The Effect of Long-term Treatment with Sulfonylurea Derivatives on Protein Metabolism in Diabetes Mellitus

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SUMMARY

In 101 diabetic adults without complications we determined before and during long-term treatment with sulfonylurea derivatives the serum protein content, electrophoretic serum composition, alkaline serum phosphatase, bromsulphalein retention, in serum, and in the twenty-four-hour urine free α-amino nitrogen and free α-amino acids were measured. The oxidative function of the liver was examined by loading with 2 gm. of methionine. The electrophoretic serum protein composition was only altered in sulfonylurea failure. After successful long-term treatment no changes in serum protein composition, alkaline serum phosphatase and bromsulphalein retention were found; however, the hyperaminoacidemia and hyperaminoaciduria decreased to normal values. The cause of this effect is probably an augmented production of insulin, which improves the oxidative deamination of amino acids in the liver.

The question of possible side effects from sulfonylurea derivatives in the treatment of diabetes mellitus has been investigated since their introduction in 1955. The observations reported by Müting[1] in 1956 showed a definite decrease in plasma protein, particularly in the serum albumin, in carbutamide failure. Later work conducted with tolbutamide, however, did not show any definite alteration in the serum electrophoretic picture.[2] Furthermore, the majority of investigators emphasize that there is no basis for believing that liver damage occurs after years of treatment with sulfonylurea derivatives. A more sensitive criterion for possible disturbances in protein metabolism is the determination of free α-amino nitrogen and free α-amino acids in serum and twenty-four-hour urine.

We investigated the serum electrophoresis pattern, free α-amino nitrogen and free α-amino acids in serum and twenty-four-hour urine, alkaline serum phosphatase, nonprotein nitrogen and bromsulphalein test in 101 diabetic adults before and during tolbutamide therapy.

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The study of this problem at the Department of Medicine of the Saarlandes University Hospital began concurrently with the introduction of the sulfonylurea derivatives in 1955. More than 300 cases of diabetes were treated with the derivatives; 101 cases were clinically followed up for periods ranging from two to five years. The results of the findings in the treatment of the 101 cases are divided into two sections, the first of which is presented here.

MATERIALS AND METHODS

The subjects were 101 diabetics (fifty-four women and forty-seven men) with an average age of fifty-six years, ranging from thirty-one to seventy-seven years of age. The average duration of diabetes in this group was four and one-half years (ranging from one to thirteen years). No particular complications of the disease were present in any of the patients. Moreover, there was no apparent reason to suspect the presence of any other disorder, particularly liver disease. The average height of the group was 166 centimeters (5′, 5″), ranging between 144 and 178 centimeters or between 4′, 9″ and 5′, 10″. The average weight was 76.6 kg. in the group of the tolbutamide successes and 72.3 kg. in the sixteen tolbutamide failures (46 to 126 kg.).

Eighty-five of the patients were successfully treated with tolbutamide, and sixteen responded negatively to the drug. In eight cases tolbutamide had no effect, and the patients were returned to insulin therapy. In the remaining eight cases of tolbutamide failures, the patients reacted negatively due to intercurrent infection (three cases) and inadequate diet (five cases). The diet prescribed consisted of 50 to 70 gm. fat, 70 to 100 gm. protein and 120 to 250 gm. carbohydrate. The average long-term dose of tolbutamide was 1.0 gm. daily.

Each of the patients was subjected to the following laboratory tests upon admission to the clinic, prior to discharge from the clinic, and subsequently on an outpatient basis: serum protein content,[3] serum electrophoresis,[4] alkaline serum phosphatase, residual nitrogen (nonprotein N) and bromsulphalein test. Free α-

amino nitrogen was determined, using a modification of the method of Moore and Stein[5] and free α-amino acids by means of paper chromatography.[6] For detailed description of the method see Müting.[7] We noted an experimental error in the α-amino-N determination of ±2.5 per cent and the quantitative paper chromatography estimation of amino acids of ±5 per cent to ±10 per cent. Blood glucoses and urine glucoses were checked three times daily; blood glucose after fasting, and twenty-four-hour urinary glucose were investigated on an outpatient basis monthly in addition to the other tests.

