

Serum Lipids and Lipoproteins in Diabetic Glomerulosclerosis

PRELIMINARY OBSERVATIONS OF THE EFFECT OF HEPARIN UPON THE DISEASE*

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The description of intercapillary glomerulosclerosis by Kimmelstiel and Wilson¹ in 1936 directed attention to the pathological picture, and to the associated clinical syndrome present in advanced cases. It was soon realized that the incidence of the pathologic lesion is quite high in diabetics, varying from 18 to 63 per cent and that it is uncommon in the absence of diabetes, although it may occur. However, knowledge of the pathogenesis of this lesion has advanced little since its initial description. Hypertension and proteinuria are not causally related since they may be absent in early cases. Likewise, the severity of the diabetes, the use of insulin, sex and age do not appear to be important. However, there is an increased incidence of the lesion with increased duration of diabetes. Two other lesions are found in practically all cases of intercapillary glom-

erulosclerosis, these are retinopathy and advanced atherosclerosis. However, either may be present without any accompanying glomerulosclerosis.

An elevated blood cholesterol has been noted in a majority of the published cases, and doubly refractile lipid droplets have been described in the urine.² Simon in 1940³ described the frequent occurrence of fatty material in the glomeruli, but it remained for Wilens, Elster and Baker,⁴ who have recently reported a thorough study of glomerular lipid in various kidney conditions, to suggest that the deposition of fat in glomeruli might be of primary importance in the development of the lesions of intercapillary glomerulosclerosis.

Recently the ultracentrifugal analysis of serum lipoproteins has been described.⁵ This method allows the quantitative determination of lipoproteins as they actually exist in serum, with cholesterol, phospholipid, neutral fat and protein all linked together in large molecules. In view of the hypercholesterolemia found in many cases of the Kimmelsteil-Wilson syndrome and the increased glomerular lipid, the serum of seventeen

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patients with clinically typical diabetic glomerulosclerosis has been ultra centrifugally analyzed for lipoproteins.* Blood cholesterol, phospholipid, ratio of cholesterol to phospholipid, and the total lipids were determined at the same time.**

OBSERVATIONS IN 17 CASES

The clinical and laboratory findings in our first fourteen cases have been presented elsewhere,⁶ and are shown in Table 1 and Table 2 plus data concerning the blood lipids and lipoproteins in three additional cases. (Five of our patients have died and the diagnosis was substantiated in the three instances in which autopsy was performed.) Table 3 shows the lipoprotein levels in our first fourteen cases compared with the mean lipoprotein values at comparable cholesterol levels in normals.

The serum cholesterol prior to the terminal state was below 300 mg. per 100 cc. in four patients. It was elevated in thirteen cases, as were the phospholipids in twelve. The ratio of cholesterol to phospholipids was elevated in eleven determinations.

The S_f 12-20 lipoproteins were markedly elevated in

the entire series of patients. Furthermore, in all cases, these classes of lipoproteins were higher (by comparison with normals at the same cholesterol levels) than would be anticipated for the degree of elevation of the serum cholesterol. (Table 3) This shift toward marked increases in the S_f 12-20 levels was most striking in those patients whose blood cholesterol was below 300 mg. per 100 cc.

In most of the cases the S_f 20-35 lipoproteins were also elevated but in several they were not. However, the S_f 35-100 classes showed no such uniform tendency.

SIGNIFICANCE OF INCREASE IN S_f 12-20 LIPOPROTEINS

One of our cases illustrates a significant point. This was the only case in our series, which serial determinations of blood cholesterol and quantitative urinary protein excretion were available to us. This man, aged 29, had diabetes mellitus for thirteen years. He used 30 units of insulin daily and his diabetic control was fairly good. Mild hypertension had been present for two years, severe diabetic retinopathy for five years. His laboratory findings, exclusive of blood and urine sugar determinations, are presented in Table 4. His serum lipid abnormality antedated the albuminuria by at least two and a half years. Furthermore, doubly refractile fat bodies were present in the urine at the time albuminuria was first noted. In this patient at least, the data suggest that the lipid metabolic error preceded the kidney involvement.

Since the average duration of life after the first renal sign of diabetic glomerulosclerosis appears is six to seven years,⁷ it would be valuable to have a diag-

* Ultracentrifugal analyses were performed at the Division of Medical Physics, Donner Laboratory, University of California, Berkeley.

