Canad. Med. Ass. J.
Aug. 5, 1967, vol. 97

# Factors Associated with Increased Prevalence of Diabetic Retinopathy:

## A Clinical Survey

A. J. SZABO, M.D.,* A. G. STEWART, M.B.† and
GUY E. JORON, M.D.,‡ *Montreal*

IMPROVED treatment of diabetes mellitus in the past 45 years, due largely to the discovery of insulin and antibiotics, has provided an increased life expectancy for the diabetic. Unfortunately this has been accompanied by the common appearance of long-term vascular complications. Retinopathy is one of the most dreaded of these complications and diabetes has become one of the leading causes of acquired blindness.[1, 2] In this context the legal definition of blindness, 20/200 vision or less, in the better eye, is used. Total blindness, inability to perceive light, is of course much rarer, whereas milder forms of retinopathy which do not interfere with useful vision are quite common.

The premature development of degenerative vascular disease in diabetes is accepted, but its pathogenesis and relationship to a specific biochemical abnormality is debated. Whether the vascular lesions in the retina are the result of the same stimulus as the other vascular lesions is also a matter of controversy. A critical summary of this literature was recently published.[3]

Unfortunately, statistically sound studies which do not imply denial of vital treatment and take into consideration all of the possible factors are difficult to design. Prospective studies are needed but will be long in harvesting. In the meantime there would seem to be some usefulness in a retrospective study if only to assess whether there is any correlation between any of the laboratory data obtained during the diabetic's life and the future development of retinopathy.

### MATERIAL AND METHODS

A survey of long-term diabetics was undertaken at The Montreal General Hospital in the period 1961 to 1963. All patients attending the outpatient diabetic clinic who had known diabetes for more than 10 years were included.

From the Department of Medicine, The Montreal General Hospital and McGill University, Montreal, Quebec.
Supported in part by National Health Grant No. 604-7-350 and by a grant from Pfizer Company Ltd.
*Diabetes Research Unit, New York Medical College, New York.
†Endocrine Clinic, Royal Infirmary, Edinburgh.
‡Associate Physician, Department of Medicine, The Montreal General Hospital; Assistant Professor, McGill University.

Reprint requests to: Dr. Guy E. Joron, The Montreal General Hospital, Montreal 25, Quebec.

TABLE I.—AGE AT TIME OF SURVEY

| *Age group (years)* | *No. of cases* | *Percentage* |
|---|---|---|
| 10 - 19 | 1 | 0.3 |
| 20 - 29 | 10 | 3.1 |
| 30 - 39 | 12 | 3.7 |
| 40 - 49 | 24 | 7.4 |
| 50 - 59 | 67 | 20.7 |
| 60 - 69 | 117 | 36.1 |
| 70 - 79 | 76 | 23.5 |
| 80+ | 17 | 5.2 |

There were 278 patients in this category. Forty-six private patients were added, making a total of 324 patients. The mean age was 61.6 years (Table I). The mean duration of diabetes was 17.2 years (Table II). One hundred and twenty-six (39%) were men and 198 (61%) were women. Forty-five per cent of patients had been followed up at this hospital for more than three-quarters of their diabetic life, 17% for one-half to three-quarters, and a further 18% for one-quarter to one-half of their diabetic life.

TABLE II.—DURATION OF DIABETES

| *Age group (years)* | *No. of cases* | *Percentage* |
|---|---|---|
| 10 - 14 | 156 | 48.1 |
| 15 - 19 | 78 | 24.1 |
| 20 - 24 | 50 | 15.4 |
| 25 - 29 | 18 | 5.6 |
| 30 - 34 | 14 | 4.3 |
| 35 - 39 | 6 | 1.9 |
| 40+ | 2 | 0.6 |

A complete history was taken of all patients and physical examination performed. Diagnostic examination consisted of urinalysis, urine culture, fasting blood sugar, blood urea nitrogen, serum cholesterol, electrocardiogram and radiograph of the chest. All of the laboratory data and weights obtained on each of the routine outpatient clinic visits were extracted from the records and averaged by 10-year periods. All of this information was coded and recorded on standard IBM cards. A card selector machine or sorter was used to study correlations.

This report confines itself to a study of correlations between retinopathy and various laboratory and clinical findings. The particular methods employed will be described in more detail.