RESULTS

Table 1 shows the serum protein composition (calculated in gram per cent) in these two groups of diabetic subjects. The values obtained for individual serum electrophoresis investigations in 100 healthy adults and fifty diabetics without complications and treated *only* by means of diet are given for comparison. It will be seen that even in uncomplicated diabetes treated by diet alone, the serum protein is lowered to an average of 7.21 gm. per cent and the serum albumin to 3.42 gm. per cent (normal 4.28 gm. per cent). The albumin content of the serum rose slightly following successful dietary treatment in the hospital. Similar results were obtained when the patient was treated with tolbutamide. Here not only the serum albumin but also the serum protein increases slightly. After an average outpatient control period of three years, the serum protein remained almost unchanged while the serum albumin rose to 4.17 gm. per cent. Thus, to a large extent, the serum protein returned to normal. The situation was different in the cases of the sixteen diabetics who did not react favorably to tolbutamide. Here the serum protein decreased from 7.28 to 6.75 gm. per cent and the serum albumin from 3.64 to 3.36 gm. per cent. The globulin fractions remained practically unchanged. At the same time the albumin content corresponded to the improvement or deterioration in the glucose tolerance.

The most important results of the α-amino-N analyses are set out in table 2. In fifty uncomplicated diabetics, treated with diet alone, the free amino-acid-N in the serum upon admission was 4.7 mg. per cent (normal 4.1 mg. per cent), and after successful dietary treatment only 4.0 mg. per cent. Similarly the amino-acids in the urine decreased from 177 mg. (normal 114 mg.) to 122 mg. per day. In the cases where tolbutamide failed, the free α-amino-N in the urine still remained high at the time of discharge (183 mg.) although the carbohydrate tolerance was slightly improved due to the change-over to insulin. Furthermore, the free amino-acid-N in the serum decreased only from 5.0 to 4.7 mg. per cent.

However, when a clinically successful treatment with

TABLE 1

Serum protein composition in diabetes before and after treatment with diet and tolbutamide

	Patients (number)	Serum protein (gm. per cent)	Albumin (gm. per cent)	α_1-globulin (gm. per cent)	α_2-globulin (gm. per cent)	β-globulin (gm. per cent)	γ-globulin (gm. per cent)	Blood glucose (mg. per 100 ml.)	Urinary glucose (gm.)	
Healthy adults	100	7.37	4.28	0.37	0.67	0.91	1.16	—	—	
Diabetes plus diet	50	7.21	3.42	0.42	0.73	0.99	1.49	244	23	Admission
Diabetes plus diet	50	7.23	3.59	0.42	0.71	1.04	1.43	182	10	Discharge (after twenty-four days)
Diabetes plus tolbutamide (failures)	16	7.28	3.64	0.44	0.78	1.04	1.32	259	31	Admission
Diabetes plus tolbutamide (failures)	16	6.75	3.36	0.36	0.74	1.07	1.30	190	10	Discharge (after thirty-seven days)
Diabetes plus tolbutamide (successes)	85	7.04	3.58	0.40	0.74	1.03	1.29	250	27	Admission
Diabetes plus tolbutamide (successes)	85	7.25	3.83	0.39	0.72	1.06	1.27	164	5	Discharge (after thirty days)
Diabetes plus tolbutamide (successes)	80	7.19	4.17	0.33	0.57	0.94	1.18	195	12	Outpatient control (after three years)

TABLE 2

Free α-amino nitrogen in serum and twenty-four-hour urine in diabetes before and after treatment with diet and tolbutamide

