be true in the low ranges of one or two units per hour not yet experimentally demonstrated. But there is undoubtedly a range in which marked increases in dosage do not greatly change effect. We believe that the area extending from 80 to 240 units for each two-hour interval is in this range, and we suspect that it extends a little below and a great deal above these limits. In support of this is that in an effective dosage range in which doubling and tripling the dosage has demonstrated no significant increase in effect, it is highly unlikely that multiplying the dosage five or ten times would produce a response not discernible in the lower area. In an unreported study of 116 severe coma cases of our own with admission bicarbonate levels of 6.8 mEq/L. or less and blood sugar levels of 700 mg. or more, there was no significant variation in the mortality of the groups receiving from 100 to 750 units of insulin during the first twelve hours of treatment, nor in fact any improvement in mortality by increasing the insulin dosage beyond 10 to 15 units per hour.

We believe that an analysis based on the principles used in this study of these three dosage levels would support this thesis if applied to published cases treated with dosage schedules on the order of five or ten times those used by us.

CAUSES OF DEATH

The mortality of 26 per cent during the 53 weeks of this study was considerably higher than we had experienced during 1949, 1950, and 1951, when the coma mortality was 11 per cent, 11 per cent, and 15 per cent for 62, 44, and 46 cases respectively. The only significant change in therapy instituted during this study was in insulin dosage. Previously all coma patients had initially received 40 units intravenously and 40 units subcutaneously, with subsequent doses varied accordingly to the change in the blood sugar.

It must be apparent that the causes of death commonly occurring in any large city or county general hospital will strike with similar frequencies among the nondiabetic and diabetic populations of such a hospital. Patients dying from these causes while simultaneously experiencing an episode of diabetic coma can properly be excluded from the mortality *of* diabetic coma, but should be included in the mortality data of patients dying *with* coincidental diabetic coma. We suggest that all data concerning deaths and diabetic coma be presented in this manner.

The eleven fatal cases in this study are presented in two groups. The first group (Table 6) comprises the 3 fatalities which we believe resulted from failure of treatment and should be classed as deaths due to diabetic coma, and possibly preventable.

TABLE 6
Deaths due to diabetic coma (treatment failures)

	Age	Sex	Duration of Treatment	Course and Cause of Death
80-unit group				
Case 1	61	F	12.5 hrs.	5-hr. delay in transfer; shock throughout; potassium 7 mEq/L. before death; autopsy showed bronchopneumonia, acute pyelonephritis.
Case 2	32	F	11.5	6 comas in 10 mos.; pulmonary edema and respiratory death; no intravenous fluids; potassium 4.5 mEq/L. before death.
240-unit group				
Case 3	31	M	18.5	Intoxicated; serum amylase 1300 units; blood pressure below 94/70 throughout; potassium 1.4 mEq/L. before death; died from respiratory failure.

It is obvious that in Cases 1 and 3 hypopotassemia was a major factor. We believe that the quantities of potassium recommended for our routine coma management would have sufficed. While it is possible that the bronchopneumonia and acute pyelonephritis in Case 1 and the shock in Case 2 would have resulted in death, the presence of these complications does not adequately reduce the responsibility for inadequate potassium therapy.

In Case 2 the coma was the sixth in ten months in a 32-year-old Negress who apparently died of respiratory failure and pulmonary edema. The serum potassium shortly before death was 4.5 mEq/L. All parenteral fluid was administered by clysis because of inability to get fluids to run properly by the venous route, because of thrombosis of the larger superficial veins resulting from previous recent coma therapy and no attempt being made at arterial or intrasternal infusion. However, intravenous therapy might have only hastened the occurrence of pulmonary edema and death. Shock did not appear until the last forty-five minutes of life.

There were eight deaths (Table 7) which we believe were not directly attributable to diabetic coma and except for Case 8 were in no way related to failure of the coma treatment.

