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## Pathogenesis of Coronary Sclerosis

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# I. A STUDY OF THE PATHOGENESIS OF CORONARY SCLEROSIS*

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Arteriosclerosis is still a poorly understood process, in spite of intensive study for more than 50 years. The feeling over the centuries has been that hardening of the arteries is the inevitable consequence of old age, and that, in fact, it is aging. There has been a growing realization, however, that the process does not proceed with uniform severity in all of the arteries, or in all individuals, and that other factors besides age sometimes seem to be of greater importance. In particular, the coronary arteries have been found to be so peculiarly vulnerable to this change in many individuals, that death may result in early life before the rest of the arteries show much evidence of arteriosclerosis. This has led to greatly increased efforts to learn more about the entire process of arteriosclerosis, and particularly about coronary sclerosis, and the factors which may affect its progression, in the hope that the disease may be better understood and perhaps modified.

It has been a difficult problem for investigators, and still remains so, to distinguish the changes in an artery which are physiological, developmental, or maturational from those which might be considered pathological or an alteration due to disease. Perhaps the distinction is entirely artificial. Another problem has been the detection or measurement of changes in the coronary or other arteries during life. Even as sensitive an instrument as an electrocardiograph shows changes only if blood flow is reduced 70% or more [18]. Visualization of coronary arteries by x-ray is in its infancy[19]. The postmortem examination of the coronary arteries and the use of experimental animals remain the most useful means of investigation.

Effects of age: In discussing some of the general factors which may influence coronary sclerosis, the most obvious one to be considered is age itself. Dr. E. T. Bell[5] has stated that the most prominent feature of arteriosclerosis is age. That age is not the only factor, and not even the most important factor, is evident from the numerous examples of severe sclerosis in young people[21]. White, Edwards & Dry[37] have even found a declining severity of coronary sclerosis in men over 59. They concluded that the process does not progress with age, at least not in a linear fashion. Holman[20] has suggested that the effects of age may be cumulative and not causative. He thinks arterial disease may sometimes be a matter of days and not decades. Arterial disease may thus progress by steps rather than as the slowly progressive disease which it is generally considered to be[25].

Sex differences: In the series of cases of coronary disease which have been published, and in the studies of the severity of coronary sclerosis in autopsy material, one other factor has been repeatedly shown to be important. Coronary disease is more severe in men than in women, and by a large margin.

To present a few examples, Willius, Smith and Sprague[42] found in over 5,000 consecutive autopsies that 34% of the males had moderate to severe coronary sclerosis compared with only 19% of females. Clawson [8] in 1939 found 2.5 males to 1 female dying of coronary disease. In hypertensives, Bell and Clawson[4] found 2.7 males to 1 female with coronary disease, and in 1949 they found 5 males to 3 females in the

*This study was done under a Postdoctorate Research Fellowship of the National Heart Institute of the U.S.P.H.S.

nondiabetic group dying of coronary disease. Master, Dack, and Jaffe[25] found a ratio of 3.4 to 1 in clinical cases.

The difference between men and women is even more striking in reports of acute coronary deaths among younger individuals[26]. Gertler[15] found only 3 females in his series of 100 coronary deaths under 40 years of age. Glendy, Levine, and White[16] found a ratio of 24 men to 1 woman under 40 with the coronary disease. Clinical coronary disease is unusual in women without hypertension or diabetes[36].

Ackerman, Dry and Edwards[1] found a marked degree of difference between male and female coronary sclerosis based on accurate anatomical dissection. P. D. White[38] has said recently that in spite of years of study the preponderance of males having coronary disease is still largely unexplained. Endocrine studies are incomplete but do not seem to be an adequate answer. He wonders if it is part of a law of nature that the males of all species from the earthworm up should live shorter lives than the females.

There have been some interesting studies done to help determine the basis of the sex difference in coronary disease. Bruger[7] experimentally tested the effect of testosterone and estrogen in the prevention of atherosclerosis in the rabbit and found that both hormones prevented deposition of cholesterol in the aorta of the female fed cholesterol but not in the male or female castrate.

White[38] found urinary 17 ketosteroids reduced in males with coronary disease compared to controls, but these individuals had been at bed rest for several weeks.

Another explanation for the sex difference in coronary sclerosis has been offered by Dock[11]. He suggested that since hypercholesterolemia was not notably more frequent in men than women, and hypertension and obesity were at least as frequent in females as males, some other factor must be searched for. He postulated that males were predisposed at birth to coronary disease by having thicker intimal layers in their coronary arteries. To determine whether this were the case, he studied the coronary arteries of 12 newborn infants of each sex. There was a wide individual variation but he found a statistical difference giving males on an average 3 times as much intima as females.

Fangman[14] studied the same problem and found out of 30 newborns that 8 males and 4 females had thickened intimas. However, Minkowski[28] reported a larger group of 122 males and 82 female infants and found no statistical difference in intimal thickness except in a group over one month of age where the children died of acute infections.

Interesting work has been done on the sociological factors which might explain the sex difference. Becker[3], studying a primitive society, the Bantu in South Africa, found an equal incidence of coronary disease in men and women. Gordon, Bland, and White[17] found a significantly greater incidence of coronary artery disease in the private hospital wards than among the charity patients. Ryle and Russell[34] found a higher rate of the disease among men holding responsible positions, and found professional and business men had ten times the rate that their wives did, while with agricultural and manual workers the wives had nearly an equal rate. This study was based on death reports in public health statistics and not on autopsy evidence.