** Cholesterol, phospholipid, and total lipids were determined at the Arteriosclerosis Research Laboratory of the Cedars of Lebanon Hospital, Los Angeles.

Cholesterol was analyzed by the Kingsley-Schaffert method. Phospholipid was determined as outlined by Peters and Van Slyke. Total lipids were measured by the turbidimetric method of Kunkel and Ahrens.

TABLE 1 Clinical findings in 17 cases of diabetic intercapillary glomerulosclerosis.

Patient	Age	Sex	Duration of diabetes Yrs.	Blood pressure	Retinopathy Grades	Blood proteins			Fat bodies in urine	Albuminuria
						Total	Albumin	Globulin		
J.U.	48	M	10	230/120	2	5.6	2.6	3.0	Not done	5 gm./L.
W.L.	57	M	19	186/102	4	7.9			Present	3.1 gm./L.
G.S.	55	M	23	164/90	2	7.5			Present	6.9 gm./L.
E.G.	51	M	24	190/100	3	5.1			Present	6.9 gm./L.
P.B.	59	M	16	200/90	2	6.5			Present	1.8 gm./L.
B.A.*	34	F	15	140/90	4	6.1	2.5	2.6	Not done	Grade 4
J.F.	29	F	14	205/120	3	5.8	2.2	2.6	Present	Grade 4
W.K.	29	M	13	170/80	4	6.0	3.8	2.2	Present	3.8 gm./L.
M.R.*	48	F	20	250/114	4	5.0	2.5	2.5	Not done	Grade 4
R.R.*	27	M	20	180/110	2				Not done	Grade 3
J.C.*	34	M	15	200/120	3	5.1	2.9	2.2	Absent	Grade 4
C.I.	58	M	20	220/120	3	6.1	3.7	2.4	Present	4.2 gm./L.
E.K.W.	22	F	18	120/90	3	6.3	4.8	1.5	Present	Grade 3
E.N.	61	M	13	190/100	2	6.5			Present	5.7 gm./L.
D.N.	51	F	21	200/110	3	6.0	2.3	3.7	Present	Grade 4
D.G.	30	F	18	180/98	3	5.8	2.6	3.2	Present	Grade 3
S.K.	32	M	17	160/95	2	7.6	4.2	3.4	Present	1.6 gm./L.

*Intercapillary glomerulosclerosis found at autopsy.

TABLE 2 Serum lipids and lipoproteins in 17 cases of Kimmelstiel-Wilson syndrome.

Patient	Age	Sex	Chol- esterol	Phospho- lipid*	C/P ratio	S _f 12-20 lipo- proteins	S _f 20-35 lipo- proteins	S _f 35-100 lipo- proteins
W.K.	29	M	760	27.0	28.2	308	120	133
E.G.	51	M	389	13.2	29.5	121	29	40
E.W.	22	F	388	15.6	24.8	142	92	68
M.R.	58	F	580	26.5	21.8	319	190	230
B.A. ¹	34	F	282			182	145	99
B.A. ²			171	8.6	19.9	152	81	86
E.N.	6 ¹	M	430	16.2	26.5	116	40	21
P.B.	59	M	389	14.0	27.8	116	61	21
W.L.	57	M	216	8.0	27.0	83	16	24
R.R.	27	M	274	11.8	23.2	100	57	64
J.U.	48	M	500	14.2	35.2	161	47	42
J.F.	29	F	389	12.8	30.4	116	40	81
C.I.	58	M	474	24.0	19.8	168	69	248
M.S.	55	M	340	11.7	29.0	71	48	52
J.C. ³	34	M	369	14.3	25.8	237	159	173
J.C. ⁴			296	12.4	23.8	145	100	161
J.C. ⁵			180	8.1	22.2	95	84	81
D.N.	51	F	500	14.8	33.8	156	Not done	Not done
D.G.	30	F	455	16.5	27.5	104	Not done	Not done
S.K.	32	M	196	10.5	18.7	83	Not done	Not done

*Phospholipid values as determined before conversion to lecithin.

¹ July 22, 1952; ² April 12, 1951; ³ January 24, 1951; ⁴ March 16, 1951; ⁵ April 13, 1951.