As part of the general physical examination, the optic fundi were examined with a Welch-Allyn ophthalmoscope in a darkened room with a constant light source. The pupils were dilated unless a specific contraindication existed. Retinopathy was graded in the following manner: Grade O, no retinopathy; Grade I, occasional microaneurysms; Grade II, numerous microaneurysms with or without occasional exudates; Grade III, extensive hemorrhages and exudates, and Grade IV, retinitis proliferans or vitreous hemorrhage.

Until the introduction of the Technicon AutoAnalyzer in the hospital laboratory in 1958, blood glucose determinations were made on venous whole blood using the Myers-Benedict picric acid method,[4] which also measures non-glucose reducing substances. All of the values were converted to the equivalent AutoAnalyzer values to permit analysis. The normal blood sugar values on venous blood in our laboratory using the picric acid method were: fasting—80 to 120 mg./100 ml. of blood; and a peak on the blood-sugar time curve following the ingestion of 100 g. of glucose that was not to exceed 180 mg./100 ml. On duplicate samples the values obtained with the AutoAnalyzer were: for fasting blood, up to 90 mg./100 ml.; and the peak not exceeding 130 mg./100 ml. The minimal laboratory findings which permitted a diagnosis of diabetes and inclusion in this series were two or more fasting blood sugars above 130 mg./100 ml. (picric acid) and/or two blood-sugar time curves where the peak was above 180 mg. occurring at one hour rather than at the half-hour, and failure to return to a level of 140 mg./100 at two hours. In borderline cases the abnormality had to be noted as well at several years' interval. Blood sugar values obtained with the picric acid method were converted to the equivalent AutoAnalyzer values originally from a graph constructed from duplicate analyses, but in practice one can accept the close approximation that the AutoAnalyzer value is three-quarters of the value obtained by the picric acid method.

Plasma or serum cholesterol was determined in the fasting state by Bloor's method,[5] as modified by Rabinowitch.[6]

Blood urea nitrogen was measured on the Technicon AutoAnalyzer, and only the final determination done at the time of the physical examination is used because for the purpose of this report, this is an end point much like retinopathy.

Urine sugar was measured semi-quantitatively using Benedict's solution and more recently Clinitest tablets. Urine acetone was measured by modifications of the Rothera reaction, all of which were less sensitive than the present Acetest or Ketostix methods. The number of urine tests positive for reducing substances or ketone bodies were expressed as a percentage of the total number of urinalyses done within each 10-year period.

Body weight was expressed as a percentage of the ideal weight for the height and build using the tables provided by the Metropolitan Life Insurance Company and derived from The Build and Blood Pressure Study (Society of Actuaries, 1959).

Blood pressure was measured in the recumbent position, three times, by auscultation, the mean value being used. The upper limit of normal was considered to be 150/90 mm. Hg.

The correlations between retinopathy and various parameters are presented graphically on histograms where individual bars represent 100% of each total. Though these histograms express percentages, the statistical evaluation was performed on the results themselves. Statistical evaluation was performed by application of the $\chi^2$ test for multiple rows and columns.[7] Correlations are considered probably significant when p is $<0.05$, significant when $<0.01$, and very significant when p $<0.001$.

## RESULTS

### *Prevalence of Retinopathy*

In Table III the prevalence of the various grades of retinopathy is shown. Because of the relatively small total number of patients in the survey and to allow statistical study, the grades of retinopathy were regrouped into three categories. Grade 0 remains separate as "negative", Grades 1 and 2 were grouped as "mild" retinopathy and Grades 3 and 4 grouped as "severe" retinopathy. Seven patients whose fundi could not be assessed because of cataracts, lack of cooperation etc. are not included in tables and figures dealing with retinopathy but are included

TABLE III.—DISTRIBUTION OF CASES ACCORDING TO SEVERITY OF RETINOPATHY

| *Original classification* | *No. of cases* | *Per cent of total* | *Joined group* | *No. of cases* | *Per cent of total* |
|---|---|---|---|---|---|
| Grade | | | | | |
| 0 | 72 | 22.2 | Negative | 72 | 22.7 |
| 1 | 92 | 28.4 | Mild | 139 | 43.8 |
| 2 | 47 | 14.5 | | | |
| 3 | 83 | 25.6 | Severe | 106 | 33.4 |
| 4 | 23 | 7.1 | | | |
| Not determined | 7 | 2.2 | Deleted | — | — |
| Total | 324 | | | 317 | |