Moschcowitz[31] pointed out that the incidence of sclerosis in the lesser circulation was about equal in men and women, and that therefore the differences which occur in such locations as the coronary arteries must be based on pressure differences or at least local changes and not on general metabolic differences.

Effect of hypertension: The fact that hypertension increases the severity of atherosclerosis, and particularly of coronary sclerosis, has been shown many

times. Bell and Clawson[4] found that 25 out of 27 patients under 50 with hypertension showed some coronary disease, a higher percentage than non-hypertensives of all ages. Davis[10] found 76% more atherosclerosis with hypertension. The incidence of coronary disease in women with hypertension was found to be about equal to that of men without hypertension.

Levy and Boas[22] found that 74% of cases of clinical coronary disease in women had hypertension.

Diabetes: One other factor which has been shown to influence intimal arterial disease is diabetes mellitus. Clawson and Bell[9] analyzed over 50,000 autopsy reports and found that fatal coronary disease was about twice as frequent in diabetic as in non-diabetic males, and three times as frequent in diabetic as in non-diabetic females. Among diabetics the sex difference in the incidence of coronary disease is almost wiped out.

In a study of autopsy findings on diabetic and non-diabetic patients, Lisa[23] found that equal severity of coronary disease occurred about 10 years earlier in the diabetics.

Root, Bland, Gordon and White[32] in 3,400 autopsies found coronary occlusions increased in diabetics, and Stearns[35] found a functionally significant degree of coronary sclerosis in 74% of diabetics.

It is evident from these reports that the presence of diabetes is an important factor in the severity of coronary sclerosis.

Effect of nutrition: The question of the effect of nutrition on the progress or incidence of coronary sclerosis has been investigated ever since it was shown by Anitschkow in 1913 that atheromas could be produced in rabbits by feeding excessive cholesterol.

Dublin[12] in 1930 from insurance statistics found mortality from coronary sclerosis to be more than twice as high in overweight persons. Malmros[24] has recently shown that mortality from coronary disease was reduced in the Scandinavian countries during the enforced low fat diet during World War II.

Wilens[39] has studied the effects of nutrition on atherosclerosis and found a relationship between obesity and severe atherosclerosis which was independent of age, sex, hypertension, heart weight, or diabetes. Ackerman[1] found consistently less atherosclerosis in undernourished persons than in average or overweight groups. Yater[43], on the other hand, found no differences in weight between young coronary deaths and controls. One difficulty has been that state of nutrition has been difficult to define, particularly when a person loses much weight in a terminal illness.

If nutrition plays a part in the causation of atherosclerosis, it seems possible that changes in the diet may have some effect on the course of the disease also. Anitschkow[2] found that he could make the lesions in rabbits' aortas disappear on a return to normal diet. Morrison[30] showed a similar resorption in rabbits fed choline and Bevans[6] in dogs.

Another approach to this problem of nutrition is the study of groups with terminally poor nutrition such as one sees in individuals dying of tuberculosis or malignancy. The idea that arteriosclerosis is less severe in persons with tuberculosis and cancer goes back to the early days of pathology. Zeek[44] quotes Rokitansky as thinking that arteriosclerosis was antagonistic to tuberculosis and Dr. T. Holmes in 1867 as saying that the aged, gouty, and rheumatic were more prone to arteriosclerosis than the phthisical, cancerous, or the young. To be sure, most of the latter patients were younger than those dying with arteriosclerosis. However, other writers have presented some evidence in favor of this view. Rosenthal[33] found a lower inclination toward atherosclerosis in carcinoma and tuberculosis groups. Wilens[40] found that there was less atherosclerosis in the aorta of individuals dying with a terminal weight loss of several months than in those of the same previous weight without a wasting disease. Meyers

[27], however, has objected to his conclusions and thinks the differences are probably due to age differences.

There is no evidence as yet that human lesions of atherosclerosis can be resorbed. There is some suggestion, however, that nutritional changes may affect the progress of the condition.

Outline of present project: The material presented here is a partial report of a research project undertaken two years ago to investigate the incidence and pathogenesis of coronary sclerosis under the guidance of Dr. E. T. Bell. It was felt that it would be worthwhile to determine whether coronary sclerosis is a process which is slowly progressive throughout life, or whether it advances by steps or stages. It was also thought that it should be possible to determine the age at which the sex difference in the severity of coronary sclerosis begins. This information might help determine the factors responsible for the difference. In such a study the effects of hypertension, diabetes, and possibly nutrition might also be studied, as well as the histological appearance of the progressive stages of the process.

It was felt that such an investigation could be done best by the thorough and accurate study of the coronary arteries in a large series of hearts removed at autopsy from individuals of every age group throughout life. Such a study would show the progress of the disease in the population, but not, of course, the progressive changes in an individual. However, the course of the disease in an individual might be inferred from the average of the group.

Previous studies of large autopsy series such as those of Willius, Smith and Sprague [42], or Gordon, Bland and White[17], for the incidence and severity of coronary disease have relied mainly on the gross observations and descriptions of the coronary arteries made by a large number of pathologists without rigid standards of what was to be considered mild, moderate, or severe. The studies of Ackerman, Dry and Edwards[1] and White, Edwards and Dry[37] are notable exceptions in that one individual graded all of the arteries. These studies, however, were done only on individuals over the age of 30.

