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# MEDICAL BULLETIN

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*Pelvic Tilt*

*Antihemophiliac Globulin*

# University of Minnesota Medical Bulletin



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# Staff Meeting Report

## The Relationship Between Pelvic Tilt and Lumbar Lordosis*

Herbert A. Schoening, M.D.†

The important roles of the forward inclination of man's pelvis and the associated lordosis of the lumbar spine in providing a stable posture have been frequently discussed in the literature.[1,2,3,4] Man's assumption of an erect posture is a favorite topic of the anthropologist.[5] Likewise, body mechanics and correct posture are of paramount importance to physical educationalists.[3,6] Physicians also have an interest in this subject because of the frequently occurring back problems secondary to disturbed body alignment. This paper will review the important factors influencing the tilt of the pelvis and will illustrate these principles through a dramatic case report of the treatment of a 34-year-old girl with extreme lumbar lordosis resulting from excessive forward rotation of the pelvis.

H. A. SCHOENING

### Normal Anatomy

The lumbar spine must respond to the base upon which it rests. This base consists of the sacrum, semi-rigidly fixed by ligaments to the innominate bones, which are joined anteriorly at the symphysis pubis. Mechanically, the pelvis is the keystone for bearing the weight of the entire trunk, upper extremities, and head and for transmitting the weight of the suprafemoral mass to the lower extremities, whether reciprocally when walking or bilaterally when standing. To balance effectively the superincumbent load of the head, arms, and trunk (H.A.T.), this precisely architectured structure rotates in its sagittal, horizontal, and frontal planes. The hip joint acts as a pivot allowing the pelvis to alter its position freely within its range of motion; by thus changing the vertebral curves above, the pelvis

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 20, 1959.

†Medical Fellow, Department of Physical Medicine and Rehabilitation

maintains man's balance in spite of his actions or attitude. Therefore, factors affecting the mobility of the hip joints will change the spatial relation of the pelvis. Hence compensatory adjustments of the spine are necessary to maintain the center of gravity over the feet.

## Normal Standing

In the standing position the center of gravity of the supra-femoral mass is located at a point 69 per cent of the thigh length vertically above the mid-hip center.[7] Kottke and Kubicek in reporting the work of du Bois-Reymond found that during relaxed standing, this center of gravity lay 9 millimeters posterior to the hip center.[8] The line of gravity, represented by a vertical drop from the center of gravity of the H.A.T., falls through or posterior to the hip and slightly anterior to the knee and the lateral malleolus of the ankle joint.[9] Therefore, in normal relaxed standing the superincumbent weight locks both the hip and the knee in extension. Ligaments then support the hip and knee joints and muscular effort is not required. Electromyographic studies on the postural muscles of the lower extremities have demonstrated electrical silence, except in the soleus muscles (which are on stretch) when standing.[10] By understanding the simple mechanics of normal upright posture, one can then analyze the factors responsible for abnormal posture.

Since the hips are fully extended in the normal upright posture, the angular relationship between the pelvis and femur must be recognized and measurable. Roentgen evaluation of the pelvi-femoral angle is an accurate technique but is expensive and not always feasible. Mundale and co-workers[11] have described a simple means of relating hip extension to the pelvis rather than to the trunk, as is the common clinical practice. They established the longitudinal axis of the innominate bone by dropping a perpendicular through the summit of the greater trochanter of the femur from a line drawn between the anterior and posterior superior iliac spines. Mundale measured hip extension in the relaxed standing position on 20 normal college women and 16 normal college men. In the men the average pelvi-femoral angle was 170°, while in the women the average was 165°. Individual measurements did not vary more than 5° on comparison with the roentgenographic mensuration.