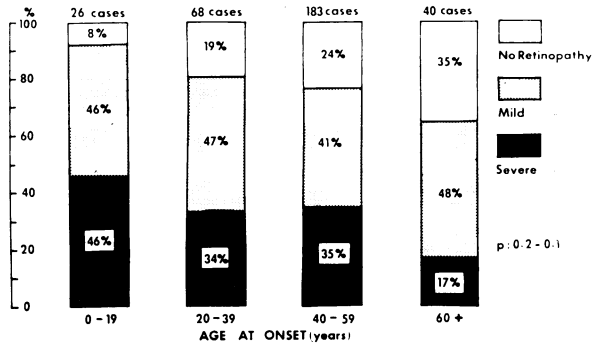


Fig. 1.—Prevalence of retinopathy relative to the age of onset of diabetes.

in others devoted to other aspects of the problem.

The prevalence and severity of retinopathy in the different age groups were not statistically different (p = 0.3-0.2), nor was it different in the various "age-at-onset" groups (Fig. 1). The lack of significant association may be due to the distribution of our patient material, the bulk of which falls into the two middle age groups or the two middle bars of this histogram. It should also be pointed out that the data relating to the age-at-onset are influenced by the fact that age at onset is inversely related to "duration" of diabetes with a correlation coefficient of 8.4. In other words, more early age-at-onset patients have a longer duration of diabetes than late age-at-onset patients, who develop the condition when they would normally be approaching the limits of life expectancy.

Duration of diabetes was associated with a progressively increasing prevalence of severe retinopathy and with a decreasing number of patients free of retinal pathology who had diabetes from 10 to 24 years but not in those over 25 years' duration (Fig. 2). We have no valid data to explain this trend.

A sex difference was not demonstrable either in the prevalence or severity of retinopathy (p =

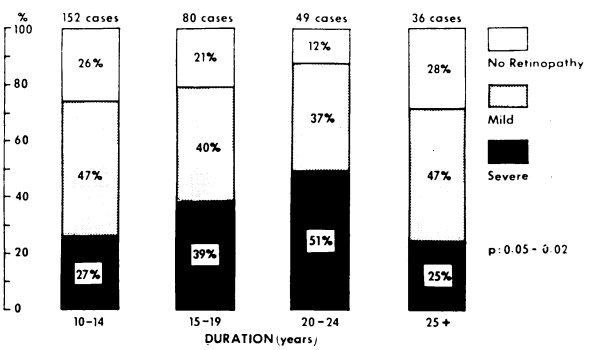


Fig. 2.—Prevalence of retinopathy relative to the duration of diabetes.

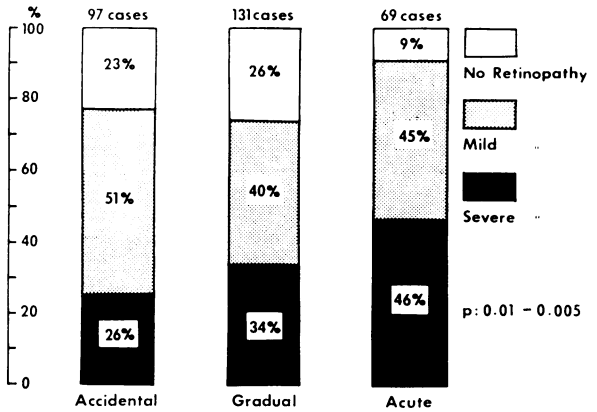


Fig. 3.—Prevalence of retinopathy among diabetics with accidental, gradual, or acute onset of the disease. Twenty-one patients who did not remember type of onset and seven patients whose retinopathy could not be assessed were excluded.

0.3-0.2), nor did the history of parity affect the distribution of retinopathy in women who had no, one or two, three or four, or five or more deliveries before the development of diabetes (p = 0.9-0.8).

Retinopathy was more common among those who had an acute onset of diabetes than among those whose diabetes was of more gradual onset or in whom diabetes was discovered accidentally (Fig. 3).