	Patients (number)	Twenty-four-hour urine (ml.)	Free α-amino-N Twenty-four-hour urine (mg. per 100 ml.)		Serum (mg. per cent)	Blood glucose (mg. per 100 ml.)	Urine sugar (gm.)	
Healthy adults	100	895 ± 224	114 ± 24	12.8	4.1 ±0.2	—	—	—
Diabetes plus diet	50	956 ± 336	177 ± 59	18.7	4.7 ±0.7	244	23	Admission
Diabetes plus diet	50	842 ± 261	122 ± 34	14.5	4.0 ±0.2	182	10	Discharge (after twenty-four days)
Diabetes plus tolbutamide (failures)	16	1,180 ± 355	232 ± 64	19.7	5.0 ±0.7	259	31	Admission
Diabetes plus tolbutamide (failures)	16	1,230 ± 420	183 ± 59	14.8	4.7 ±0.5	190	10	Discharge (after thirty-seven days)
Diabetes plus tolbutamide (successes)	85	1,840 ± 436	253 ± 79	24.3	5.0 ±0.6	250	27	Admission
Diabetes plus tolbutamide (successes)	85	920 ± 260	154 ± 38	16.7	4.2 ±0.3	164	5	Discharge (after thirty days)
Diabetes plus tolbutamide (successes)	80	1,390 ± 372	206 ± 86	14.8	4.4 ±0.4	195	12	Outpatient control (after three years)

tolbutamide took place, the amino-acid excretion in the urine decreased from 253 to 154 mg. while the free amino acids in the serum fell from 5.0 to 4.2 mg. per cent. It was found that after a period of outpatient treatment with tolbutamide, which averaged three years, the free α-amino-N in the serum rose once more to 4.4 mg. per cent while that in the twenty-four-hour urinary sample increased to 206 mg. At the same time the volume of urine increased from 920 to 1,390 ml. The blood glucose level ranged on an average from 164 mg. per 100 ml. to 195 mg. per 100 ml. and the glycosuria from 5 to 12 gm. per day.

Table 3 shows the free amino-acid composition of the deproteinized serum in uncomplicated diabetics be-

TABLE 3

Free amino acids in serum of diabetic adults before and after treatment with diet or tolbutamide in hospital

	Normal (100)*		Diabetes plus diet (50) Admission		Diabetes plus diet (50) Discharge		Diabetes plus tolbutamide (80) Admission		Diabetes plus tolbutamide (80) Discharge	
	M	σ	M	σ	M	σ	M	σ	M	σ
Aspartic acid	1.2	0.4	1.2	0.4	1.0	0.3	1.2	0.3	0.9	0.3
Glutamic acid	1.4	0.3	1.6	0.5	1.5	0.4	1.6	0.4	1.3	0.4
Lysine	1.3	0.3	1.6	0.6	1.3	0.3	1.9†	0.5	1.4	0.3
Arginine	1.1	0.3	1.0	0.5	1.2	0.3	1.2	0.4	1.4	0.3
Histidine	1.3	0.3	1.5	0.5	1.5	0.3	1.5	0.4	1.5	0.3
Tyrosine	1.2	0.3	1.7	0.5	1.4	0.7	1.9	0.5	1.5	0.6
Tryptophane	1.3	0.3	1.7	0.6	1.4	0.4	1.6	0.8	1.5	0.5
Phenylalanine	1.0	0.2	1.1	0.3	1.1	0.3	1.4	0.4	1.1	0.2
Hydroxyproline	ø	—	ø	—	ø	—	ø	—	ø	—
Proline	1.4	0.3	1.6	0.4	1.4	0.3	1.6	0.4	1.4	0.3
Cystine	0.6	0.2	0.8	0.4	0.7	0.3	0.9	0.4	0.5	0.2
Methionine	0.3	0.1	0.9	0.3	0.5	0.2	0.9†	0.3	0.4	0.1
Taurine	1.5	0.5	1.6	0.5	1.7	0.6	1.7	0.7	1.8	0.6
Leucine	1.3	0.2	1.6	0.6	1.4	0.4	1.7	0.7	1.4	0.4
Isoleucine	0.7	0.2	0.7	0.3	0.7	0.3	0.9	0.3	0.8	0.2
Valine	2.3	0.5	2.6	0.7	2.3	0.7	2.9	0.8	2.5	0.3
Glycine	2.3	0.5	2.6	0.9	2.7	0.7	2.5	0.8	2.0	0.6
Alanine	2.5	0.7	3.3	0.9	3.0	0.5	3.6†	0.9	2.9	0.5
Serine	1.4	0.3	1.6	0.4	1.3	0.4	1.5	0.4	1.5	0.2
Threonine	1.1	0.2	1.4	0.4	1.2	0.3	1.5	0.4	1.0	0.3
Glutamine	2.3	0.5	3.2	1.2	2.6	1.8	3.7†	1.1	2.2	1.7
Total	27.5		33.3		29.9		35.7		29.0	
α-amino-N	4.1 ± 0.2		4.7 ± 0.7		4.2 ± 0.2		5.0 ± 0.6		4.2 ± 0.3	

