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MEDICAL PROGRESS

ORAL CONTRACEPTIVES AND CARDIOVASCULAR DISEASE

(First of Two Parts)

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WHEN oral contraceptives became generally available during the early 1960s, their use increased rapidly, initially in North America and then elsewhere. By 1965, approximately 15 per cent of all married women 15 to 44 years of age in the United States were taking oral contraceptives; by 1973, this figure had increased to 25 per cent, or about 6.6 million.[1] Use in the United States peaked during the mid-1970s but has continued to increase in many other countries.[2] Worldwide, it is estimated that about 54 million women were using oral contraceptives by 1977.[2]

Evidence suggesting that oral contraceptives might have effects on health other than the prevention of unwanted pregnancy began to appear shortly after the drugs were introduced. In 1961, a general practitioner in Suffolk, England, described the occurrence of pulmonary embolism in a woman taking Enovid-10 (9.85 mg of norethynodrel with 150 μg of mestranol) for treatment of endometriosis.[3] Numerous other reports of thromboembolic disease in women using oral contraceptives followed, and by 1963 it was apparent that carefully planned epidemiologic studies were necessary to determine whether these case reports represented coincidence or causation.[4]

The epidemiologic evaluation of oral contraceptives began with the issue of thromboembolic disease and has since been greatly expanded. The major tools of this research effort have been retrospective or case-control studies and prospective or cohort studies.[5]

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Case-control and cohort studies provide two somewhat different measures of the relation between oral-contraceptive use and the occurrence of disease: relative risk and attributable risk. Relative risk, which is the ratio of the incidence of a disease among oral-contraceptive users to that among nonusers, is useful as a tool of epidemiologic research but is inadequate as an indicator of risk in the usual sense. Attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers, better conveys the clinical importance of an effect of oral contraceptives on the occurrence of disease. For example, if oral contraceptives increased the incidence of a disease from one case per 10,000 women per year (among nonusers) to 10 cases per 10,000 women per year (among users), the relative risk (10) would be the same as if the increase in the incidence of the disease were from 10 cases per 10,000 women per year (among nonusers) to 100 cases per 10,000 women per year (among users). However, in the former instance, oral contraceptives would be responsible for only nine cases of disease per 10,000 users per year (the attributable risk), whereas in the latter instance the drugs would be responsible for 90 cases per 10,000 users per year.

During the late 1960s, case-control studies provided convincing evidence that women using oral contraceptives were at increased risk for venous thromboembolic disease[6-10]; the case-control approach has also been used to investigate the effect of oral contraceptives on the occurrence of other forms of cardiovascular disease,[11] malignant and benign neoplasia,[12] and other disorders. In 1968, three cohort studies involving a total of more than 80,000 women (nearly half of whom were taking oral contraceptives) were es-

tablished, two in Great Britain and one in the United States. Since 1974, these cohort studies have provided a wealth of information concerning the effects of oral contraceptives on morbidity, mortality, and such physiologic indicators of health status as blood pressure, glucose tolerance, and serum lipoproteins.[13-25] Other epidemiologic methods, such as the compilation and examination of unusual case reports[26] and the comparison of trends in mortality statistics with trends in oral-contraceptive use[27] (to identify coincident changes), have also been useful in evaluations of the relation between oral-contraceptive use and the occurrence of disease. In addition, numerous laboratory investigations have explored the effects of oral contraceptives on physiologic processes that may be important in determining how these drugs influence health and the occurrence of disease.

After nearly 20 years of widespread oral-contraceptive use and almost as many years of epidemiologic research and scientific and public debate about the effects of oral contraceptives on the health of women, it is currently believed that the most important effect other than the prevention of unwanted pregnancy is an increase in the risk of cardiovascular disease — specifically, the risks of venous thromboembolic disease, myocardial infarction, and stroke.[11,17,21] For some women, especially those about 35 years of age or older who smoke cigarettes, the increased risk of cardiovascular disease that has been found to arise during oral-contraceptive use appears to overshadow the risks to health from pregnancy or from the use of other methods of fertility control.[28] This obviously has important implications for medical practice, and it is probably partly responsible for the decline in oral-contraceptive use that has occurred in the United States since the mid-1970s.