The degree of pelvic inclination is directly related to the extensibility of the hip joint.[8] If there is tightness in the flexor ligaments and the fascia surrounding the flexor muscles of the hip joint, the pelvis will be rotated forward, assuming a more horizontal attitude. The variation in degree of pelvic inclination

in persons with normal hip extension can also be explained by the relationship of the sacrum to the innominate bones at the sacroiliac joints. If the sacrum is more horizontally oriented, as is commonly seen in the android pelvis,[12] the sacral angle will be wider. To determine the orientation of the innominate bones to the inclination of the sacrum, the angle between the longitudinal axis of the innominate bones and the plane of the superior surface of $S_1$ was measured by the author from roentgenograms of 19 normal physical therapy students. This angle varied considerably, ranging between 47° and 80°.

The degree of pelvic inclination influences the inclination of the superior surface of $S_1$ and is related to the angle formed between the last lumbar and the first sacral vertebrae. The range of values in normal individuals is quite wide. In a study of the roentgenograms of 100 normal men over 40, Splithoff[13] found the angle of inclination of the superior surface of $S_1$ to vary between 25° and 74°. Von Lackum[1] and Mitchell,[2] both of whom measured the sacral angle on normal cadavers, arrived at average values of 42° and 41° respectively. Von Lackum also reported a wide range of angles varying from 28° to 80°. The wide range of "normal" values for pelvic inclination—as indicated in the above studies as well as in studies measuring the lumbosacral angle[14]—suggests that the postures of the individuals measured were not, in fact, all "normal."

The final important postural variable is the degree of lumbar lordosis in the normal standing posture. This can be determined roentgenographically by measuring the angle found between the planes of the superior surface of the first lumbar and the superior surface of the first sacral vertebrae. In 11 normal young women studied in this department, the lumbar lordosis was found to average 60°. The greatest contributor to this angle was the $L_5$-$S_1$ articulation, which measured 20°. The $L_4$-$L_5$ interspace had an angle of 16°, and progressing up the lumbar spine, one finds decreasing angulation. Keegan's study of the lumbar curve showed similar relationships.[15]

### Abnormal Posture

As limitation of hip extension develops, the pelvis tilts forward. The center of gravity of the suprafemoral mass will then lie anterior to the hip and knee joints, necessitating contraction of the hip extensor muscles to maintain balance. In a young, flexible person, the lumbar spine compensates by hyperextending so that the center of gravity of the head, arms, and trunk is displaced backward and a new balance is reached. As the degree of hip flexion contracture increases, the lumbar lordosis

becomes more exaggerated, until the limit of back extension is reached. At this point, the posture decompensates and the afflicted individual reverts to the quadruped stance by using crutches or canes to broaden the weight-bearing base.

If the spine loses its mobility as a result of degenerative changes or disease, compensatory lumbar lordosis cannot occur. The resultant posture is again that of the quadruped, as the hip flexing force of gravity necessitates the use of walking aids. Flattening of the lumbar spine and loss of hip extension secondary to prolonged sitting or immobilization in bed often necessitate the use of a cane in the later years.

## Case Report

The following case report illustrates the relationship between hip flexion contractures, excessive pelvic tilt, and lumbar lordosis. The patient, a 34-year-old white woman, had extreme lumbar lordosis which followed the alteration of her normal postural mechanics resulting from muscular dystrophy. She was admitted to the Physical Medicine and Rehabilitation Service of the University of Minnesota Hospitals for treatment designed to restore orthograde ambulation.

The first sign of her disease was bilateral facial weakness and atrophy noted at the age of three years. No further muscular weakness was observed until the patient was 11 years old, when weakness of her upper extremities was detected and a diagnosis of muscular dystrophy was made.

By the age of 15, weakness in the lower extremities was developing and a progressing lumbar lordosis was noted. At 24 years the patient required assistance when walking, and over the next 10 years independent ambulation became progressively difficult. At the age of 33, the patient was confined to a wheelchair.

Serial examinations of the muscular strength were made on the patient over the 12 year period prior to this hospital admission. From the initial examination at age 18 until the patient was about 25 years old, her weakness did not increase. For the next three years her strength was noted to decline but thereafter did not change during the following six years.