*Number of patients.
†$p < 0.001$ in comparison with normal adults.

fore and after instituting treatment with diet or tolbutamide. Compared to the normal values obtained in 100 healthy adults the values for lysine, alanine, glutamine and methionine usually returned to normal following the treatment by diet or tolbutamide. The content of the individual free amino-acids in the twenty-four-hour urinary sample altered correspondingly (table 4). Here increases are seen in the content of lysine, tyrosine, tryptophane, cystine and taurine, particularly of alanine and glutamine and, above all, of methionine. Furthermore, the total sum of the individual free amino-acids approximately corresponds to the amino-acid-nitrogen content $\times$ 6.25. This factor is derived from the figure of 16 per cent nitrogen which represents the average proportion of nitrogen contained in proteins ($100/16 = 6.25$).

The relationship between success or failure with tolbutamide therapy and the content of amino acids in the urine is seen most clearly by studying the course of the disease.

Figure 1 shows the course followed by blood glucose, glycosuria and α-amino-N in the twenty-four-hour urinary sample as well as the twenty-four-hour urinary output in a sixty-eight-year-old diabetic, height 1.72 metres, weight 80 kg. His diabetes had been present for three years and previously was treated with diet alone. Four weeks prior to admission he complained of severe thirst and tiredness. On admission the blood glucose was found to be between 165 mg. per 100 ml. and 290 mg. per 100 ml. and there was a glycosuria of around 30 gm. per day. At the same time the free amino-acid excretion in the urine was very greatly raised. Following the ingestion of 2 gm. methionine it reached 602 mg. α-amino-N. After five days administration of tolbutamide the amino-aciduria became almost completely normal. Only a slight rise in the urinary α-amino-N was seen after ingestion of methionine. Blood glucose values now lay between 120 mg. per 100 ml. and 190 mg. per 100 ml. There was no glycosuria.

Figure 2 shows an example of an unsuccessful transfer to tolbutamide. The patient was a sixty-seven-year-old woman, height 1.67 metres and weight 65 kg., who had suffered from diabetes of medium severity for ten years. Since the onset of the diabetes she had self-administered 32 units Protamin-Zinc Novo and was extremely eager to be changed to one of the oral hypoglycemic agents. As we had anticipated, this attempt failed. The subsequent insulin requirements rose to 64 units.