The purpose of this article is to summarize current information about the effects of oral contraceptives on the occurrence of venous thromboembolic disease, myocardial infarction, and stroke, and to integrate with this information the results of certain laboratory investigations that suggest how oral contraceptives may influence the occurrence of these diseases. However, it should be noted that this presentation is subject to three important limitations. First of all, the current information on the effects of oral contraceptives on the occurrence of venous thromboembolic disease, myocardial infarction, and stroke is derived almost exclusively from epidemiologic research conducted in Great Britain, the United States, and the Scandinavian countries, where the incidence of these diseases is high. The results may not pertain to other populations, especially those in which the incidence of these diseases is low. Secondly, in general, the information presented here aggregates the effects of the various progestogen-estrogen oral contraceptives that were used in Great Britain, the United States, and similar countries from the late 1960s through the late 1970s; a large proportion of these preparations contained one of several progestogens in combined formulation with 50 μg of either mestranol or ethinyl estradiol.[2,14,18] Nevertheless, consideration is given to the effects of different progestogen and estrogen types and dosages on the occurrence of venous thromboembolic disease, myocardial infarction, and stroke whenever the available data permit. Thirdly, this article is intended as a synthetic and interpretive overview of major findings, not as a detailed critique of the methodologic strengths and weaknesses of the various studies cited. However, a considerable effort has been made to emphasize the findings that are most clearly established and to qualify those that are potentially important but less firmly estabished.

Venous Thromboembolic Disease

Oral contraceptives have been found to increase both the risk of overt venous thromboembolic disease[11] and the occurrence of subclinical thrombosis that is extensive enough to be detected by laboratory procedures such as ^{125}I-fibrinogen uptake[29,30] and plasma fibrinogen chromatography.[31] Epidemiologic data indicate that the overall incidence of overt superficial or deep venous thromboembolic disease among previously healthy, nonpregnant women of reproductive age in Great Britain (and presumably in the United States and similar countries) who are not using oral contraceptives is about one new case per thousand women per year.[16,20] Among comparable women who are using oral contraceptives, the overall incidence of overt superficial or deep venous thromboembolic disease is about three new cases per thousand women per year.[16,20] In contrast, laboratory data suggest that the overall incidence of spontaneously resolving, subclinical thrombosis extensive enough to be detected by plasma fibrinogen chromatography may be on the order of one episode (average duration, about one month) per woman per year among apparently healthy, nonpregnant women of reproductive age who are not using oral contraceptives, and on the order of three episodes per woman per year among comparable women who are using them.[31] (These estimates are derived from the data of Alkjaersig et al.[31] with the formula: incidence = prevalence ÷ mean duration. The data on which they are based are somewhat controversial, but they do suggest that subclinical thrombosis occurs much more frequently than overt venous thromboembolic disease.) The most plausible explanation for these findings is that oral contraceptives potentiate the intravascular coagulation that occurs in response to thrombotic stimuli,[32] causing proportionally similar increases in the risk of overt venous thromboembolic disease and in the frequency with which subclinical thrombosis is extensive enough to be detected by plasma fibrinogen chromatography.

Current Oral-Contraceptive Use, Past Use, and Duration of Use

Epidemiologic research has found that the risk of overt venous thromboembolic disease increases dur-

ing the first month of oral-contraceptive use,[10] and then remains constant regardless of the duration of use, although few data on continuous use for more than three years are available.[10,33] When oral contraceptives are discontinued, the risk of overt venous thomboembolic disease declines within one month to the level found among women who have never used the drugs.[10,16] Thus, it appears that only current use increases the risk of overt venous thromboembolic disease. Similarly, the occurrence of spontaneously resolving, subclinical thrombosis that is detectable by plasma fibrinogen chromatography has been found to increase during the first month of use and then to remain constant for up to eight years of continuous use.[31]

Magnitude of Risk Attributable to Oral Contraceptives

The magnitude of the increase in the risk of overt venous thromboembolic disease that occurs during oral-contraceptive use has been measured in numerous case-control and cohort studies.[11] In the case-control studies, the relative risk of overt venous thromboembolic disease in current users, as compared with nonusers, has been found to be approximately 3 for idiopathic superficial venous thrombosis (i.e., first episodes of superficial venous thrombosis in previously healthy women), in the range of 4 to 11 for idiopathic deep venous thrombosis or pulmonary embolism, and in the range of 1.5 to 6 for venous thrombosis or pulmonary embolism in women with conditions that predispose to the development of venous thromboembolic disease (e.g., preexisting vascular disease, metabolic disorders, and surgery or trauma).[6-10,33-39] These findings have been similar in studies carried out in Great Britain[6-9,34] and in the United States.[10,33,36-39]