TABLE 3 Lipoprotein levels in Kimmelstiel-Wilson syndrome compared with the mean lipoprotein levels at comparable levels in normals.

Patient	Chol- esterol	S _f 12-20 Lipo- proteins	Mean S _f 12-20 Levels in Nor- mals at this Cholesterol Level	S _f 20-35 Lipo- proteins	Mean S _f 20-35 Levels in Nor- mals at this Cholesterol Level	S _f 35-100 Lipo- proteins	Mean S _f 35-100 Levels in Nor- mals at this Cholesterol Level
W.K.	760	308	Unavailable	120	Unavailable	133	Unavailable
E.G.	389	121	75	29	33	40	97
E.W.	388	142	75	92	33	68	97
M.R.	580	319	Unavailable	190	Unavailable	230	Unavailable
B.A.							
7/22/50	282	182	51	145	31	99	70
B.A.							
4/12/51	171	152	30	81	28	86	42
E.N.	430	116	82	40	34	21	107
P.B.	389	116	75	61	33	21	97
W.L.	216	83	40	16	29	24	53
R.R.	274	100	49	57	31	64	68
J.U.	500	161	96	47	34	42	124
J.F.	389	116	75	40	33	81	97
C.I.	474	168	90	69	35	248	118
G.S.	340	71	65	48	32	52	84
J.C.							
1/24/51	369	237	70	159	33	173	91
J.C.							
3/16/51	296	145	54	100	31	161	73
J.C.							
4/13/51	180	95	32	84	29	81	44

nostic method available which might indicate the early development of this serious complication of diabetes. Some investigators feel that proteinuria is an early sign, others feel it is an indication of advanced renal disease and not necessarily indicative of glomerulosclerosis. In the series reported by Mann, Gardner and Root, they found that cholesterol elevation occurred coincident

with signs of renal involvement. Our data reveal marked elevation of the S_f 12-20 lipoproteins in this disease, occurring in some cases when the serum cholesterol was not elevated. Whether a rise in the concentration of this group of lipoproteins is an early finding in glomerulosclerosis remains to be determined in long term studies of diabetics. Our findings suggest this pos-

sibility. At this time the relationship, if any, between the S_f 12-20 lipoproteins and the alpha-2 globulin which Rifkin and Petermann⁸ found to be elevated in this disease is not clear.

The relation of glomerulosclerosis to renal arteriosclerosis has been the subject of considerable discussion. Advanced atherosclerotic disease has been present at autopsy in all cases. Elevation of certain serum lipoproteins is found in association with atherosclerotic disease and our data, showing an even greater elevation of these same classes of lipoproteins in diabetic glomerulosclerosis, further suggests a relationship between the two. However, renal atherosclerosis occurs in the absence of glomerulosclerosis. It has been shown⁴ that when the kidney glomeruli contained considerable lipid material there was also a large amount of arteriolar lipid, but the latter could be demonstrated when no lipid was present in the glomeruli. Furthermore, intercapillary glomerulosclerosis is not found in myxedema, lipid nephrosis or xanthoma tuberosum, diseases in which the S_f 12-20 serum lipoproteins are very high. These considerations suggest that whereas the elevation of certain serum lipoproteins is associated with both atherosclerosis and intercapillary glomerulosclerosis, in the latter there may be an additional glomerular factor present which facilitates the deposition of serum lipoproteins in the glomeruli.

THERAPY

The possibility that elevated S_f 12-20 and S_f 20-35 serum lipoproteins may be etiologically involved, at least in part, in the pathogenesis of the kidney lesion suggested that it was important to observe the effect of reducing the elevated lipoprotein levels upon the clinical course of the disease. This may be accomplished by a low fat diet, or by the injection of heparin.⁹ One of us (H.E.) has given heparin* for the past six months to two patients with advanced diabetic glomerulosclerosis, and to one patient who probably has an early stage of the kidney lesion. Only preliminary observations will be presented at this time.

The first patient was a man, age 29, who had had diabetes for thirteen years, was hypertensive, and had been blind for five years because of diabetic retinopathy. He was markedly edematous, had albuminuria with doubly refractile lipid droplets, a low serum albumin and markedly elevated blood lipids. His diabetic course was fairly stable on 30 units NPH insulin

* Supplied by Lederle Laboratories, Inc.