Although the blood glucose rose to a maximum of

TABLE 4

Free amino acids in twenty-four-hour urine of diabetic adults before and after treatment with diet or tolbutamide in hospital

	Normal (100)*		Diabetes plus diet (50)				Diabetes plus tolbutamide (80)			
			Admission		Discharge		Admission		Discharge	
	M	σ	M	σ	M	σ	M	σ	M	σ
Aspartic acid	11	4	17	6	14	5	22†	6	16	5
Glutamic acid	23	8	31	14	25	12	39†	12	24	9
Arginine	15	3	20	8	15	6	29	8	18	6
Lysine	49	14	79†	36	55	28	79†	37	76	31
Histidine	72	23	83	34	62	18	97	37	59	12
Tyrosine	14	3	23†	10	19	6	29†	11	19	6
Tryptophane	14	3	26†	11	19	7	33†	12	20	7
Phenylalanine	11	3	16	7	13	5	22†	7	14	5
Hydroxyproline	ø	—	ø	—	ø	—	ø	—	ø	—
Proline	ø	—	ø	—	ø	—	ø	—	ø	—
Cystine	50	13	78	33	50	18	76	32	67	25
Methionine	20	7	45†	23	30	12	66†	20	31	8
Taurine	62	27	95	36	53	19	93	40	51	18
Leucine	12	3	17	8	14	5	20†	10	14	4
Isoleucine	7	2	8	3	9	4	12	4	9	3
Valine	22	7	25	10	22	8	30	8	21	5
Glycine	207	48	258	99	234	75	302†	124	202	53
Alanine	46	13	90†	39	58	30	169†	—	71	10
Serine	25	7	34	10	25	10	42†	15	24	7
Threonine	16	5	22	9	20	6	30†	9	22	6
Glutamine	46	13	65	33	49	20	92†	47	58	23
Total	722		1,032		786		1,284		816	
α-amino-N	114	24	177	59	122	34	253	79	154	38
ml. twenty-four-hour urine	895	244	956	336	842	161	1,040	436	920	260

*Number of patients.
†$p < 0.001$ in comparison with normal adults.