Examination of muscular strength on the patient's admission to the Physical Medicine and Rehabilitation Service showed trace function in the abdominal muscles and hamstrings, poor function in the hip extensors, and good function in the hip flexors, knee extensors, and triceps surae. This strength is usually adequate for ambulation with canes, but the structural deformities manifested by severe hip flexion contractures precluded biped walking. By the technique described by Mundale, the

patient's hip extension measured 115° on the right and 100° on the left. The lumbar lordosis, as measured by the angle between the planes of the superior surfaces of the first lumbar vertebra and first sacral vertebra, was 86°—i. e., 26° more than the average of the normal group.

The bilateral hip flexion contractures were released surgically. Through anterior crescent shaped incisions, the tensor fascia lata and iliotibial band were sectioned. The rectus femoris and the sartorius were divided. The remaining fibrotic structures which were not definitely identifiable were also divided. Since the anterior capsules of the hip joints were not contracted, they were not cut. The nerves and blood vessels across the joint were found to be under tension limiting complete extension. The skin also was under tension when sutured and was bound tightly to the musculature of the thigh and pelvis by subcutaneous fibrosis. Following closure, the legs were enclosed in bilateral long leg casts. As a result of this surgical intervention, the patient gained 15° of hip extension on the right and 20° on the left. In addition to the described hip flexion contractures, the patient also had contractures of the triceps surae causing limitation of ankle dorsiflexion. Two weeks before his surgery, Z-plasties of the gastrocnemius tendons had been performed; this procedure together with a prolonged stretching of the plantar flexors, permitted the patient to develop dorsiflexion to a neutral position.

On the fourth day after surgery, daily supine stretches to the hip flexor muscle groups were instituted. With hips flexed to 90° the anterior superior iliac spines were strapped to the posterior shell of a body cast to fix the bony pelvis. In the Thomas position, the hip flexor areas of both legs were stretched independently for a period of one-half hour a day, seven days a week. At first only the weight of the leg provided the stretching force, but later weights were added to the dependent leg above the knee to increase the force of the stretch. Simultaneously with the supine stretch, friction massage was instituted to mobilize the skin above the incision. The massage was directed toward the incision from above and below in a direction perpendicular to the incision line itself. Supine stretches of this type were maintained for one month, and by these means the patient gained an additional 30° of hip extension on the right and 35° on the left; this gave her a maximum hip extension of 160° on the right and 155° on the left.

At the second month after surgery, prone stretching of the hip flexors was substituted for the supine stretch. In the prone stretch, the pelvis is also fixed. The hips are first flexed to 90°, and a strap across the ischial tuberosities is applied to hold the

bony pelvis against a narrow board. A second board placed under the leg is propped up into position, forcing the leg that is being stretched into extension. This prone stretching was carried out for two half-hour periods daily until the patient was discharged. At discharge the patient had a maximum hip extension of 173° on the right and 162° on the left. The combination of surgical intervention and daily stretching initiated immediately thereafter restored a total of 62° of extension on the right and 58° on the left to bring the patient's maximum hip extension within the normal range.

As hip extension improved, ambulation training was started, and a direct attack on the fixed lumbar lordosis was instituted. To stretch the lumbar spine into flexion a prolonged gravity stretch in the prone position was attempted without success. Later a turnbuckle plaster body cast was applied, but this too was unsuccessful in increasing lumbar flexion because the pelvis could not be fixed satisfactorily.

Finally, a Williams brace proved successful in providing a continuous stretch into lumbar flexion. The Williams brace exerted a flexing force on the lumbar spine by applying pressure anteriorly on the lower thoracic vertebrae and on the sacrum. Counterpressure was applied in a posterior direction on the abdomen by a canvas apron. As the exaggerated lordosis gradually decreased, the straps joining the lateral uprights to the sacral bar were shortened, thereby increasing the flexing force.

To determine the gains made in decreasing the patient's lumbar lordosis, roentgenograms were taken in maximum forced flexion of the lumbar spine. The measurements of the patient's lumbar lordosis by the technique described earlier in this paper were compared with normal maximum forced flexion as reported by Keegan.[15] On admission, the patient had 55° of lumbar lordosis caused by maximum flexion of the lumbar spine. Eleven months after the Williams brace was applied, the patient had gained 25° but was still lacking 42° of lumbar flexion when compared with Keegan's data.