Methods: The study here reported consisted of the thorough examination of 536 hearts removed at autopsy during 1949, 1950, and 1951. These were collected from autopsies performed by Fellows of the Pathology Department at the University Hospital or from the Minneapolis outside and coroner's service. A considerable number were obtained from the Ancker Hospital in St. Paul. These hearts were obtained at random without regard for the cause of death, except that particular attempts were made to obtain hearts from persons killed by accidental means, and from individuals in the younger age groups, in order to obtain adequate numbers in these groups for significant comparison. The autopsy reports of these individuals were examined to determine cause of death, symptoms or signs of heart disease, evidence of hypertension or diabetes, and age, sex, body weight, height, and weight of the heart.

The number obtained (536) is only a fraction of the approximately 3,000 annual autopsies recorded in the Pathology Department. It represents, however, a fair sample of the total material and is adequate in most instances for statistical analysis.

Each of the three major branches of the coronary arteries of each heart was sectioned at approximately two millimeter intervals from the orifice at the aortic valve to the smallest vessel which could be followed grossly. The cuts were made with a sharp blade at right angles to the lumen, and the artery wall carefully examined. The sections of the artery thus cut which showed the greatest degree of sclerosis were taken for histological examination. The total length of the artery was measured and the position of each section taken was recorded by measurement from the orifice, or in the case of the left circumflex branch, from its origin in the main left coronary artery.

The positions of branches were also recorded. At least two histologic sections of each of the three main arterial branches were taken for routine haematoxylin and eosin preparations, and, in addition, other blocks were taken for fat and other special stains. The gross examination of the arteries was done with care, each heart taking from 30 minutes to an hour to examine.

The grading of the severity of the arteriosclerotic process was done on the basis of examination of the histological preparation. This offered an opportunity to compare various criteria for the evaluation of the atherosclerotic process.

In some previous series[1] and 37, grading has been based entirely on the reduction in size of the lumen of the artery. Others have used the thickness of the intima as the basis for evaluation. These are both easily determined and measurements, therefore, can be made with considerable accuracy. Particularly in the younger age groups, however, it may be questioned whether the thickening of the intimal layer and consequent reduction in the size of the lumen is actually to be regarded as arteriosclerosis or as a developmental or maturational process in the vessel which should be looked upon as physiological. There may also be changes in the structure of the artery wall without a remarkable change in the size of the lumen.

The grading of the severity of the atherosclerosis was based on one section stained by hematoxylin and eosin of each of the three major branches of the coronary arteries, the right, left main and descending, and left circumflex branches. The particular section used was chosen because it showed the most severe degree of sclerosis. This is then representative of the most severe area of sclerosis produced in that artery and is not to be considered an average of the entire artery.

It was felt that, in addition to measurements of the size of the lumen and thickness of the intima, some criterion should be selected which would be as characteristic as possible of atherosclerosis alone, as distinguished from other changes. It was also desired to find a criterion which would indicate the earliest recognizable changes and would mirror the development of the lesion in a morphological sense without regard only for the size of the lesion or the amount of artery which was involved. Criteria for the degrees of sclerosis were therefore selected which were based on the degree of infiltration of the intima.

Grade one on the basis of infiltration was selected as the earliest recognizable change in the intima, which was the appearance of a loosening of the structure of the tissue at the luminal surface with occasional small pockets of homogeneous material between the fibers, and very occasional foam cells. It is difficult to be certain in some cases whether the earliest changes seen might not be artifacts.

Grade two was applied to those arteries which showed the infiltration extending into the deep layers of the intima up to the internal elastic lamina, with small areas of hyalinization and perhaps more foam cells near the lumen.

Grade three was applied to arteries which showed broad streaks of smooth hyaline material in the depths of the intima, often with many foam cells. In addition, there might be separation of fibers in the media.

Grade four was applied to those sections which showed a confluent, large area of hyalinized or necrotic material in the depths of the intima containing cholesterin and often calcium crystals, in addition to large numbers of foam cells and often disruption of the media.

Whether this infiltrate in the intima is blood plasma, or primarily lipoid or an altered protein is not decided. With haematoxylin and eosin staining, this change in the early stages has the appearance of edema; with fat stains, droplets of lipoid are seen early in the process,

first however next to the internal elastic lamina. It was found to be impossible to estimate the degree of lipoid infiltration independently of the criteria just described.

It is evident that most investigators would concider the first two grades based on these criteria as early atherosclerosis, and would base most of their further grading on the size of the more fully developed atherosclerotic plague.

The numerical grades of 0 through 4 for each of the three branches were simply added and not averaged so that each case, then, could have a numerical grade based on this criterion of from 0 to 12 without the necessity of using decimal fractions.

The degree of degeneration of the internal elastic lamina was likewise graded independently from 0 to 4. Grade one consisted of the first visible splittings of the elastic lamina. Grade two was applied to those arteries showing actual breaks in the lamina but in which more than 1/2 of the lumen was still surrounded. Grade three was applied when less than 1/2 of the original lamina remained, and Grade four when no recognizable lamina was present. This grading was done on the hematoxylin and eosin sections although elastic stains were prepared in many cases in confirmation. These numbers for each artery were also added, giving a total grade of 0-12 for each heart.

The relative area of the lumen was calculated by measuring the average diameter of the lumen and of the whole artery and comparing their squares, the size of the lumen being expressed as a percentage of the size of the artery. The thickness of the intimal layer was estimated as a fraction of the thickness of the entire wall, and this was converted into a percentage. The outside diameter of each artery was measured in millimeters. The average of the measurements for each of the three main branches was taken in expressing these last three figures for each case.

Results: A total of 536 hearts were examined. They are divided into decades according to age at death with separate groups for the newborns and the infants from 1 to 12 months of age. (Table I) The proportion of females is slightly higher (41%) than in the entire autopsy series (36%)[9]. There are relatively more young individuals also than in the entire autopsy series, as a special attempt was made to secure hearts of these ages.