Case-control studies provided the first clear evidence that oral contraceptives do increase the risk of overt venous thromboembolic disease,[6-10] and such studies have been very useful in exploring the relation between oral contraceptives and other factors that influence the risk of venous thromboembolic disease. However, the most reliable source of information about the risk of overt venous thromboembolic disease that is attributable to oral contraceptives is the data from the two British cohort studies that were initiated in 1968.[11,16,17,20,21] In general, the results of these cohort studies are quite compatible with the results of the case-control studies, although the cohort studies have found relative risks of overt venous thromboembolic disease (in current users as compared with nonusers) that tended toward the lower end of the range reported from the case-control studies. The reason for this is not clear, although it does seem possible that physicians participating in organized cohort studies may be somewhat more cautious than others are when prescribing oral contraceptives. Because attributable risk is more meaningful clinically than relative risk, the results of these cohort studies will be emphasized here.

Table 1 shows estimates of the incidence of overt venous thromboembolic disease among current users and nonusers and estimates of the relative and attributable risk; with one exception,[38] these figures are derived from the British cohort studies.[11,16,20] Because of sampling variation and other methodologic problems, the figures (especially for postoperative venous thrombosis) are only approximate. However, they do serve to illustrate major findings. Three main points can be seen from these data.

First of all, oral-contraceptive use in Great Britain (and presumably in the United States and similar countries) during the late 1960s to mid-1970s was responsible for about 19 cases of overt idiopathic venous thromboembolic disease (first episodes of venous thromboembolic disease in previously healthy women) per 10,000 current users per year.[16,20] Approximately half these cases involved superficial leg veins only[16]; the other half involved deep leg veins, other sites, or pulmonary embolism.[16,20] Although oral contraceptives have been clearly shown to increase the risk of death from venous thromboembolic disease,[7] this effect is rare.[17,21] During over 450,000 woman-years of follow-up that began with over 60,000 women (about half using oral contraceptives) in 1968, the British cohort studies have observed only five fatalities from venous thromboembolic disease (three in current users and two in past users).

Secondly, the relative risk of postoperative venous thrombosis (about 2) is lower than that of idiopathic deep venous thrombosis or pulmonary embolism (about 4), but the attributable risk is higher.[11,16,20]

Table 1. Oral-Contraceptive Use and Risk of Venous Thromboembolic Disease.*

Type of Venous Thromboembolic Disease	Incidence		Relative Risk	Attributable Risk
	Current User	Nonuser		
	no. of cases/ 10,000 women/yr			*no. of cases/ 10,000 current users/yr*
Idiopathic †				
Superficial leg vein[16]	19	8	2	11
Deep leg vein, other sites, or pulmonary embolism[16,20] ‡	11	3	4	8
In women with predisposing conditions				
Postoperative venous thrombosis[11]	61 §	30 §	2	31 §
In women with any predisposing condition,¶ venous thrombosis or pulmonary embolism[38] ‖	Unknown	Unknown	2	Unknown

*All figures are rounded to the nearest integer.

†First episodes of venous thromboembolic disease in previously healthy women.

‡Figures represent averages from the references cited.

§Incidence per 10,000 surgical procedures.

¶E.g., preexisting vascular disease, metabolic disorder, and surgery or trauma.

‖Eighty-eight per cent of the cases included were venous thrombosis or pulmonary embolism; 12 per cent were arterial thrombosis.

If the postoperative period is approximately three months, the risk of postoperative venous thrombosis that is attributable to oral contraceptives is about 10 cases per 10,000 current users per month, whereas the risk of idiopathic deep venous thrombosis or pulmonary embolism attributable to oral contraceptives is less than one case per 10,000 current users per month.[11,16,20] This illustrates the importance of relying on attributable risk as the primary measure of the clinical importance of an effect of oral contraceptives on the occurrence of disease.