### *Correlation of Retinopathy with Renal Disease*

Severity of retinopathy correlated well with different aspects of renal disease. Severe retinopathy was seen in almost one-half of patients

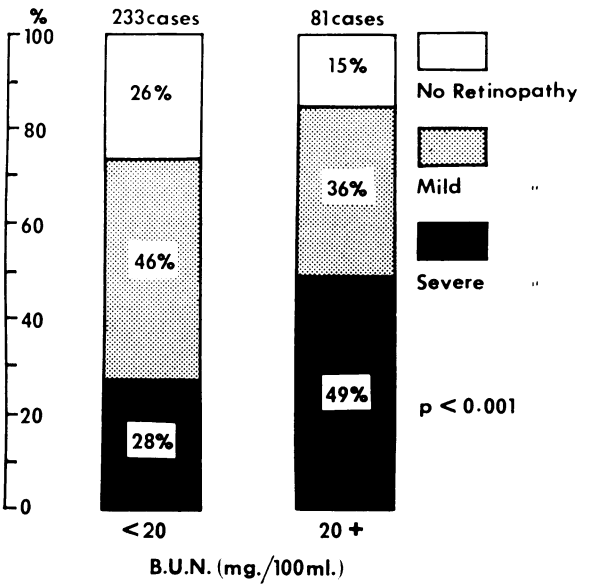


Fig. 4.—Relation of diabetic retinopathy to the blood urea nitrogen.

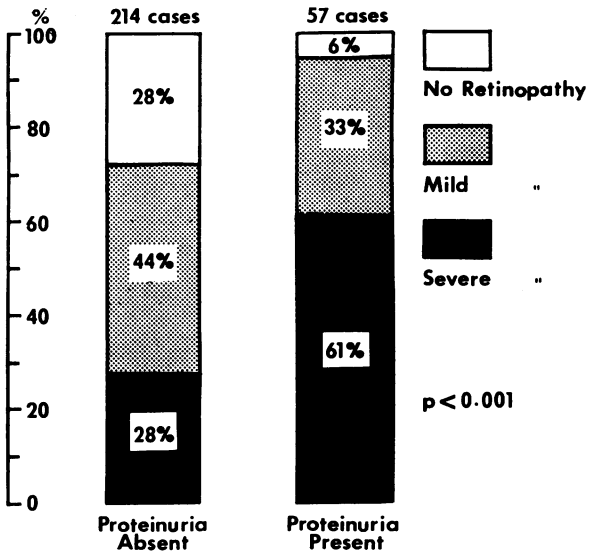


Fig. 5.—Prevalence of retinopathy among diabetics with proteinuria on one or more occasions.

who had an elevated blood urea nitrogen on the day of the physical examination, whereas only one-quarter of those with a normal blood urea nitrogen had severe eye changes (Fig. 4). The P value of this association is less than 0.001, which is highly significant. Similarly there is a strikingly high prevalence of severe retinopathy among those who had proteinuria on one or more occasions (Fig. 5).

A less commonly mentioned correlation which was also highly significant was demonstrated between retinopathy and a positive urine culture, past or present (Fig. 6). Before 1956 this meant,

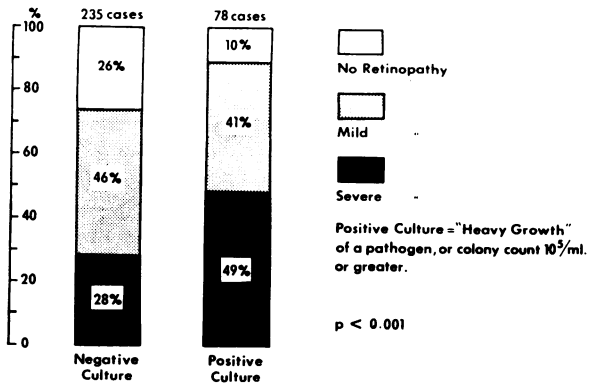


Fig. 6.—Relation between diabetic retinopathy and positive urine culture at any time.

as a minimum, a catheter urine culture reported as "heavy growth" and since 1956, catheter or mid-stream urine specimens having bacterial counts of 100,000 bacteria or more per ml.

*Correlation of Retinopathy with Hypertension*

Though the prevalence of all grades of diabetic retinopathy was not much higher in hypertensive than in normotensive cases, the prevalence of advanced retinopathy was greater in those with diastolic hypertension than in those with normal diastolic pressures (Fig. 7). For