The ambulation program was initiated one month after hip surgery and consisted of balance training and knee control in the parallel bars. Four weeks later the patient began walking in the parallel bars with a tibial lift on the right to assist foot dorsiflexion. Three months after surgery she was walking out of the parallel bars with Canadian crutches. Endurance and strength gradually improved until the patient was able to walk 50 yards without stopping. She later graduated to standard canes for balance only and was able to discard her wheelchair. The patient was able to re-establish orthograde ambulation because the

structural problems of hip flexion contractures, excessive forward tilt of the pelvis, and exaggerated lumbar lordosis had been corrected.


## Summary

The maintenance of the erect human posture without expenditure of muscular energy is dependent on pelvic inclination and lumbar lordosis. The degree of pelvic inclination is directly related to the extensibility of the hip joints. The lordosis of the lumbar spine is a compensatory mechanism to maintain the center of gravity of the head, arms, and trunk over or posterior to the hip joint centers. As the pelvis tilts forward, lordosis increases. With rotation in the opposite direction, flattening of the lumbar spine occurs. Therefore, factors influencing the mobility of the hip joints will alter the attitude of the pelvis and of the lumbar spine.


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# Staff Meeting Report

## An Assay of Antihemophiliac Globulin Activity in the Carrier Female*†

Herschel P. Bentley, Jr., M.D.‡
and
William Krivit, M.D., Ph.D.§

Since Hay,[1] in 1813, described the first pedigree of hemophilia in the Appleton-Swain family, many attempts have been made to demonstrate an abnormal coagulation mechanism in the human carrier female. These have ranged from determinations of clotting times[2,3] to the more refined studies of the thromboplastin generation test,[4,5,6,7] prothrombin consumption,[8] plasma recalcification times,[6] and antihemophiliac globulin (AHG) assays.[9] Some of these studies have shown that a slight coagulation defect exists in carriers, but most reports have failed to confirm conclusively that carriers have abnormal coagulation mechanisms. Pitney and Arnold,[7] however, using a sensitive modification of the thromboplastin generation test, showed recently that a mild deficiency of AHG existed in a majority of the female carriers they studied. Therefore, a very sensitive assay method for AHG seems imperative if one is to demonstrate this possible AHG deficiency in carriers.

H. P. BENTLEY

Shinowara,[10] Quick *et al.*,[11] and Georgatsos *et al.*[12] have demonstrated a clotting factor in human red blood cell stroma, termed "erythrocytin" by Quick,[13] which is liberated after hemolysis of erythrocytes. This factor has been shown to have a very weak thromboplastic action as it will change only 7 per cent of one unit of prothrombin to thrombin when substituted for thromboplastin in the normal one-stage prothrombin time.[10]

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‡Medical Fellow, Department of Pediatrics
§Assistant Professor, Department of Pediatrics

Presumably, however, erythrocytin interacts with antihemophiliac globulin (AHG) in platelet poor normal plasma to cause a pronounced increase in the prothrombin consumption values as measured by the method of Quick.[13] In contradistinction, if this erythrocytin is added to platelet poor plasma from a patient with AHG deficiency, the prothrombin consumption values do not change. Therefore, if increasing minute amounts of normal plasma are added to a substrate of erythrocytin and hemophiliac plasma, the increasing prothrombin consumption values bear a direct linear relationship to the increasing amounts of normal plasma added. By means of this technique the minute difference between the AHG content of 0.0005 ml. and 0.0008 ml. of normal plasma can be detected. The purpose of this study is to determine whether or not a deficiency in the plasma AHG content in carrier females can be detected by this method.

## Clinical Material

The hemophiliac patients in this study were previously proved to have AHG deficiencies by the thromboplastin generation test. Unless otherwise specified, all had severe hemophilia and did not have a partial deficiency of AHG. Since they all had normal bleeding times, none of the patients could be classified as exhibiting "vascular hemophilia."