Thirdly, the relative risk of venous thrombosis or pulmonary embolism among women with a variety of medical, surgical, or traumatic conditions that predispose to venous thromboembolic disease is similar to the relative risk of postoperative venous thrombosis (about 2).[11,38] The incidence of venous thrombosis or pulmonary embolism among current users and nonusers in this group and the attributable risk have not been determined. However, it is prudent to assume that the attributable risk of venous thrombosis or pulmonary embolism among women with any predisposing condition is substantially higher than that of idiopathic deep venous thrombosis or pulmonary embolism.

Estrogen and Progestogen Content of Oral Contraceptives

There appears to be a direct correlation between the estrogen content of oral contraceptives and the risk of overt venous thromboembolic disease.[16,37,40,41] The most impressive finding is that oral contraceptives containing 50 to 80 μg of either mestranol or ethinyl estradiol seem to be only about one third to one half as likely to precipitate fatal or nonfatal pulmonary embolism as oral contraceptives containing 100 to 150 μg of these estrogens.[40] Recent data suggest that the use of oral contraceptives containing only 30 μg of estrogen may further reduce the risk of death from pulmonary embolism,[41] but this finding could be due to chance, and more data are needed. Relevant data have not shown a clear relation between the progestogen content of most oral contraceptives and the risk of pulmonary embolism or other deep venous thromboembolic diseases, although an effect may be present for some progestogens (e.g., potentiation of the estrogenic effect by megestrol acetate or diminution by norethynodrel).[40] However, one study has found a direct correlation between the amount of norethindrone acetate in oral contraceptives containing this progestogen and the risk of idiopathic superficial leg-vein thrombosis.[16] In addition, plasma fibrinogen chromatographic studies have found that one progestogen-only oral contraceptive (containing ethynodiol diacetate) increased the occurrence of subclinical thrombosis extensive enough to be detected by this approach.[31] Thus, the progestogenic component of at least some oral contraceptives appears to increase the occurrence (or size) of small thrombi that either remain subclinical or become large enough only to occlude superficial veins, but it is primarily the estrogenic component that has been found to increase the risk of development of a thrombus extensive enough to occlude a deep vein or form a pulmonary embolus.

Relation between Oral Contraceptives and Other Risk Factors

Although oral contraceptives may increase the risk of venous thromboembolic disease to a similar extent among all women, it seems more likely that the increase in risk is concentrated in specific groups of women who are somehow predisposed to this effect. The few data available on the effect of oral contraceptives on the risk of venous thromboembolic disease among women who are undergoing surgery[11,20] or who have any medical, surgical, or traumatic disorder that predisposes them to venous thromboembolic disease[38] have already been considered (Table 1). This discussion will focus on idiopathic venous thromboembolic disease — i.e., first episodes of venous thromboembolic disease in previously healthy women.

The risk of idiopathic superficial or deep venous thromboembolic disease that is attributable to oral contraceptives appears to be unrelated to age, socioeconomic status, or parity (although the incidence of idiopathic superficial venous thrombosis does increase with age among both users and nonusers).[10,16,33] The information on cigarette smoking and body weight is somewhat contradictory,[9,10,16,39,42] but it is unlikely that either mild obesity[10,39] (≤15 per cent overweight for age and height[10]) or cigarette smoking[9,16,42] has any substantial effect on the risk of idiopathic superficial or deep venous thromboembolic disease that is attributable to oral contraceptives.

In a collaborative study carried out in the United States, Great Britain, and Sweden, the risk of idiopathic deep venous thromboembolic disease was found to be related to ABO blood type.[43] Among previously healthy, nonpregnant women not using oral contraceptives, the risk of idiopathic deep venous thromboembolic disease was found to be about twice as large in women with blood types A, B, or AB as in women with blood type O. Among comparable women using oral contraceptives, the increase in risk for blood type A, B, or AB, as compared with type O, was about threefold. These findings appear to demonstrate a genetic susceptibility to idiopathic deep venous thromboembolic disease, and they suggest that oral contraceptives multiply the effect of this genetic susceptibility, so that the risk of idiopathic deep venous thromboembolic disease that is attributable to oral contraceptives may be only about four cases per 10,000 current users per year among women of blood type O, but about 12 cases per 10,000 current users per year among women of blood type A, B, or AB.[16,20,43]

Pathogenesis of Venous Thromboembolic Disease Attributable to Oral Contraceptives