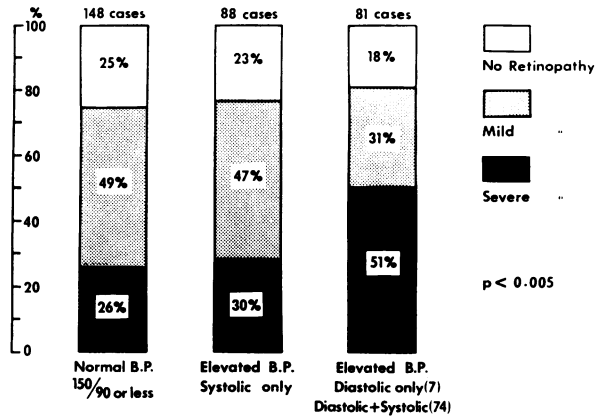


Fig. 7.—Correlation between severity of diabetic retinopathy and blood pressure.

these calculations the actual blood pressure at the time of the survey examination was used, hypertensive history was disregarded and patients receiving antihypertensive medication were classified according to the actual measurement, i.e. as normotensive, if the readings were 150/90 mm. Hg or less with medication.

*Arteriosclerosis*

There was complete lack of correlation between diabetic retinopathy and gross large vessel disease in this group of patients. Prevalence of grades of severity of retinopathy was studied among: 28 amputees ($p = 0.5$-$0.3$); 61 patients with definite history of claudication ($p = 0.2$-$0.1$); 62 patients with angina pectoris ($p = 0.8$-$0.7$); 70 patients with electrocardiographic evidence of myocardial infarction or severe coronary insufficiency ($p = 0.5$-$0.3$). All of these groups were compared with patients who did not have evidence of large vessel disease.

*Control of Diabetes*

Control of diabetes was assessed by the following parameters: fasting blood sugar, weight, ketonuria and glycosuria. All of these were recorded at each clinic or office visit. In addition, serum cholesterol was also often recorded. The total numbers of determinations recorded and thus represented in this study are as

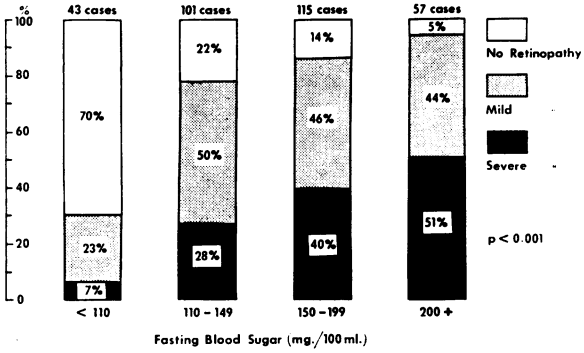


Fig. 8.—Correlation between severity of diabetic retinopathy and the mean fasting blood sugar levels—mean of decade means.

follows: 8924 fasting blood sugars, 2677 fasting serum cholesterols, 9971 weights, and 11,839 urinalyses. The average of these determinations by decades was calculated and the mean of decades was used for the correlation with retinopathy.

Prevalence of retinopathy and, indeed, the prevalence of the more severe forms of retinopathy were significantly higher in groups of patients with the higher mean fasting blood sugar values ($p < 0.001$) (Fig. 8). The linear increase of prevalence of retinopathy with increasing hyperglycemia is easily appreciated. This relation between increasing hyperglycemia and retinopathy was studied in subgroups of age at onset. It was then found that this almost linear progression of prevalence was even more pronounced when only those patients were analyzed whose onset of diabetes was recognized at 30 years of age or more.

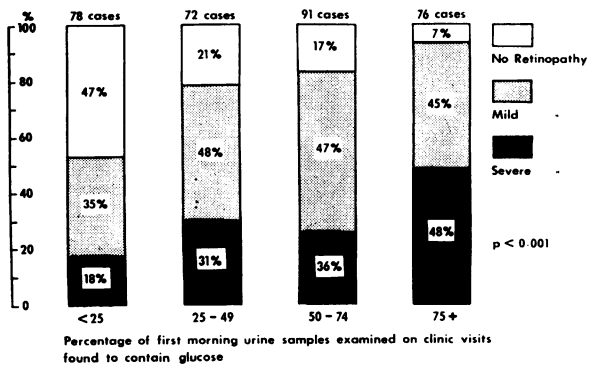


Fig. 9.—Correlation between the severity of retinopathy and the prevalence of fasting glycosuria.

The correlation with glycosuria mirrors the trend observed with mean fasting blood sugars (Fig. 9). Ketonuria was not associated with a particularly high prevalence of retinopathy.

Retinopathy was fairly evenly distributed among those whose mean weight was less than 110%, 110 to 124%, or more than 125% of estimated normal ($p = 0.25$-$0.2$). Mean fasting blood sugar values were evenly distributed among the similar weight groups.