Date	Cholesterol	Urinary Proteins in Grams	Serum Protein	Serum Creatinine	% of Normal Creatinine Excretion
4/29/47	592	0/24 hrs.	7.3		
10/10/47	391	0/24 hrs.			
8/24/48	310	0/24 hrs.			
4/6/49	472	0/24 hrs.	7.25	1.13	78
12/30/49	354	0.50/24 hrs. (oval fat bodies in urine)	6.5	0.96	70
9/8/50		1.03/24 hrs.	5.8	1.61	31
3/20/51	760	2.8/24 hrs.	5.6	1.4	

daily. He was placed in the hospital on August 18, 1951 for study, and during the first two weeks there was no change in the clinical picture on all types of diuretic therapy. He was then given (intravenously) 100 mg. heparin daily. After the first week his edema gradually decreased and disappeared. It is noteworthy that a discrete maculo-papular rash that had been resistant to therapy for several years cleared up within three weeks. After discharge on September 28, 1951, he was kept on 100 mg. heparin daily for two weeks and then it was given three times a week. After one month of this regimen the edema reaccumulated, the rash recurred somewhat, and he was readmitted to the hospital from December 24, 1951 to January 17, 1952. During this hospital stay he received all types of diuretic therapy with no improvement or weight loss. No heparin was given. After discharge he was again placed on 100 mg. heparin daily, and in three weeks he lost thirty pounds of edema fluid and the rash again disappeared. His laboratory findings are shown in Table 5. In this advanced case there was a slight decrease of proteinuria on daily heparin therapy, a slight rise in the blood albumin, and a marked drop in the S_f 12-20 lipoproteins with no change in the total cholesterol. When heparin therapy was reduced to 100 mg. three times a week, the proteinuria increased, the serum albumin fell slightly, the S_f 12-20 lipoproteins rose slightly, and clinically he became worse. When heparin was stopped, the serum albumin fell still further. Unfortunately the laboratory findings when daily heparin was resumed were lost.

The second patient was a man of 48 years with long standing diabetes, hypertension, retinopathy, marked albuminuria, high blood cholesterol (500 mg. per 100 cc) and very high S_f 12-20 lipoproteins (161 mg. per 100 cc). His laboratory data is presented in Table 6. Again on 100 mg. heparin daily there was a slight drop in the proteinuria, a subsequent increase when heparin was given three times a week, a marked rise when it

TABLE 5 W.K. variations in serum proteins, proteinuria and serum lipoproteins with heparin therapy.

Date	Alb.	Glob.	Protein- urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	S _f 12-20	Chol.	P-L	Heparin Dose
8/20	2.7	2.4	3.4	1.41				None
8/29	2.6	2.6	3.3	1.40	164	750	24.0	
9/8	2.9	2.9	2.97	.99				100 mgm. I.V. daily from 8/30/51 to 10/12/51
9/14			2.83	.87	62	900	26.0	
9/20			2.22	1.05	73	750	18.0	
9/28	3.0	2.8	2.6	1.18				
10/24	3.5	2.4	4.1	2.4				100 mgm. 3x weekly from 10/14 to 12/24
11/30	2.8	2.1	3.0	1.82				
12/24	2.9	2.7	3.38	1.77	82	800	19.0	
1/25	2.2	4.2	3.8	1.8				None from 12/24

TABLE 6 J.U. variation in serum albumin, globulin and proteinuria with heparin therapy.

Date	Alb.	Glob.	Protein- urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	Heparin Dose
2/6	3.3	2.2	5.0	2.60	None
10/4	3.4	2.4	3.3	1.50	
10/10	4.1	2.2	5.72	2.20	100 mgm. I.V. daily from 10/8/51 to 11/11/51
10/17	4.1	2.4	3.66	1.95	
10/22			.845	1.14	
10/31	4.1	2.4	2.18	1.36	
11/9	4.8	2.2	2.1	1.34	
12/7			3.8	1.73	100 mgm. 3x weekly from 11/11 to 2/5
1/25	3.8	2.9	4.8	1.87	
4/4	3.8	2.6	8.7	3.0	None 2/5 - 4/4
5/7	3.6	2.3	5.39	2.58	100 mgm. 3x weekly 4/4 on

TABLE 7 S.K. variations in serum proteins and in proteinuria with heparin therapy.