Oral contraceptives appear to cause endothelial proliferation and other changes in the structure of

veins and arteries,[44] a decrease in the rate of venous blood flow,[45] and an increase in the coagulability of blood, involving many changes in the platelet, coagulation, and fibrinolytic systems.[46-49] In general, these effects are similar to the changes seen late in pregnancy; they are thought to be primarily related to the estrogenic component of oral contraceptives and are believed to increase the occurrence of venous thrombosis. However, because subclinical thrombosis appears to occur frequently and only rarely progresses to become overt venous thromboembolic disease, the specific effects of oral contraceptives that are primarily responsible for increasing the risk of overt venous thromboembolic disease (and perhaps for increasing the detectability of subclinical thrombosis) are probably those that involve a decrease in the ability to halt the progression of intravenous coagulation (by inactivating the enzyme thrombin or some of its antecedents)[32] or to dissolve fibrin clots that threaten to compromise venous circulation.[50]

Antithrombin III

The major plasma inhibitor of thrombin is antithrombin III, an enzyme that inactivates thrombin, activated factor X (or X_a, which converts prothrombin to thrombin), and certain other enzymes involved in the generation of thrombin.[32,51,52] The quantity of antithrombin III in plasma (or serum) can be directly measured by immunologic assays, and the antithrombin III activity of plasma (or serum) can be indirectly measured by functional assays of the rate at which a test specimen inactivates thrombin or X_a.[32,52]

Numerous studies have demonstrated that a genetic deficiency in antithrombin III is accompanied by an increased risk of overt venous thromboembolic disease[51,53,54]; in genetically deficient persons, both the quantity (determined by immunologic assay) and the activity (determined by functional assay) of antithrombin III have been observed to be substantially below normal.[32] In contrast, women using oral contraceptives have been observed to have normal or nearly normal levels of antithrombin III (by immunologic assay), whereas antithrombin III activity (by functional assay) has been found to be substantially decreased.[32,52] This disparity between quantitative and functional measurements of antithrombin III has been demonstrated in both plasma and serum of women using oral contraceptives,[32,52] and therefore it cannot be due to the consumption of antithrombin III that occurs during coagulation; this consumption would produce only a difference between plasma and serum levels, not a difference between the results of quantitative and functional assays in plasma or serum.[55,56] The decreased activity of antithrombin III that has been described during oral-contraceptive use has been found to appear within the first month of use,[57] to be unrelated to the duration of use,[32] and to disappear within one month after oral contraceptives are discontinued.[57] During oral-contraceptive use, the proportion of women whose antithrombin III activity is approximately 60 per cent of normal or lower appears to be increased from about 2 per cent (the proportion among nonusers) to about 16 per cent[32]; a reduction in antithrombin III activity of about 50 per cent or more is believed to increase the risk of overt venous thromboembolic disease substantially,[53] and a reduction of 20 per cent or more has been found to be highly predictive of the occurrence of subclinical venous thromboembolic disease that is extensive enough to be detected by ^{125}I-fibrinogen uptake.[30] Oral contraceptives containing 75 to 150 μg of mestranol or ethinyl estradiol appear to decrease antithrombin III activity to a greater extent than do oral contraceptives containing only 50 μg.[58] When given without estrogen, most progestogens do not appear to decrease antithrombin III activity, although one, lynestrenol, has been found to do so; this progestogen is believed to undergo greater conversion to metabolic products with estrogenic activity than others do.[59] Antithrombin III levels (measured by immunologic assay) have been observed to be lower in women of blood types A, B, and AB (especially type A_1) than in women of blood type O, probably because of increased consumption of antithrombin III that is related to increased activation of factor X, the origin of which is uncertain.[60] However, the important question of whether oral-contraceptive use is accompanied by a critical decrease in antithrombin III activity (50 per cent or greater) more frequently in women of blood types A, B, or AB than in women of blood type O has not been answered.