Although the sections for microscopic examination were taken without regard to distance from the origin of the artery, but only on the basis of severity of sclerosis, there is still a remarkable similarity in position of the blocks selected. Practically all are within the first 25% of the length of the artery. (Table II) There is a slight tendency for distal progression with age.

Relation to age and sex: When the degree of sclerosis as measured by the degree of infiltration in the intima is compared in the separate age groups, there is seen to be a progressive increase in the scale beginning with childhood and extending through the seventh decade (Table III). Almost from the outset the males have considerably more sclerosis in each decade. However, the difference between males and females is not significant in the sense of being more than twice the standard error of the difference between the means until the age group 10-19 years. The leveling off at the 8th decade noted by previous series[1, 37] is most likely due to the survival of a few individuals with "remarkable hearts."[41]

When the relative area of the lumen is plotted in the same manner, there is a similar progressive decrease beginning in childhood (Table IV). Here the differences between males and females appear to be less on the chart, but there is a statistical significance in the age group of 1-9 years.

A very similar curve is obtained when

relative thickness of the intima, as expressed by its percentage of the artery wall, is plotted (Table V). Here again the males have a greater thickness in every decade, with an almost equal progression up to the age of 50 years and with slight leveling off beyond that point. It is notable that here the first mathematically significant difference appears in the group from 1 month to 12 months of age.

When the absolute diameter of the coronary arteries is plotted the male arteries are found to be slightly larger (Table VI). The difference between male and female is not significant until the 20-29 year age group. It was somewhat unexpected to find the size of the artery increasing up to the 6th decade but this possibly represents dilatation or loss of elasticity rather than any continued growth. It is interesting that Ehrich, de la Chapelle and Cohn[13] found the same effect, and that Moritz and Oldt[29] found that measuring the outside diameter of an arteriole is more useful in determining thickening of the wall than measuring the inside diameter.

A similar comparison of the degree of elastic lamina degeneration gives a somewhat similar curve, except that the results are more scattered, and in many of the decades there is no statistically significant difference between males and females (Table VII).

It is notable from this comparison that it is relatively immaterial whether one measures intimal thickness, size of lumen, or degree of infiltration of the intima, in estimating coronary sclerosis.

Traumatic deaths: As a control group, to eliminate the possibility that there had been selection of cases having severe coronary disease, those cases which died of trauma were selected from the whole group. It was found that there were 53 males and 29 females. These were scattered through the entire age range and consisted of persons involved in car accidents, shootings and other deaths by external means. It was felt that coronary artery changes should be no greater or less in this group than in the entire population, and that the effects of terminal illness would be eliminated.

In order to obtain more cases in a control group, those individuals who died of acute brief illnesses which were unrelated to cardiovascular disease were also added. These consisted mainly of acute infectious diseases. The degree of sclerosis in this group closely resembled those of the traumatic group of the same age and sex, and gave an additional number of 30 males and 26 females.

The degree of coronary sclerosis of these individuals gives a closely similar curve to that of the whole group, although they represented only 26% of the group (Table VIII). When the figures for males and females are combined for these two groups, the lines are seen nearly to overlap. There is no statistically significant difference in the two series.

Sclerosis in malignancy: Another group of cases, those dying with a malignant neoplasm, were also separated out from the group. It was found that the general average of the degree of coronary sclerosis in those dying with malignancy was considerably below that of those dying of other causes (Table IX). There is a mathematically significant difference between the two groups. This difference is difficult to explain. One possibility is that many of these individuals were subjected to long periods of inanition and partial starvation and that the difference might be due to nutritional changes.

Sclerosis in hypertension: From the entire group, those cases were selected which showed a heart weight at least 50 Grams in excess of that range which would be predicted from the patient's height, using the figures of Zeek[45]. Those which showed evidence of other cardiac disease such as valvular lesions which might have produced the hypertrophy were not included.

There were 77 males and 39 females in this group of hypertensives. All of the remaining hearts were put in the non-hypertensive group although a few were enlarged for reasons other than hypertension.

A comparison of the two groups shows that there is a remarkable difference between them especially in the age range of 30 to 49 years (Table X). Removal of the hypertensives from the entire group does not influence appreciably the progressive increase in the degree of sclerosis with age which is seen in the non-hypertensive group, and it has no effect on the sex ratio of the remaining cases.

Diabetes: Only 18 cases of diabetes are included in this group (Table XI). When the degree of sclerosis is plotted and compared with that of the whole group there is seen to be an irregular increase which in the 5th decade has statistical significance. Seven of the diabetics also had hypertrophied hearts. With removal of these from the group the curve remains approximately the same. There were too few diabetics to draw any reliable conclusions about its effect on the atherosclerotic process.

Clinical coronary disease: As a final comparison, the cases of patients having symptoms of, or death from, coronary sclerosis were ranged against the entire group with regard to degree of sclerosis. Most of these individuals died of the disease. There were 30 men and 6 women. Three were below 40 years of age. It will be seen that this group has very severe involvement of the arteries and usually of all three branches. This suggests that severe disease of all branches is necessary before symptoms are produced. A similar relationship is seen when the size of the lumen is used in comparison.

It is evident that the curve for males comes much closer to the "danger area" of clinical coronary disease than that of females. This is one way of showing the increased susceptibility of males to clinical symptoms of coronary disease.