The first case was that of a 64-year-old woman in coma some fifteen to thirty hours before admission, whose blood pressure remained below 74/40 for five hours before death despite all the supportive means noted in the table protocol. She was in a satisfactory state as to blood sugar and serum bicarbonate levels, and the serum potassium level of 2.9 mEq/L. was not in our experience sufficiently low to cause significant respiratory or cardiac embarrassment. The serum amylase of 1780 units very likely is indicative of acute pancreatitis. The second and third cases were previously unknown diabetics who entered in deep coma and were found at autopsy to have necrosis of the renal papillae and lung abscess, and an infarct of the entire small bowl, respectively. The fourth case was a previously unknown diabetic with a typical history of lobar pneumonia who remained in shock throughout the twenty hours of her treatment. She died apparently of the pneumonia and heart failure after making a rather good chemical recovery. The fifth patient was also a previously unknown diabetic who developed coma on a surgical ward while undergoing treatment for multiple stab wounds of the head, neck and chest and died of a massive intratracheal hemorrhage after chemical recovery from the coma. The sixth, a 60-year-old woman, made a rapid chemical and physical recovery from her coma but did not respond mentally and refused all oral feedings. Her death four and one-half days later from pulmonary edema and effusion resulted from administration of ex-

TABLE 7
Deaths due to complications

	Age	Sex	Duration of Treatment	Course and Cause of Death
160-unit group				
Case 1	64	F	15.5 hrs.	Coma 15-30 hrs.; white-cell count 2900; serum amylase 1780 units; intra-arterial blood infusion; i.v. venoxyl, neosynephrine; blood pressure <74/40 for 5 hrs. before death; blood-sugar level 343 mg./100 cc.; serum bicarbonate level 30 mEq/L.; potassium 2.9 mEq/L. before death.
Case 2	58	F	2.5 hrs.	Previously unknown diabetic; urine sediment negative; autopsy showed necrosis of renal papillae, lung abscess.
Case 3	83	F	19 hrs.	Unknown diabetic; hgb. 17 gm.; always in shock; autopsy showed infarct of entire small bowel.
Case 4	52	F	20 hrs.	Unknown diabetic; chills, fever, pleurisy; always in shock; chemical recovery; died from heart failure and pneumonia.
Case 5	47	M	6.5 hrs.	Unknown diabetic; chemical recovery from coma; autopsy showed intratracheal hemorrhage from stab wounds.
Case 6	60	F	4.5 days	Recovered from coma; refused oral feedings; given intravenously; autopsy showed pulmonary edema and effusion, 40-gm. pancreas.
240-unit group				
Case 7	27	M	5 hrs.	Found unconscious; shock; bilateral active pulmonary tuberculosis.
Case 8	48	F	5.5 hrs.	Alcoholic; always in shock; anuric; terminal bicarbonate 17 mEq/L.; potassium 1.3 mEq/L.; autopsy showed lobar pneumonia, interstitial pancreatitis, inflamed periportal triads of liver.

cessive parenteral salt and fluid. The seventh and youngest patient was an escapee from a tuberculosis sanitarium who was found unconscious and died without recovery from shock with bilateral diffuse active pulmonary tuberculosis. The eighth patient according to the autopsy examination died of lobar pneumonia, interstitial pancreatitis, and inflammation of the hepatic periportal triads. However, it should be noted that she was also in a state of severe hypopotassemia, anuria, and shock, and from these standpoints might also be classed as a case of treatment failure. Our experience with these diseases found at autopsy, however, leads us to believe death would have occurred even if chemical recovery had been brought about.

The corrected mortality, then, (the mortality due only to diabetic coma) is 7 per cent.

SUMMARY

1. Forty-three consecutive episodes of diabetic coma were treated as similarly as possible as to sodium, potassium, chloride and fluid intake, but were divided by lot into three groups in regard to insulin therapy. Twelve patients received 80 units, 18 received 160 units, and 13 received 240 units of insulin intravenously initially, and similar doses subsequently at approximately two-hour intervals until the blood sugar fell to such levels as to necessitate alteration in dosage.

2. The gross mortality was 26 per cent and the mortality due to diabetic coma and its complications was 7 per cent. The largest single cause of death was hypopotassemia.

3. Statistical analysis of the data demonstrated that changes in the insulin dosage from 80 to 160 to 240 units every two hours failed to influence the duration of clinical diabetic coma, the time required to lower the blood sugar to 300 mg. or less, or the time required to raise the serum bicarbonate level to 20 mEq/L. or more. There was no significant difference among the three dosage groups in the rate at which the blood sugar fell or the rate at which the serum bicarbonate rose.

ACKNOWLEDGMENT

We wish to express our appreciation to Frederick J. Moore, M.D., Professor of Experimental Medicine, University of Southern California School of Medicine, for suggestions and statistical analysis of the data.

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DISCUSSION

ALEXANDER MARBLE, M.D., (*Boston*): Drs. Smith and Martin are to be congratulated on having carried through a program of clinical investigation in which there were many different participants. This is certainly an achievement as anyone who has attempted this sort of thing will attest.