Date	Alb.	Glob.	Protein- urea gms. in 24 hrs.	Proteinuria gms./1000 cc.	Heparin Dose
8/24	5.0	1.9	.335	.16	None
8/29	4.1	2.2	.386	.19	None
9/6	4.8	2.1	.871	.21	100 mg. I.V. daily from 8/30/51 to 10/14/51
9/14	4.9	2.1	.259	.09	
9/24			0	0	
9/28	4.8	2.1	0	0	
10/24	4.5	2.0	.312	.12	100 mg. I.V. 3x weekly from 10/12/51 to 1/25/52
11/30	4.4	1.9	.179	.05	
1/25/52	4.3	2.7	.30	.08	

was stopped, and very little change when he was again given 100 mg. heparin three times weekly. Unfortunately in this patient the lipoprotein changes on heparin therapy are not available.

The third patient, a 32-year-old diabetic of long standing, had early retinopathy, slight but persistent albuminuria, and a blood cholesterol of 196 mg. per 100 cc., but a high S_f 12-20 lipoprotein value of 83 mg.

per 100 cc. Although admittedly a diagnosis of early glomerulosclerosis cannot be proven, heparin was given. The findings are presented in Table 7. There was a complete disappearance of albuminuria after several weeks of 100 mg. daily heparin, with a return of the proteinuria when the heparin dose was reduced to 100 mg. three times weekly although perhaps not to the former levels. Here again the lipoprotein changes after heparin are not available at this time.

Although the observations are few, from the laboratory standpoint there seems to be a tendency for proteinuria, in cases of diabetic glomerulosclerosis, to decrease slightly with heparin therapy. Apparently 100 mg. heparin daily is necessary for at least several weeks before this occurs.

In one patient there was clinically a remarkable decrease of edema on two occasions when all other types of therapy had failed. A long standing skin rash, previously resistant to therapy, disappeared after heparin was given for several weeks. (It should also be noted that in one of these patients, as in several other diabetics with atherosclerotic disease, there apparently was a decrease in insulin requirements while on heparin.) We feel that the improvements seen are related to the effect of heparin on the serum lipoproteins. Incidentally no untoward reactions were noted after six months of heparin therapy intravenously or subcutaneously. Lee-White clotting times returned to normal in six hours in all instances so that their routine determination is unnecessary.

We have observed the effect of a rigid low fat diet in only one case thus far. This is patient J. C. in Table 2. It can be seen that there was a progressive drop in the serum lipids and lipoproteins over several months. The cholesterol fell from 369 mg. per 100 cc. to 296 and then to 180. The S_f 12-20 lipoproteins fell from 237 mg. per 100 cc. to 145 and finally to 95 which is

still quite high. This patient was in preterminal uremia, however, so that it is not certain that the effects observed were due to the diet.

It is apparent that much further investigation is required before conclusions can be drawn as to the long term effects in diabetic glomerulosclerosis of these therapeutic means directed at lowering the S_f 12-20 and S_f 20-100 lipoproteins. It should be emphasized that any considerable reversal of previously existing disease cannot be anticipated. The most that one could expect is a cessation of, or at least a reduction in the rate of progression of the disease. However, any definite and maintained evidence of improvement in kidney function, even though slight, would indicate improvement in existing disease, and give rise to reasonable hope of arresting the progress of the disease. Our very preliminary observations are encouraging in this regard.

SUMMARY

The serum cholesterol, phospholipids, total lipids, and the S_f 12-20, 20-35 and 35-100 lipoproteins ultracentrifugally analyzed, have been determined in 17 cases of diabetic glomerulosclerosis. Elevated cholesterol and phospholipids were found in most of the cases. The most striking finding was a marked elevation of the S_f 12-20 class of lipoproteins in all cases, and of the S_f 20-35 class in nearly all patients. These lipoproteins were markedly elevated even when the cholesterol was normal. Furthermore the elevation of the S_f 12-20 lipoproteins was higher than would be expected at the elevated cholesterol levels. The data suggests that these classes of serum lipoproteins may be important, along with other factors, in the production of the kidney lesion. It is also suggested that elevated S_f 12-20 lipoproteins may be an early finding indicative of the potential development of glomerulosclerosis.