It must be emphasized again that these findings relate to a group of individuals and not to the disease process as it occurs in a single individual. That connot be studied during life except when it reaches a very severe stage. However, it may be assumed that the disease process in the individual will conform to the average progress of the disease in the general population.

Conclusion: The results obtained by this survey indicate that coronary sclerosis is a progressive disease process beginning early in life. It progresses at a nearly uniform rate, gradually leveling off after the age of 50. The process is related to age, the terminal decline in severity probably being due to survival of a few unusual individuals.

The sex difference between males and females in degree of sclerosis begins early in childhood. The intimal thickness, at least, shows a difference which is significant below one year of age. This suggests that endocrine or sociological differences may not be the primary factors in the sex difference. The sex difference decreases in the elderly age groups, but does not disappear.

The effects of hypertension on the progression of coronary disease is shown by these data to be similar to the relationship found by others. In many age groups the differences between hypertensives and non-hypertensives are greater than the differences between males and females. Beyond the age of forty there is little progression of sclerosis with age in hypertensives of this degree.

Those cases in which death or symptoms occurred from coronary disease at any age showed a severe degree of sclerosis in all of the three main branches of the coronary system. There was a reduction in the size of the lumen to less than 30% of the area of the artery. This indicates that there is a wide reserve in the coronary circulation, and that indi-

viduals usually must have severe coronary disease before it is evident clinically. Males are shown to approach the critical level of coronary sclerosis at an earlier age than females, in general about ten years earlier.

The differences found in the degree of sclerosis between persons dying with malignant disease and others is not easy to explain. The difference in middle life is about of the same magnitude as the sex difference. This finding lends support to the suggestion that a drastic reduction or change in nutrition may affect the sclerotic process. It also suggests that there is a possibility of regression of atherosclerotic lesions in the human.

The comparison of various methods of grading the atherosclerotic process demonstrates that it makes relatively little difference which component of the sclerotic process is used for a basis for comparison. The intima thickens, the lumen is reduced, the elastic lamina degenerates, the artery enlarges, and the intima becomes infiltrated with plasma or lipoid, at about the same rate. This does not necessarily hold true for the individual case, however. There is considerable individual variation in this respect. In general, the processes in the three main arteries of each individual heart have a similar appearance, the process being slightly more advanced in the left descending artery.

Summary:

1. A series of 536 hearts from autopsies of individuals of both sexes from birth to 89 years of age were examined by dissection of the coronary arteries to determine the severity of atherosclerosis.

2. The arteries were graded on the basis of the most severe degree of sclerosis found in each vessel by microscopic examination. The degree of infiltration of the intima, area of lumen, thickness of the intima, degree of elastic degeneration and diameter of the artery were graded or measured independently and the results compared.

3. The degree of coronary atherosclerosis was found to increase progressively with age from early childhood through the seventh decade at a nearly uniform rate.

4. Coronary atherosclerosis was found to be significantly more severe in males than in females of the same age even in the first decade of life.

5. The degree of atherosclerosis was found to be much greater in hearts with hypertrophy due to hypertension than in hearts of non-hypertensives of the same age and sex.

6. Diabetics generally showed a more severe degree of coronary sclerosis than the average, although only 18 cases of diabetes were encountered.

7. Death or serious symptoms from coronary disease were found to be associated with an advanced degree of sclerosis of all the main coronary arteries.

8. Individuals dying with malignant neoplastic disease were found to have significantly less severe coronary disease than those dying without malignancy. This appears to be related to nutritional changes.

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TABLE I

TOTAL HEARTS STUDIED

| Ages | Males | Females | Combined |
|---|---|---|---|
| NB-1 Mo. | 15 | 10 | 25 |
| 1-12 Mo. | 12 | 12 | 24 |
| 1-9 Yr. | 29 | 16 | 45 |
| 10-19 | 23 | 18 | 41 |
| 20-29 | 28 | 20 | 48 |
| 30-39 | 31 | 26 | 57 |
| 40-49 | 44 | 30 | 74 |
| 50-59 | 47 | 28 | 75 |
| 60-69 | 42 | 28 | 70 |
| 70-79 | 29 | 25 | 54 |
| 80-89 | 14 | 9 | 23 |
| Total | 314 | 222 | 536 |

TABLE II

DISTANCE FROM ORIGIN OF ARTERY TO SITE OF MOST SEVERE SCLEROSIS
(in Percent of Artery Length)

| | Males | Females |
|---|---|---|
| NB-1 Mo. | 19% | 22% |
| 1-12 Mo. | 14 | 19 |
| 1-9 Yr. | 17 | 20 |
| 10-19 | 21 | 20 |
| 20-29 | 20 | 22 |
| 30-39 | 23 | 21 |
| 40-49 | 23 | 22 |
| 50-59 | 24 | 23 |
| 60-69 | 25 | 27 |
| 70-79 | 25 | 23 |
| 80-89 | 25 | 24 |

TABLE III

DEGREE OF ATHEROSCLEROSIS (INFILTRATION)
(Graded 0-12)

| | Males | Females | Combined |
|---|---|---|---|
| NB-1 Mo. | 1.4 | 1.4 | 1.4 |
| 1-12 Mo. | 2.6 | 2.2 | 2.4 |
| 1-9 Yr. | 3.1 | 2.8 | 3.0 |
| 10-19 | 5.0 | 3.5 | 4.3 |
| 20-29 | 5.6 | 4.0 | 4.9 |
| 30-39 | 7.6 | 6.6 | 7.1 |
| 40-49 | 8.8 | 6.9 | 8.0 |
| 50-59 | 9.5 | 7.5 | 8.8 |
| 60-69 | 10.4 | 9.1 | 9.9 |
| 70-79 | 10.8 | 10.1 | 10.6 |
| 80-89 | 10.6 | 10.2 | 10.4 |

The difference between male and female groups is 2.6 times the standard error ($\pm$ .57) at ages 10-19.