The results are most instructive and bear out the clinical impression that in the average case of diabetic acidosis and coma, there comes a point at which with increasing dosage of insulin, the law of diminishing returns operates. From the standpoint of clinical research, the contribution of Drs. Smith and Martin is most important and valuable. However, if a similar technic were carried over into the routine management of diabetic coma by physicians everywhere, certain patients would be lost who otherwise might recover. The reason for this is that in actual practice there is no such thing as an "average" patient. Each case presents its own problems which must be handled individually.

In order to illustrate what I mean, let me take two extremes. On the one hand, let us suppose that we have adopted a schedule calling for 80 units of insulin initially with 80 units or less every two hours depending upon the behavior of the blood and urine tests for sugar. If there happened to appear a patient with coma of unusual severity or of unusual duration prior to admission or with whom for one reason or another insulin resistance was extremely marked, such a patient might die before enough insulin was administered. Thus a patient who, with management of the ordinary type might require 1000-2000 units of insulin for recovery, would have received only 320 units at the end of 6 hours. On the other hand, let us suppose that we are following a schedule calling for 240 units initially and 240 units or less every two hours. Let us suppose that a patient is presented whose age is below that covered in the series by Drs. Smith and Martin, say a child, age 8 or 10 years, and that diabetes is of recent onset. Even the initial dose of 240 units would represent such an excess that one might well have considerable difficulty in keeping the child out of dangerous hypoglycemia even with the constant infusion of glucose.

The above is not intended as a criticism of the work just presented provided it is regarded as clinical research. As far as actual practice is concerned, it would appear wisest to individualize treatment and to gauge the dosage and time of administration of insulin, the administration of fluid and electrolytes and other measures according to the particular needs of the individual patient. There are many factors which affect the insulin needs in the patient with diabetic coma. These include age, duration of the diabetes, type of previous treatment and the presence of complications. In our own group, we have come to believe over the years that large doses of insulin given initially provide for a more prompt and sure recovery from diabetic coma than do smaller doses given at intervals over a period of 6 to 12 hours. We believe that determination of the blood sugar at intervals of 2 to 3 hours during the early hours of treatment provides an excellent basis for evaluating the insulin needs of the patient under treatment. In recent years we have learned the great value of the semiquantitative test of the plasma acetone on the initial blood sample as a rough guide to insulin needs. This information can be obtained within five minutes of the time of first seeing the patient and long before values for blood sugar and carbon dioxide content are available.

Although in our group we try to use potassium either parenterally or orally as indicated in the individual case, we believe in exercising great caution unless the urinary output is thoroughly adequate.

I agree with Drs. Smith and Martin that in a presentation of results of treatment of cases of diabetic coma, it is instructive to indicate those in which it seems reasonably certain that death was not due to the acidosis but to complications. However, it would be most unwise if all deaths in any given series were not reported. Otherwise, it becomes too easy to stray from acceptable standards. It is our own policy to report as a death from diabetic coma, any case in which the patient enters in diabetic coma and does not leave the hospital alive.

KENDRICK SMITH, M.D., (*Los Angeles*): It is a privilege to have such a well-known authority on coma as Dr. Marble to discuss this paper, and I very much appreciate, and I know Dr. Martin does, his very kind words.

Frankly, we undertook this study in an effort to find out if we were using large enough doses of insulin since they differed very widely from those published in the literature. I must say that we were surprised that we were unable to demonstrate any significant statistical difference in the outcome based on these data.

I must say that prior to the statistical evaluation of the data, it seemed that the 240-unit schedule was much more effective than either of the other two. This impression was not confirmed, however, under close scrutiny. However, I am still sure that all of us as clinicians would be inclined to use as large or as small doses of insulin as we think needed in the individual case.

Sodium Content on Dietary Food Labels

New regulations under the Federal Food, Drug, and Cosmetics Act, requiring the labels of "salt free" or "low sodium" food products for dietary use to declare sodium content in milligrams of sodium per 100 mg. of the food and per average serving, will go into effect on September 29, 1954. The "average serving" is required to be expressed in common terms, such as number of slices, cookies, or wafers, or in cupfuls, tablespoonfuls, or teaspoonfuls.

In recent years, the increase in packing of special foods for persons suffering from high-blood pressure and certain types of heart, liver, and kidney diseases has been accompanied by variation and confusion in labeling terminology. Many products labeled "salt free" or "no added salt" contained substantial amounts of sodium, sometimes naturally present in the food, sometimes added in the form of baking powder or other ingredients.

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