Heparin, which markedly reduces the S_f 12-100 classes of lipoproteins, has been given for six months in three cases of diabetic glomerulosclerosis. When administered in doses of 100 mg. daily, a reduction of S_f 12-20 lipoproteins occurred. There was a slight elevation in the serum albumin where it initially was low. There was a striking improvement clinically. These preliminary results are encouraging. We believe that clinical trial with long term heparin administration, and/or the low fat diet, are indicated since reduction of the serum S_f 12-100 lipoproteins may arrest the progress of this fatal kidney complication of diabetes.

DISCUSSION

DR. ALEXANDER MARBLE, (*Boston*): In June, 1950 I was privileged to visit Dr. Gofman in his laboratories in Berkeley. There were many others who did so at that time. I was impressed with his enthusiasm for large-scale studies, the organization and equipment of his laboratories and the amount of activity going on. At that time, two years ago, most of us knew scarcely anything about lipoproteins and the talk about S_f 12-20 and other classes of lipoproteins seemed a foreign jargon. Today we speak freely of such matters but often our knowledge is more superficial than we would like it to be. We are indeed indebted to Dr. Gofman and his associates in bringing to the attention of the profession, the probable relationship of large lipoprotein molecules to the development of atherosclerosis.

It is fitting that the studies in certain laboratories during the past two years have included diabetic patients. Indeed, in Dr. Gofman's early clinical observations he reported upon measurements in diabetic individuals and called attention to the need for further data in this regard.

As is well known to you and Dr. Gofman, his reports have met with varying degrees of acceptance. Some have maintained that the level of the blood cholesterol affords as good or better index of present or future atherosclerosis and its sequelae than does an abnormal lipoprotein pattern. There have been other objections which have been discussed or hinted at today. However, the results reported by Dr. Engelberg, Dr. Barach and Dr. Keiding with diabetic patients do suggest a definite correlation between the level of certain classes of lipoproteins and the degree of control of diabetes and complications in the patient. All will admit that present impressions are subject to change or revision as further data are accumulated.

The paper of Drs. Engelberg, Jones and Gofman is of great interest to us since their findings in patients with diabetic nephropathy are consistent with those of our group as just reported by Dr. Keiding. Indeed, in a paper published in 1949, Dr. Root along with Drs. Mann and Gardner reported an increase in the blood cholesterol in all but 3 of 22 patients with intercapillary glomerulosclerosis.

I noted that Dr. Engelberg stated that his patient W. K. had had well controlled diabetes and yet displayed persistent hypercholesteremia. I wonder if in this case familial hypercholesteremia had been ruled out?

Dr. Engelberg's report of his current studies with

heparin on patients with intercapillary glomerulosclerosis is instructive and we will await with interest results regarding the effect of heparin on this and other states in which an abnormal lipoprotein pattern exists.

It is worthwhile to call attention again to one finding which has emerged from the work in Boston which Dr. Keiding reported. I refer to the relationship between retinitis and the incidence of elevated values for the S_f 12-20 lipoproteins. Arterial calcification showed a much less striking relationship. One must admit, however, that arteriosclerosis of medial type as shown by x-ray in our studies may, at least theoretically, not parallel the degree of atherosclerosis which is much more difficult to assay in a study such as ours. However, the fact that there was a strong positive correlation between retinitis—which is a unique and early manifestation—and abnormal lipoprotein pattern is of especial interest, since it suggests some common basis for the origin of late vascular sequelae in the diabetic in the eyes, arteries and kidneys. As to the exact mechanism of this, and just what factors are primary and what secondary, we can only speculate at the present time. Furthermore, arterial disease should not be considered in terms of lipoids alone to the exclusion of other factors such as the physico-chemical characteristics of the so-called "ground substance." Not to be forgotten is the possible role of disturbance of the metabolism or structural organization of the complex mucopolysaccharides. Clarification of these problems must await further study.

DR. ROBERT L. JACKSON (*Iowa City, Iowa*): As Dr. Marble just mentioned, I agree that there is a need for serial determinations to elucidate this problem.

We have observed that our group of diabetic patients who maintain an excellent or good level of control have approximately normal serum cholesterol values, and that our group of patients in fair or poor control have marked fluctuations in serum cholesterol values. The cholesterol values were evaluated on the basis of serial determinations, and the level of control of the good or excellent group is considerably higher than for any group reported here today. The importance of using objective criteria for establishing level of control cannot be overemphasized.