Fibrinolytic Activity

The fibrinolytic capacity of blood derives from the conversion of circulating plasminogen to plasmin, an enzyme that degrades fibrin and fibrinogen.[50] In blood, this conversion is effected by plasminogen activators, which are released by endothelial cells.[50] The amount of plasminogen activator present in endothelium can be determined by histochemical techniques, and the capacity of a person to increase the spontaneous fibrinolytic activity of blood (which is normally low) through accelerated release of plasminogen activators from endothelium can be determined by measurement of the fibrinolytic activity of blood before and after venous occlusion.[50]

Studies in patients with venous or arterial thromboembolic disease have generally found that the spontaneous fibrinolytic activity of blood and the fibrinolytic response to venous occlusion are subnormal.[50,61-64] Therefore, it initially seems paradoxical that ethinyl estradiol has been found to increase both the spontaneous fibrinolytic activity of blood and the fibrinolytic response to venous occlusion (at least one progestogen, medroxyprogesterone acetate, does not appear to have this effect).[50] However, these effects of the estrogenic component of oral contraceptives appear to be accompanied by a decrease in the plasmin-

ogen-activator content of endothelium,[65] indicating that increased fibrinolytic activity during oral-contraceptive use[47] probably represents increased release of plasminogen activators from endothelium in response to increased intravascular coagulation — a response that may not be adequate in all women. This concept is supported by studies in women who have had overt venous thromboembolic disease during oral-contraceptive use: After oral contraceptives have been discontinued and recovery from venous thromboembolic disease has occurred, the proportion of these women who have subnormal amounts of plasminogen activators in vein-biopsy specimens and subnormal fibrinolytic responses to venous occlusion has been found to be greater than the corresponding proportion among similar women not using oral contraceptives who have no history of overt venous thromboembolic disease.[64,66] The implication is that women in whom overt venous thromboembolic disease develops during oral-contraceptive use do not have an adequate increase in fibrinolytic activity in response to the increased subclinical thrombosis that occurs during oral-contraceptive use.

In summary, current information suggests that oral contraceptives increase both the risk of overt venous thromboembolic disease and the occurrence of subclinical venous thromboembolic disease, primarily by increasing the size of the intravenous clots formed in response to endothelial injury or other stimuli that lead to thrombin formation. This effect appears to be primarily due to the estrogenic component of oral contraceptives, to involve decreased antithrombin III activity, and probably to be exacerbated in women who do not have an appropriate increase in fibrinolytic activity in response to increased intravenous clotting.

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MEDICAL INTELLIGENCE

PROGNOSIS IN POSTURAL (ORTHOSTATIC) PROTEINURIA

Forty to Fifty-Year Follow-up of Six Patients after Diagnosis by Thomas Addis

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THE excellent prognosis traditionally offered to patients with postural (orthostatic) proteinuria has come under some suspicion in recent years; it has been stated that "large numbers of carefully studied patients will have to be followed over long periods of time before the natural history of postural and intermittent proteinuria can be finally elucidated." [1] To study this question, we reevaluated six patients in whom the diagnosis was made by Thomas Addis 42 to 50 years ago. Three had died of nonrenal causes (pulmonary carcinoma, myocardial infarction, and trauma) 42, 45, and 50 years after diagnosis; no renal disease was ever detected in any of these three. The other three are alive 42 to 45 years later, without proteinuria and with apparently normal renal function, although one initially had an extremely severe disease process with decreased renal function. Three of the five men had transitory urinary-tract infections within the past decade. Thus, one can expect long-term survival of patients with postural proteinuria.

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METHODS

Of 54 records of patients in whom Addis had made the diagnosis of "orthostatic albuminuria," [2] six had been saved by one of us (D.A.R.), who had seen four of these six patients with Addis and reported on two of them.[3,4]

The basic method of study at that time consisted of sediment counts personally performed by Addis or D.A.R. and determination of protein excretion rates in timed urine samples of about eight hours collected at night with the patient recumbent and every four hours or so consecutively by day with the patient in a nonrecumbent position. Frequently, every voiding of urine was timed and examined. Occasionally great care was needed to ensure rest in bed for hours before the start of the collection of the all-important specimen obtained during recumbency. Protein, detected with techniques using heat and acetic acid, was measured according to the method of Shevky and Stafford, which depends on the volume of protein precipitated by phosphotungstic acid (Tsuchiya's reagent) and packed by standardized centrifugation in a tube with a graduated, narrow neck.[5] The upper limits of normal were considered to have been 0.20 g for protein, 10,000 casts, 2,000,000 erythrocytes, and 2,000,000 leukocytes and epithelial cells, with all values expressed per 24 hours.[4]

All six patients were traced. Information about their states of health was obtained either from them and from hospital and other records, through the kindness of many physicians, friends, and sub-