Prevalence of retinopathy among patients whose mean serum cholesterol was less than 230 mg. was not different from the prevalence among those whose mean cholesterol was higher ($p = 0.7$-$0.5$). The average level of serum cholesterol over the years does not therefore seem to be a useful prognostic sign with respect to retinopathy. However, this does not deny that once there has been extensive damage to the eyes and kidneys, it is common to find the cholesterol elevated. When the frequency of mean cholesterol levels less than 270 mg. or more than 270 mg. was tabulated in groups with mean fasting blood sugars less than 110 mg., 110 to 149 mg., 150 to 199 mg. and over 200 mg. per 100 ml., the distribution appeared completely random ($p = 0.9$-$0.8$).

Retinopathy was more prevalent and more frequently severe in patients who were receiving insulin at the time of the survey than in those being treated with oral agents or diet alone. It is impossible to separate the factors which may be responsible here: severity of disease, control, co-operation, complications etc., nor is the time relationship between the use of insulin and the development of retinopathy evident.

## Discussion

In this study care has been taken to avoid defining diabetic control, considering it as good or bad or prejudging the importance of any finding. There is the subconscious danger of moralizing and assuming that only the patients who follow the prescribed treatment do well. There is also the obvious danger that since we do not know the chemical disturbances directly responsible for degenerative changes, it is impossible to be sure that we are not going in a direction opposite to that for which we are aiming. An example of this would be the current interest in serum triglycerides which seem to be a better index of degenerative vascular changes than cholesterol and where it has been shown that in some cases the therapy which lowers the cholesterol raises the triglycerides. Thus all of the laboratory results and weights recorded at the time of each clinic or office visit have been abstracted from the chart and averaged out by 10-year periods. No findings obtained during hospitalization have been included, since these suppose the probability of intercurrent illness and the relatively greater number of analyses during a short interval would tend to distort

the average picture. With the exception of the assessment of retinopathy which carries a degree of subjective interpretation, all other parameters are quantitative and objective. When this survey was initiated no other study had been reported using all the accumulated data for evaluation of retinopathy. In 1963 Carpenter and Taylor[8] briefly reported on a study using this same approach. It is hoped that a more extensive report from this group will be forthcoming. The advent of computers will greatly facilitate studies of this type. However, it is readily admitted that the major correlations drawn here have previously been reported by others.[3, 9-15]

Studies reporting correlations between control and progression of retinal lesions have largely dealt with juvenile diabetics. In contrast, the large majority of patients in this study were over 40 when their diabetes was discovered.

This survey shows that there is a highly significant correlation between the prevalence and severity of retinopathy and the average fasting blood sugar, but that there is no significant correlation with obesity. Therefore, in so far as retinopathy is concerned, normoglycemia should be the goal even though this may require administration of insulin and may result in further weight gain. This in fact was not commonly done in the group of patients reported here. It has been our clinical impression that such fatter, less hyperglycemic diabetics have a higher incidence of cardiovascular renal complications and a shorter life span, but we have no statistically valid proof to substantiate this. However, this survey does show that there is no correlation between large-vessel disease, coronary insufficiency and retinopathy. Without denying the apparent logic of trying to achieve normal biochemical findings, it would seem reasonable to consider that other clinical findings such as obesity and hypertension may be of greater significance to life expectancy.

The correlation between renal damage and retinopathy has been widely observed. However, this is not constant and the relationship is not clear. The strong correlation with bacteriuria has not been sufficiently stressed in the past, and this may be an important contributing factor which could be amenable to treatment, although it might also be secondary to concomitant renal damage. This correlation has recently been confirmed by Vejlsgaard.[16] Likewise a positive approach to the control of hypertension may prevent serious deterioration of vision.

It had been hoped at the beginning of this survey that comparisons between subgroups would have permitted evaluation of certain clinical impressions in the broad field of degenerative complications. In order to measure the importance of a variable, each subgroup must be as homogeneous as possible, e.g. age at onset, duration of diabetes, insulin dependency, percentage of ideal weight, blood pressure, blood sugar, etc. Unfortunately it was found that the subgroups became too small to permit statistical study. In the case of retinopathy, it was felt justified to use the opposite approach and form larger groups. This, however, risks blurring the image. Several thousand cases would be required and it would seem that cooperative studies between institutions might yield useful information even from retrospective studies of this type. It might even be possible to study the effects of different approaches to treatment.