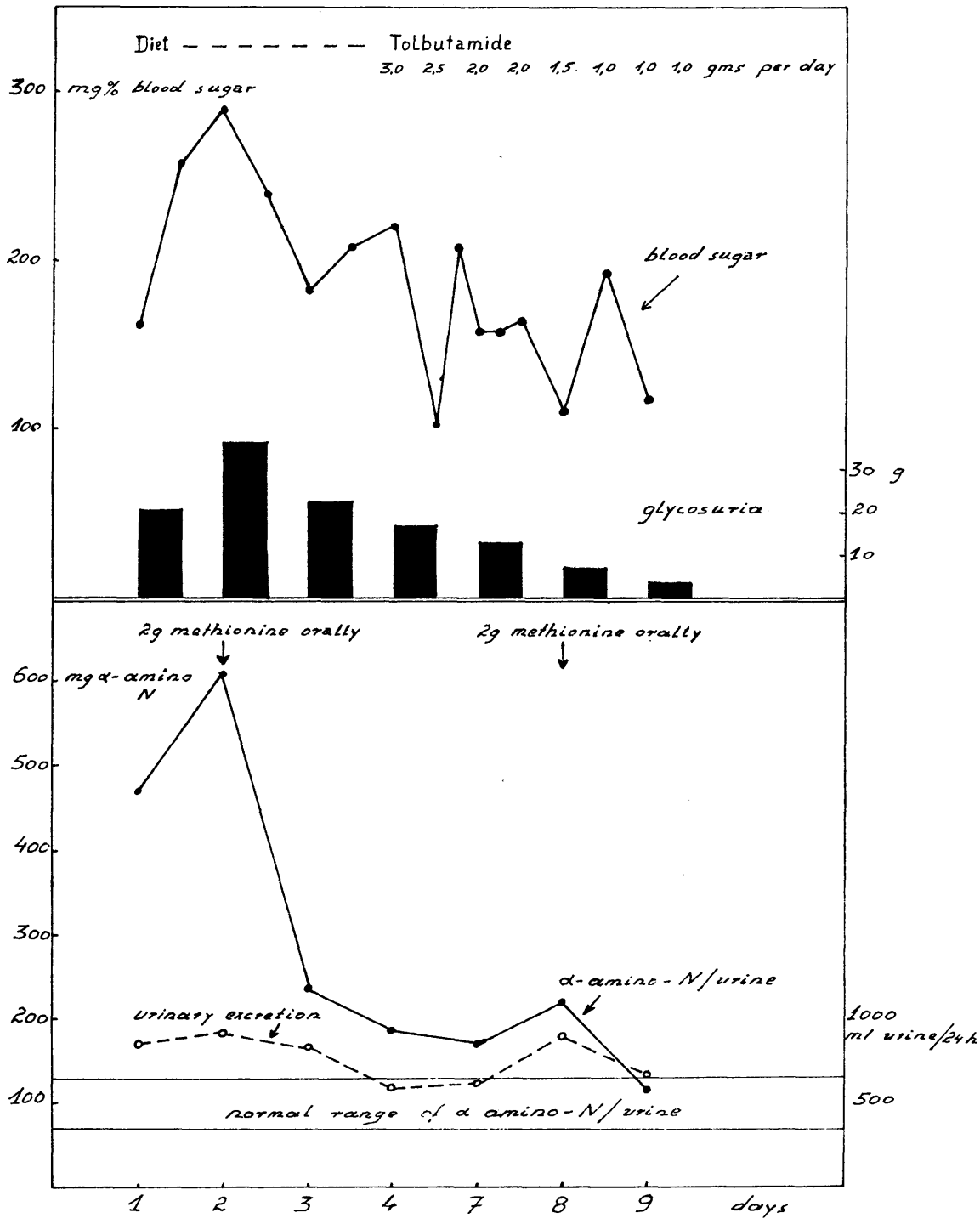

Fig. 1. Aminoaciduria in diabetes before and during successful treatment with tolbutamide.