In some cases with serial cholesterol determinations we have noted a significant lowering of the cholesterol value at the time of or after, a severe or mild infection. Temporary fluctuations in cholesterol levels may account for the occasional observation of a normal or low

cholesterol value in association with a high S_f 12-20 lipoprotein value.

DR. JOHN W. GOFMAN (*Berkeley, California*): It is a source of considerable personal satisfaction to me to see, some two and one-half years after the original investigations of the ultracentrifuge method of studying lipoproteins, a society like the Diabetes Association presenting four papers of great clinical significance, associating such important problems as control of diabetes and vascular complications to lipid measurement.

Dr. Hanig has pointed out that if one excludes those diabetics who have the Kimmelstiel-Wilson syndrome and those with vascular disease, and outlying high values, the net average is not too much greater—if at all greater—than the average for so-called normals. I think this may be a little misleading. Actually, what are we after in a study of diabetics with respect to lipoproteins or cholesterol level? We are after a very specific answer. Is it something about diabetes itself which predisposes to vascular complications, or is it something about the lipid metabolism of diabetes which predisposes to vascular complications?

Now this is a matter of some concern, because if it is not just the lipid factor, we have to look at such possibilities as focal factors in the structure of arteries and such items as these in the effort to explain the increased incidence of vascular disease among our diabetic population. I do not think that any of the evidence that we have obtained, or the evidence Dr. Hanig has obtained, has disagreed but in one respect, and that is that there are certainly many diabetics, a large proportion of them, who have what we have to call perfectly normal or low lipoprotein levels. I think this is agreed, and I think it would be pretty hard, clinically, to prove that all diabetics develop excessive vascular disease. What we really can say is that diabetics develop more vascular diseases than the average population. We also know they may go a long time without developing clinical vascular disease. Therefore, if we exclude from our population all the diabetics who have manifested vascular disease from our study of lipoproteins, we are going to leave over a residue of diabetics who should closely correspond to our normal population, if we assume that the lipoproteins, alone, represent the factor predisposing the diabetics to vascular disease.

I should prefer to see Dr. Hanig's data presented with all the diabetics with vascular disease, the extremes included, and the Kimmelstiel-Wilson patients

included, because if we exclude all these patients, we are excluding those who have already manifested the very thing we are trying to find out if diabetics are predisposed to, namely: vascular disease. I think this obscures the situation to some extent, but in no way obscures the significance of his data.

With respect to Dr. Barach's paper, I was much interested in seeing his finding of the higher incidence of high values of S_f 12-20 lipoproteins in female diabetics as compared with males. I must say that our data are on a much smaller scale in diabetics than Dr. Barach's. Our preliminary data showed this same finding, and in the clinical literature there are several reports to the effect that female patients with diabetes develop vascular complications in excess of those experienced by males. Accordingly, then, this finding of Dr. Barach's would be consistent with the elevated lipoprotein level being a prime factor in accounting for the excessive vascular disease in females as compared with males.

The data which he found in diabetes and obesity—namely, that there is no elevation of the S_f 12-20 level in diabetic obese patients as compared with diabetic non-obese patients—is something we have never tested. In normals we find that obesity definitely does predispose to an elevated level of the S_f 12-20, and even more, to elevated levels of lipoproteins from S_f 20 to 100. However, this relationship, even in normals, is a very low one. While there are average trends in one direction, it is still true that there are many very lean individuals with high levels and many obese individuals with low levels.

In the papers by both Dr. Keiding and Dr. Barach I think a very important point was struck upon which I realize is controversial among the experts on diabetes, namely: "Will we reduce vascular complications by good control of our diabetics?" Both of these papers indicated that at least for this group of lipoproteins—which we have good evidence are associated with vascular disease—there is definitely a trend toward higher levels of these lipoproteins in the patients with poor control. I think this finding by both groups of workers is of great importance.