The criteria established for the definition of carriers were similar to those of Merskey and MacFarlane.[8] Definite carriers were established as: 1) mothers who had two or more children with either hemophilia or proved carrier states or both; 2) mothers with only one hemophiliac or proven carrier offspring and with a positive family history of classic hemophilia; 3) daughters of hemophiliac males. The probable carriers were defined as mothers who had one hemophiliac offspring proved to have severe AHG deficiencies or proven carrier but no other family history of hemophilia.

## Material and Methods

The *substrate* for the test consisted of erythrocytin, hemophiliac plasma, and aged serum.

The *hemolysate* containing *erythrocytin* was prepared by the method of Georgatsos.[12] Nine volumes of blood were collected in a siliconized syringe and mixed with one volume of 0.1 M sodium oxalate solution. This was centrifuged for five minutes at 1000 r.p.m., and the plasma and buffy coat were removed. The plasma was replaced with an equal volume of 0.85 per cent saline and was mixed thoroughly by gentle tilting. The mixture was again centrifuged at 1000 r.p.m. for five

minutes and the supernate was removed. The cells were resuspended by being tilted in an equal volume of 0.85 per cent saline after which the mixture was centrifuged at 2000 r.p.m. for 20 minutes; this step was repeated three times. At the end of this time, the cells were resuspended in a volume of saline equal to the original plasma volume, were vigorously mixed by stirring, and were frozen at −20° C. for 12 hours. The hemolysate was then thawed and distributed in 1 ml. aliquots and was stored at −20° C. (It can be repeatedly thawed and refrozen without losing its potency.)

*AHG-deficient plasma* for the substrate was obtained from known hemophiliac male patients who were shown to have prothrombin consumption times of 8 to 10 seconds as determined by the method of Quick.[13] If the substrate plasma had a prothrombin consumption value above 8 to 10 seconds, the resulting erythrocytin prothrombin consumption values were above the range of normal. The blood was drawn and mixed thoroughly but gently with 1 ml. of 0.1 M sodium oxalate solution per 10 ml. of blood. This was centrifuged at 3500 r.p.m. for 20 minutes, and the plasma was then immediately frozen at −20° C. in 1 ml. aliquots. Only two donors were used as the sources of hemophiliac plasma throughout the study; their plasmas gave identical prothrombin consumption values.

*Aged serum* was prepared by the method of Quick.[13]

The quantities of *substrate* material consisted of 0.1 ml. of hemolysate containing erythrocytin, 1.0 ml. of AHG deficient plasma, and 0.001 ml. of aged serum.

*Test plasma* was obtained by drawing 5 cc. of blood from the fasting patient (normal, hemophiliac, or suspected carrier) by means of a siliconized syringe and needle. This 5 cc. of blood was added to 0.5 ml. of 0.1 M sodium oxalate solution and was immediately centrifuged at 10,000 r.p.m. in the International cold centrifuge at 4° C. for 10 minutes. The resultant platelet poor plasma was carefully pipetted off and was either used immediately or frozen rapidly by immersion in a dry ice and acetone mixture for later use. The plasmas that had been frozen were thawed by being placed in a water bath at 37° C.

The test plasma was diluted just before the beginning of the procedure by having 0.11 ml. of test plasma accurately pipetted into 9.9 ml. of 0.85 per cent saline. The resulting diluted plasma was then added in aliquots of 0.01 ml., 0.025 ml., 0.05 ml., 0.08 ml., and 0.1 ml. respectively to tubes containing the substrate material.

The test plasma and substrate mixture were allowed to incubate together at 37° C. for one minute, after which 0.1 ml.