TABLE IV

AVERAGE RELATIVE AREA OF LUMEN AS PERCENT OF AREA OF ARTERY

| | Males | Females |
|---|---|---|
| NB-1 Mo. | 62% | 61% |
| 1-12 Mo. | 52 | 58 |
| 1-9 Yr. | 48 | 54 |
| 10-19 | 47 | 49 |
| 20-29 | 44 | 50 |
| 30-39 | 38 | 40 |
| 40-49 | 33 | 35 |
| 50-59 | 30 | 34 |
| 60-69 | 27 | 34 |
| 70-79 | 25 | 29 |
| 80-89 | 21 | 34 |

S. E. of diff. = $\pm$ 2.6 at age 1-9 yrs.
The difference is 2.3 times the S. E.

TABLE V

AVERAGE THICKNESS OF INTIMA AS
PERCENT OF THICKNESS OF ARTERY WALL

| | Males | Females |
|---|---|---|
| NB-1 Mo. | 15% | 12% |
| 1-12 Mo. | 27 | 15 |
| 1-9 Yr. | 32 | 26 |
| 10-19 | 43 | 39 |
| 20-29 | 47 | 42 |
| 30-39 | 61 | 57 |
| 40-49 | 68 | 60 |
| 50-59 | 74 | 65 |
| 60-69 | 77 | 71 |
| 70-79 | 80 | 77 |
| 80-89 | 81 | 70 |

S.E. of diff. = $\pm$ 4.1 at age 1-12 mos.
Diff. = 2.9 times the S.E.

TABLE VI

AVERAGE OUTSIDE DIAMETER OF
CORONARY ARTERIES IN MILLIMETERS

| | Males | Females |
|---|---|---|
| NB-1 Mo. | 0.8 mm. | 0.7 mm. |
| 1-12 Mo. | 1.1 | 1.0 |
| 1-9 Yr. | 1.3 | 1.3 |
| 10-19 | 2.0 | 1.9 |
| 20-29 | 2.4 | 2.0 |
| 30-39 | 2.7 | 2.5 |
| 40-49 | 3.0 | 2.4 |
| 50-59 | 3.1 | 2.6 |
| 60-69 | 3.5 | 3.1 |
| 70-79 | 3.6 | 3.1 |
| 80-89 | 3.6 | 3.2 |

S.E. of diff. = $\pm$ 0.059 at age 20-29 yrs.
Difference = 6.7 times the S.E.

TABLE VII

AVERAGE DEGREE OF INTERNAL
ELASTIC LAMINA DEGENERATION
(Graded 0-12)

| | Males | Females |
|---|---|---|
| NB-1 Mo. | 3.4 | 3.1 |
| 1-12 Mo. | 4.6 | 3.3 |
| 1-9 Yr. | 5.7 | 4.7 |
| 10-19 | 6.6 | 6.3 |
| 20-29 | 7.4 | 6.6 |
| 30-39 | 7.7 | 7.3 |
| 40-49 | 8.1 | 6.9 |
| 50-59 | 8.0 | 6.5 |
| 60-69 | 8.8 | 7.4 |
| 70-79 | 8.6 | 8.2 |
| 80-89 | 9.8 | 8.9 |

S.E. of the difference at ages 40-49 is $\pm$ 0.078. The difference is 15 times the standard error.

TABLE VIII

DEGREE OF SCLEROSIS IN DEATHS FROM TRAUMA AND ACUTE ILLNESS
(Graded 0-12)

| | Cases | Males | Females | Combined |
|---|---|---|---|---|
| NB-1 Mo. | 10 | 1.7 | 1.0 | 1.5 |
| 1-12 Mo. | 6 | 2.3 | 2.3 | 2.3 |
| 1-9 Yr. | 22 | 3.1 | 2.6 | 2.9 |
| 10-19 | 11 | 5.0 | 3.8 | 4.6 |
| 20-29 | 25 | 5.1 | 3.7 | 5.4 |
| 30-39 | 23 | 7.5 | 5.8 | 6.6 |
| 40-49 | 16 | 9.6 | 7.4 | 8.9 |
| 50-59 | 13 | 9.3 | 8.8 | 9.2 |
| 60-69 | 9 | 9.7 | 8.3 | 9.6 |
| 70-79 | 3 | 10.0 | 10.0 | 10.0 |
| 80-89 | 0 | ---- | ---- | ---- |
| | 138 | | | |

S.E. of diff. = $\pm$ 0.38 at age 60-69
Diff. = 0.30

TABLE IX

DEGREE OF SCLEROSIS IN DEATHS FROM MALIGNANT NEOPLASMS
(Graded 0-12)

| | Cases | Males | Females | Combined | Non-Malignant |
|---|---|---|---|---|---|
| NB-1 Mo. | 0 | --- | --- | --- | 1.4 |
| 1-12 Mo. | 2 | 4.0 | --- | 4.0 | 2.2 |
| 1-9 Yr. | 5 | 2.7 | 3.5 | 3.0 | 3.0 |
| 10-19 | 8 | 6.0 | 3.4 | 4.4 | 4.4 |
| 20-29 | 5 | 5.0 | 3.0 | 4.6 | 5.0 |
| 30-39 | 3 | 6.0 | 4.0 | 5.3 | 7.2 |
| 40-49 | 22 | 8.0 | 5.8 | 6.9 | 8.5 |
| 50-59 | 25 | 9.0 | 6.5 | 7.6 | 9.4 |
| 60-69 | 24 | 9.9 | 8.1 | 9.3 | 10.2 |
| 70-79 | 21 | 10.4 | 10.1 | 10.3 | 10.8 |
| 80-89 | 6 | 11.5 | 12.0 | 11.7 | 10.1 |
| | 121 | | | | |

S.E. of diff. between malignant & non-malignant cases = ± 0.66 at ages 40-49. The difference = 1.6 or 2.4 times the S.E.