I made a quick statistical calculation on Dr. Keiding's data as shown on the slides, and one can reach a fair conclusion. He said that the lipoproteins showed a very different picture from the cholesterol. This, as many of you know, is something that we have claimed for some time, and which has been contested by some people. Actually, with Dr. Keiding's data, I believe we can say

that the elevation of 12-20 lipoproteins and the elevation of the 20-100 lipoproteins is the complete story of the difference between his retinitis cases and the non-retinitis cases; one could show by calculation that the slight elevation in cholesterol—or even moderate elevation in cholesterol—is only that which would be expected for the elevation in these particular lipoproteins, in this particular class of lipoproteins. It should be emphasized again that now that we have methods for looking at all the forms of cholesterol in the blood, we cannot any longer be satisfied to lump them all together and to say that this is the *total* cholesterol or the *total* lipoproteins.

We are interested in knowing—in a diabetic as well as any other patient—what is the nature of this disturbance which causes these patients to have an elevation at one particular region. For instance, in Dr. Engelberg's paper, he pointed out that the Kimmelstiel-Wilson patient has an elevation in the 12 to 35 region, but not so much in the 35-100, indicating that lipid metabolism in the control of serum transport, at least, is a rather complicated thing, and that these subfractions can differ from one disease entity to another. For example, we have seen these pictures differ in the diabetic in acidosis as compared with the diabetic with Kimmelstiel-Wilson disease. Although two patients may have 500 milligrams per cent of blood cholesterol, their lipoprotein patterns are just as different as night and day in many terms of which classes of lipoproteins are elevated. This simply indicates that what we need to know is something about the metabolic factors that control the transformation of one lipoprotein into another, and thus explain why some are elevated in certain diseases.

DR. ENGELBERG (Closing): In answer to Dr. Marble, the serial data, as we said, are incomplete. In one patient, available data did suggest that elevated serum lipoproteins antedated signs of kidney involvement. Of course, considerable further study is necessary.

We feel that since increased glomerular lipid has been found in Kimmelstiel-Wilson disease, and we have found increased serum lipoproteins, it suggests that the serum lipoproteins are the source of the glomerular lipids, and are probably one of the factors involved in the progression of the pathological picture.

About the use of heparin, it is certainly our feeling at this time that it is clearly experimental. However, the preliminary findings are somewhat suggestive, and the fact that heparin is a physiological substance which

reduces large lipoprotein molecules to smaller molecules of a more normal type suggests its use in an attempt to delay the progress of this disease.

In the use of heparin in these cases, or in a much larger series of cases of atherosclerosis, we have not encountered any serious complications, because the anticoagulant factor is of short duration (approximately six hours following each injection). Minor complications such as sensitivity reactions and lumbar pain are easily avoided by changing the brands of heparin used.

However, I want to reiterate that it is our feeling that this is purely experimental therapy, and much further study is needed before conclusions can be reached.

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A Seasonable Gift for the Editors

Here is what the editors would like for Christmas—and indeed for the whole New Year.

They would like to receive a reasonable number of topflight new manuscripts, perhaps 250, from which they could make their choice, containing 800 to 4,000 words each, recently typed with double or triple spacing (including the case reports, footnotes and references), with a reasonably fresh ribbon. They would like to have the references limited to those of real significance, following accurately the style of the Cumulative Quarterly Index Medicus. (The only impression that "inflated bibliographies" make is a bad one.)

Needless to say, perhaps, any paper that is fit to be published is written in as good English as the author can muster, and is then rewritten at least twice, with a number of words discarded at each writing; for anything that is worth saying at all is usually said twice as well in half the number of words. Its tables and charts are few and simple and properly captioned. In its final state it is crystal-clear and informative and meets some need other than that of the author for publicity.

After all, the only really valid reason for writing a scientific medical article is to present the results of useful investigation or seasoned experience, thus adding to the sum of medical knowledge; or to bring together and correlate existing knowledge in order to make it more easily available. Only occasionally is a single case worth reporting, to remind the Journal's readers of the existence of some condition that may cause diagnostic confusion or to add to the knowledge of its treatment; it should be reported with the utmost brevity. A case report should always point the moral, whether or not it may adorn a tale.

The editors would like to find in their stockings the promise of a series of inspired and carefully worded editorials on a variety of pertinent subjects, and a salty but amiable correspondence suitable for publication. They would be pleased with a strict observance of deadlines on all promised material. Given these things, a circulation that continues to expand and a growing list of contented advertisers, they would believe that there really is a Santa Claus!

—Editorial, *New England Journal of Medicine*,
December 20, 1951