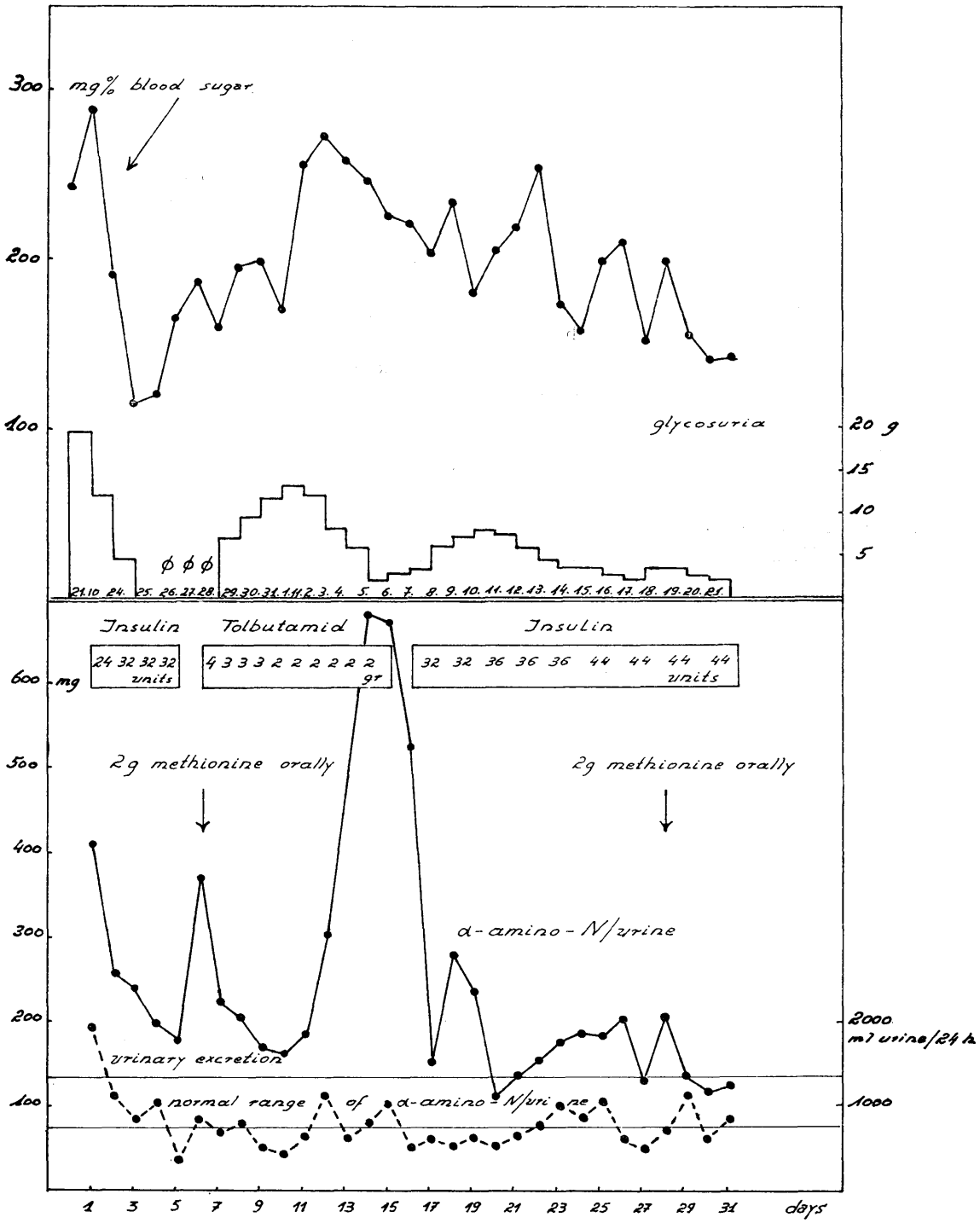

FIG. 2. Aminoaciduria in diabetes mellitus before and after treatment with tolbutamide (late failure).

280 mg. per 100 ml. at the beginning of metabolic decompensation, the amino-aciduria simultaneously rose to ten times the normal, while the volume of urine was only slightly increased. When the insulin dosage was renewed the blood glucose values returned slowly to normal and the amino-aciduria fell more rapidly.

DISCUSSION

When uncomplicated diabetes mellitus is treated with tolbutamide, it is possible to restore a previously pathological serum protein level to normal. The amount of albumin rises when tolbutamide is administered. Even after tolbutamide is administered for two to five years no dysproteinemia is detected. Alkaline serum phosphatase, serum lability tests, nonprotein nitrogen and bromsulphalein retention remain normal although blood glucose and glycosuria increase slightly.

When a patient does not respond satisfactorily to tolbutamide the serum albumin and protein usually fall. This fall, however, is not statistically significant. When the patient is changed to insulin the serum protein remains normal.

In treatment of the adult-onset form of diabetes, diet combined with tolbutamide is as successful in returning the serum albumin to normal as is diet alone.

It is known from the investigations of Miller and co-workers[8] that the synthesis of albumin takes place specifically in the liver. This process apparently is stimulated by the administration of tolbutamide as long as insulin secretion is stimulated in the pancreas. If this fails, then a decrease in albumin formation in the liver ensues. A brief deterioration in carbohydrate metabolism will often have little or no effect on the serum proteins in diabetes without complications. It is only when a case of diabetes is slowly getting worse that the serum albumin falls. Simultaneously in prolonged acidosis an increase in the $alpha_2$ and gamma globulins occurs. In the uncomplicated diabetic with a relatively mild adult-onset diabetes investigated by us, however, the globulins fractions were normal. In summary, it may be said that the serum proteins are not altered even after many years of treatment with tolbutamide.