TABLE X

DEGREE OF SCLEROSIS IN CASES WITH HYPERTROPHIED HEARTS DUE TO HYPERTENSION
(Graded 0-12)

| | Cases | Males | Females | Combined | Non-Hypertensive |
|---|---|---|---|---|---|
| 20-29 | 2 | 7.5 | --- | 7.5 | 4.8 |
| 30-39 | 13 | 8.9 | 10.2 | 9.4 | 6.5 |
| 40-49 | 22 | 10.1 | 10.3 | 10.1 | 7.0 |
| 50-59 | 20 | 10.3 | 8.1 | 9.9 | 8.3 |
| 60-69 | 33 | 11.0 | 10.0 | 10.6 | 9.1 |
| 70-79 | 19 | 11.0 | 10.4 | 10.7 | 10.5 |
| 80-89 | 7 | 11.7 | 10.7 | 11.1 | 9.9 |
| | 116 | | | | |

S.E. of diff. between hypertensives and whole group at age 40-49 = ± 0.63. Difference = 2.1 or 3.3 times the S.E.

TABLE XI

DEGREE OF SCLEROSIS IN DIABETICS
(Graded 0-12)

| | Cases | Degree |
|---|---|---|
| 10-19 Yr. | 1 | 3 |
| 20-29 | 1 | 8 |
| 30-39 | 3 | 10 |
| 40-49 | 4 | 10 |
| 50-59 | 1 | 8 |
| 60-69 | 4 | 11.5 |
| 70-79 | 4 | 11.5 |
| 80-89 | 0 | ---- |
| | 18 | |

S.E. of diff. = $\pm$ 1.0 at age 40-49 yrs.
Difference = 2.0 or twice the S.E.

TABLE XII

DEGREE OF SCLEROSIS AND RELATIVE AREA OF LUMEN IN CASES WITH DEATH OR SYMPTOMS OF CORONARY DISEASE
(Graded 0-12) (Lumen in Percent)

| | Cases | Degree | Lumen |
|---|---|---|---|
| 20-29 | 1 | 10 | 26% |
| 30-39 | 2 | 10.5 | 23.5 |
| 40-49 | 6 | 11.2 | 15.8 |
| 50-59 | 10 | 10.9 | 20.7 |
| 60-69 | 11 | 11.6 | 19.8 |
| 70-79 | 5 | 11.6 | 15.6 |
| 80-89 | 1 | 12.0 | 6.0 |
| | 36 | | |

S.E. of diff. in Degree of Sclerosis at age 40-49 between whole group and coronary group = $\pm$ 0.48
or difference = 67 times the S.E.

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## II. MEDICAL SCHOOL NEWS

### Coming Events

Nov. 26 - Dec. 1 Continuation Course in Child Psychiatry for Pediatricians and General Physicians

November 27 Special Lecture; "Facts and Theories of Comparative Psychiatry;" Dr. Eduardo Krapf; Owre Amphitheater; 8:15 p.m.

November 28 Special Lecture; "Mental Health Problems of Aging;" Dr. Eduardo Krapf; Museum of Natural History Auditorium; 8:15 p.m.

January 3 - 5 Continuation Course in Gynecology for General Physicians

January 7 - 9 Continuation Course in Pediatrics for General Physicians

### Faculty News

Dr. Wesley W. Spink, Professor of Medicine, spent the past summer in Europe as a representative of the World Health Organization and the Food and Agriculture Divisions of the United Nations. Dr. Spink visited England, France, Italy, Yugoslavia, and Switzerland obtaining information on brucellosis. In addition to his specific mission concerned with brucellosis as a health and economic problem in these countries, Dr. Spink also visited many medical schools and teaching hospitals. While in London, he addressed the Microbiology Section of the International Congress of Clinical Pathology. In this address he emphasized some of the accomplishments and some of the hazards of chemo- and antibiotic therapy. Since his return to this country in September, Dr. Spink has related some of his observations to members of the Department of Medicine at several of the Department's weekly luncheon meetings.

Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics, participated in the dedication of the Sick Children's Hospital in Toronto, Ontario, on October 19. During the meetings which were held as a part of the dedicatory celebration, Dr. McQuarrie spoke on the subject, "The Problem of Spontaneous Hypoglycemia in Children."

Dr. Howard L. Horns, Assistant Dean, and Dr. George N. Aagaard, Director of Continuation Medical Education, attended the meeting of the Association of American Medical Colleges held in French Lick Springs, Indiana, October 29 to 31.

A large delegation from the Department of Medicine attended the meetings of the Central Society for Clinical Research in Chicago November 2 and 3. Members of the department who presented papers included the following: Dr. Richard V. Ebert, "Determination of the Blood Flow through Nonventilated Portions of the Normal and Diseased Lung;" Dr. Edmund B. Flink, "Two New Tools for the Study of Adrenal Dysfunction;" Dr. Samuel Schwartz, "Experimental Porphyria in Rabbits;" Dr. Rudi Schmid, "A Study of the Porphyrins of Bone Marrow and Liver in the Various Forms of Porphyria."