***Summary*** The prevalence of retinopathy was determined in 324 diabetics who had their disease for more than 10 years. This was correlated with the accumulated clinical and laboratory data in the patients' records.

Severity of retinopathy increased linearly in adult diabetics with increase in the average fasting blood sugar.

Increased prevalence of retinopathy was observed in patients who had frequent glycosuria, hyperglycemia, diastolic hypertension, proteinuria, bacteriuria, elevation of blood urea nitrogen and acute onset of diabetes. It also increased with the duration of the disease.

Obesity, parity, serum cholesterol levels and different parameters of arteriosclerosis did not correlate with retinopathy in this group of patients.

***Résumé*** La rétinopathie à été étudiée chez 324 diabétiques qui souffraient de la maladie depuis plus de 10 ans. Les relations possibles entre la rétinopathie et l'évolution clinique du diabète et les analyses de laboratoire pendant la durée de la maladie furent étudiées.

La gravité de la rétinopathie suit une fonction linéaire chez le diabétique adulte, augmentant en fonction de la glycémie à jeun moyenne.

Une plus grande fréquence a été notée chez les diabétiques qui présentaient souvent des épisodes de glycosurie, d'hyperglycémie, d'hypertension diastolique, de protéinurie, de bactériurie, d'augmentation de l'azote protéique et dont le diabète avait débuté de façon aiguë. La rétinopathie a aussi augmenté de fréquence avec la durée de la maladie.

Obésité, nombre de grossesses, cholestérolémie et divers critères de l'artériosclérose ne présentaient aucune corrélation avec la rétinopathie parmi les malades de ce groupe.

We wish to acknowledge the help and advice given us by Dr. A. F. Fowler, who also permitted us to study some of his patients. Dr. G. Ferguson kindly assisted with the statistical evaluation.

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# CURRENT PROGRESS

## Sex Determination, Sexual Differentiation and Intersex Development

KEITH L. MOORE, Ph.D.,* *Winnipeg*

I HAVE been intrigued by intersexuality for over 15 years—not as a pediatrician or obstetrician, but as an embryologist and cytologist. My research has been aimed at two aspects: (a) the etiology of intersexuality and, as an extension of this, its possible prevention; (b) the cytological diagnosis of sex as an aid to sex assignment, especially during infancy, and to differential diagnosis of sex abnormalities.

Fifteen years ago, few doctors were much concerned with the tragic status of intersex patients, because there was little agreement about the etiology of intersexuality, the criteria on which sex assignment should be based, or the management of individual cases. The problem of intersexuality in man had reached an impasse, and often both the doctor and the patient were confused. I was fortunate at this time in being able to work with Dr. Murray Barr on a new approach to this exceedingly difficult problem.

During the last decade great strides have been made in our understanding of intersexuality and, as a result, patients with this condition now have more likelihood of living a *reasonably* normal life. But all the problems have not been solved; in fact, many new ones have emerged. There has been an avalanche of publications in the last few years on sex chromosomal abnormalities, and many clinicians may wonder how much of this new knowledge is applicable to practice. In the present communication I will attempt to focus some of this vast new knowledge of sex chromosomes on the practical problems of diagnosis and management of intersexuality in man.

The first significant observations on human chromosomes were made in 1912. Von Winiwarter,[1] studying sections of testicular tissue, observed 47 chromosomes; this number did not include a Y chromosome because he could not see one. Although this number is now known to have been wrong, von Winiwarter came close to the number that is now considered correct. In 1923 Painter,[2] also studying chromosomes in human testes, concluded that 48 chromosomes were present and that a small Y chromosome *was* present. Painter's observations were accepted widely.

Few people doubted the correctness of the chromosome number of man until 1956 when Tjio and Levan,[3] working in Sweden and using newly developed techniques, reported that they could count only 46 chromosomes in prepara-

From the Department of Anatomy, Faculties of Medicine and Dentistry, University of Manitoba, Winnipeg 3, Manitoba.

A paper presented as part of a Symposium on Intersexuality at the Second Western (Prairie) Regional Meeting, The Royal College of Physicians and Surgeons of Canada, Saskatoon, November 25, 1966.

Supported by the Medical Research Council of Canada.

*Professor and Head, Department of Anatomy, Faculty of Medicine, University of Manitoba.

Reprint requests to: Professor K. L. Moore, University of Manitoba, 750 Bannatyne Ave., Winnipeg 3, Manitoba.