More sensitive than serum protein analyses is the determination of free amino acids in diabetes mellitus. Even in uncomplicated diabetes the free amino acid content in serum and urine are significantly raised. In diabetic acidosis—if urinary excretion is still normal—the aminoaciduria may rise from three to ten times the normal. Altogether, as much as 1,000 mg. and more of free and peptide bound α-amino-N (i.e. 6-10 gm. amino acids) may be excreted daily. This catabolic situation is complicated by a diminished oxidative deamination of amino acids, especially of sulfur-containing amino acids. This could be demonstrated by loading with 2 gm. of methionine in 250 diabetic subjects.[9] In untreated diabetes the nonoxidized methionine in urine after 2 gm. of methionine per os is distinctly increased, the free sulfate content of urine is not augmented. After successful therapy with insulin or sulfonylurea derivatives the oxidation of methionine to sulfate is increased, the nonoxidized methionine in urine is decreased, and the α-amino-N of serum and urine is decreased.[10-12]

The anabolic effect of sulfonylureas on the protein metabolism in diabetes mellitus may be explained by an increased production of endogenous insulin.[13] Quantitatively and qualitatively its action corresponds completely to that of insulin injections. The increase of aminoaciduria and the slight rise of values for blood glucose and urinary glucose after three years of outpatient sulfonylurea-therapy is certainly for the most part attributable to the fact that the diet is less strictly observed and intercurrent infections often occurred. According to my experience with 5,000 cases of diabetes in adults a hyperaminoaciduria is very often the first sign for a late diabetic acidosis. Therefore a regular control of free α-amino-N in serum and especially in urine using the simple modified ninhydrine reaction can be recommended during a longtime treatment with sulfonylureas.

SUMMARIO IN INTERLINGUA

Le Effecto de Prolongate Therapia con Derivatos de Sulfonylurea Super le Metabolismo de Proteina in Diabete Mellite

In 101 adultos diabetic sin complicationes, nos ha determinate ante e durante prolongate cursos therapeutic con derivatos de sulfonylurea le contento seral de proteina, le composition electrophoretic del sero, le phosphatase alcalin del sero, le retention seral de bromsulphaleina, e le libere α-amino-nitrogeno e α-aminoacidos del sero e del urina de vinti-quatro horas. Le function oxydative del hepate esseva examinate per un cargation con 2 g de methionina. Le composition electrophoretic del proteinas seral esseva alterate solmente in disfallimento de sulfonylurea. Post successose cursos prolongate de therapia, nulle alterationes in le composition del proteinas seral, in le phosphatase alcalin del sero, e in le retention de bromsulphaleina esseva constatate. Tamen, le hyperaminoacidemia e le hyperaminoaciduria declinava a valores normal. Le causa de iste

effecto es probabilemente un augmentate production de insulina que meliora le deamination oxydative de aminoacidos in le hepate.

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Chemicals in Food

Publication 887 of the National Research Council, Washington, D.C., is a recent report of the Food Protection Committee. It is entitled "The Use of Chemicals in Food Production, Processing, Storage, and Distribution."

Presented is a discussion of some of the technologic reasons for the use of chemicals in the food industry, the problems associated with this use, the research undertaken by industry and government to solve these problems, and the legal measures established to ensure protection of the public by governing the use of chemicals in foods.

Every chemical used in food production and processing should serve one or more of these purposes: improve nutritional value, enhance quality or consumer acceptability, improve the keeping quality, make the food more readily available, or facilitate its preparation.

In recent years there has been considerable discussion of the possibility that hazards may result from the use of additives in the production and processing of foods. There has been no justification for any of the exaggerated viewpoints that have been expressed, but it is true that many new chemicals have been and are being introduced and that it is well to examine the existing situation.

As our population grows and becomes increasingly urbanized, less and less agricultural land per capita and proportionately less of the population can be devoted to the production of food. To provide a constant, wholesome, and adequate supply of food for this population, increased production per acre and per man, and increased reliance on protection of the food from deterioration during storage and distribution, will be required. Technologic and scientific applications will have to assume increasing roles in providing and protecting the food supply. New chemical aids to production, processing, packaging, and distribution will be among those applications.

Experience has amply demonstrated that chemical aids of this kind can be used safely and beneficially. Competent, strong regulatory agencies and a public-spirited, ethical industry give confidence that they will be so used in the future.

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