The Mid-West Section of the American Federation for Clinical Research met in Chicago Thursday, November 1. Dr. William Stead presented a paper on "The Nature of the Immediate Physiologic Adjustment to Thoracic Surgery." Dr. James Hammarsten, also of the Department of Medicine at the Veterans Hospital, spoke on "The Effects of Adrenalin Upon Renal Function and Electrolyte Excretion."

* * *

### New Minnesota Medical Foundation Members

Arnold E. Naegeli, M.D., California
Irvine Ariel, M.D., New York City
Quain and Ramstad Clinic, Bismarck
George E. Moore, M.D., Minneapolis
Scott M. Smith, M.D., Salt Lake City, Utah
H. L. Neuenschwander, M.D., Tennessee
Richard M. Halpern, M.D., California
Davis S. Malen, M.D., Baton Rouge, La.
Ada M. Smith, Minneapolis
John D. Tobin, M.D., Minneapolis
Maxine O. Nelson, M.D., Minneapolis
Mrs. William Furlong, Minneapolis
Robert J. Brotchner, M.D., St. Paul
W. A. Knight, Jr., M.D., St. Louis, Mo.
Fargo Clinic Library, Fargo, North Dakota
Mankato Clinic, Mankato

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

November 12 - 17, 1951

Monday, November 12 - H O L I D A Y

Tuesday, November 13

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; Physiology Library.

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staffs; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - Selected Topics, Permeability and Metabolism; Nathan Lifson; Physiology Library.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U.H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Veterans Hospital Staff; Doctors Fink, O'Loughlin, et al.; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 2:30 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor Annex.

10:00 - Psychiatric Grand Rounds; J. C. Michael and Staff; 3rd Floor Annex.

11:00 - Pediatric Rounds; Dr. Platou; 7th Floor.

Veterans Administration Hospital

8:30 - Surgery Staff Seminar; Conference Room, Bldg. I.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

1:30 - Liver Rounds; Samuel Nesbitt.

Tuesday, November 13 (Cont.)

Veterans Administration Hospital (Cont.)

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, November 14

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler, Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staffs; Todd Amphitheater, U. H.

12:30 - 1:20 Radio-Isotope Informal Conference; Subject to be announced; Dr. Lifson; 12 Medical Sciences.

1:30 - Conference on Circulatory and Renal Systems Problems; M. B. Visscher; Physiology Library.

4:00 - 5:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Sta. 42,U.H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

5:00 - 6:00 Vascular Conference; Todd Amphitheater, U. H.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

7:00 - 8:00 Dermatology Journal Club; Dining Room, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; Robert Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Dr. Platou; 7th Floor Annex.

11:00 - Pediatric Rounds; Dr. Top, 7th Floor.

12:00 - Surgery Seminar; Dr. Zierold; Classroom.

Wednesday, November 14 (Cont.)

Minneapolis General Hospital (Cont.)

12:15 - Pediatric Conference; 4th Floor Annex.

1:30 - Pediatric Rounds; Dr. Huenekens and Dr. Ulstrom; 4th Floor Annex.

2:00 - 4:00 Infectious Disease Rounds; 8th Floor.

4:00 - 5:00 Infectious Disease Conference; Classroom, 8th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, November 15

Medical School and University Hospitals

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

12:30 - Physiological Chemistry Seminar; Separation of Lipids by New Physical Techniques; J. S. Hamilton; 214 Millard Hall.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theater.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Report of Medical Mission to Iran; Leo G. Rigler; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor.

8:30 - Neurology Rounds; Dr. Heilig, 4th Floor Annex.

9:00 - Neurology Grand Rounds; J. C. Michael and Staff; Station A.

11:00 - Pediatric Rounds; Dr. Platou; 7th Floor.

## Thursday, November 15 (Cont.)

Minneapolis General Hospital (Cont.)

11:30 - Pathology Conference; Main Classroom.

1:00 - 2:00 Fracture - X-ray Conference; Dr. Zierold; Classroom, 4th Floor Annex.

2:00 - Psychiatry Rounds; Dr. Benton; 4th Floor Annex.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

## Friday, November 16

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; The Hypothalamus and Bulbar Poliomyelitis; Ian Brown and A. B. Baker; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 Dermatology Seminar; W-312, U. H.

4:00 - Neurophysiology Seminar; 113 Owre Hall, Medical Science Bldg.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Dr. Nelson; 4th Floor.

## Friday, November 16 (Cont.)

Minneapolis General Hospital (Cont.)

11:00 - Pediatric Rounds; Dr. Top; 7th Floor.

11:00 - Pediatric-Surgery Conference; Drs. Wyatt and F. Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Drs. Zierold and Coe; Classroom.

1:30 - Pediatric Rounds; Dr. Ulstrom, 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg.I.

1:30 - Chest Conference; Wm. Tucker and J. A. Meyers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

## Saturday, November 17

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; Wallace H. Cole and Staff; M-109, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-221, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:15 - 10:00 Surgery-Roentgenology Conference; J. Friedman, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - 12:30 Anatomy Seminar; The Present Status of the Problem of Fixation for Electron Microscopy, Richard H. Swigart; Contour Mapping of Cortical Auditory Potentials, Nathaniel A. Buchwald; 226 Institute of Anatomy.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Dr. Gibbs; 5th Floor.

11:00 - 12:00 Pediatric Clinic; Dr. Thomas and Dr. May; Classroom, 4th Floor Annex.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.