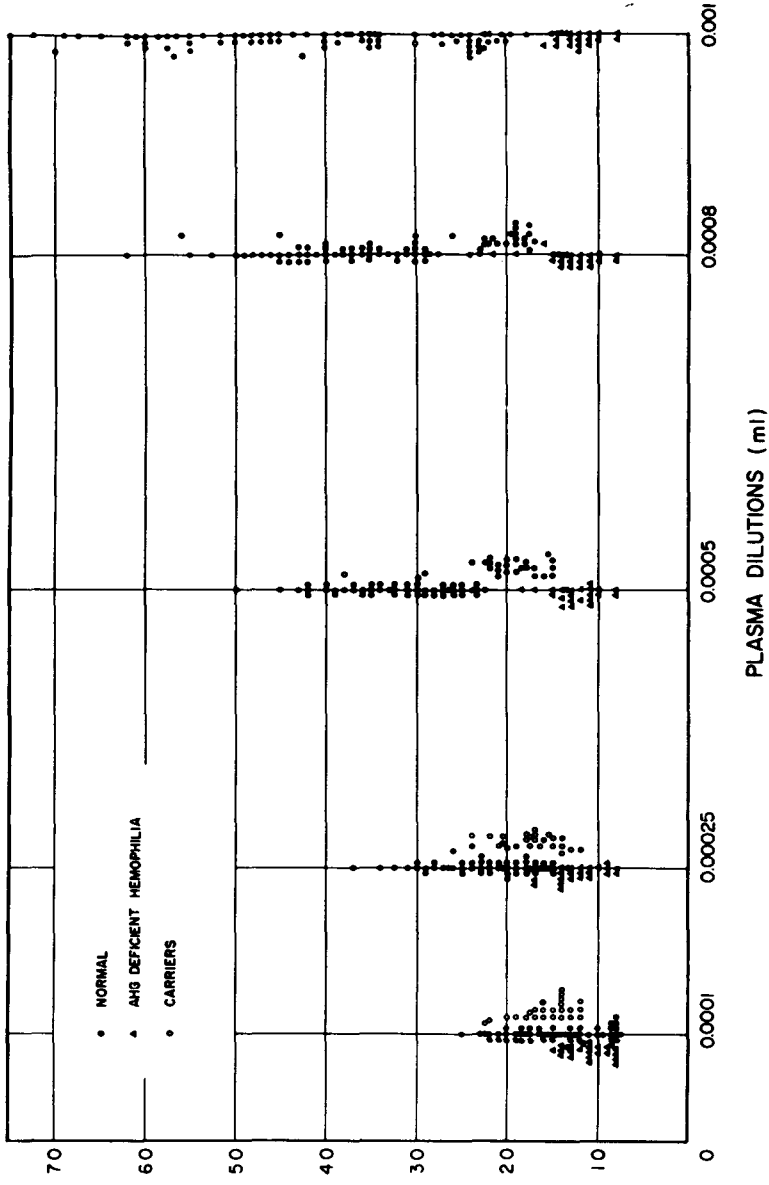


Fig. 1. Demonstration of the erythrocytin prothrombin consumption time in seconds at various plasma dilutions of normals, female carrier, and hemophiliac patients

of 0.25 M calcium chloride solution was added. The tubes were then carefully observed for formation of a solid clot. Exactly 15 minutes after clotting occurred, the clot was loosened with a stirring rod. The tube was then centrifuged at 2500 r.p.m. for one minute and returned to the water bath and incubated for 45 minutes longer. The serum in each tube was then measured for prothrombin content by the method of Quick.[13]

The source of fibrinogen was human plasma treated with barium sulfate prepared by mixing 100 mg. barium sulfate per 1 ml. plasma; shaking constantly for five minutes; centrifuging; and then using the supernatant plasma.

One-tenth ml. of barium sulfate-treated plasma, 0.1 ml. rabbit brain thromboplastin (Difco Laboratories), and 0.1 ml. of 0.025 M calcium chloride solution were mixed and allowed to incubate for a few seconds at 37° C. One-tenth ml. of the test serum was then blown into the mixture, and the time in seconds

TABLE 1

MODIFIED ERYTHROCYTIN TEST ON NORMALS

| | Prothrombin Consumption in Seconds | | | | | | Prothrombin Consumption in Seconds | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Controls | .01 | .025 | .05 | .08 | .1 | Controls | .01 | .025 | .05 | .08 | .1 |
| 1 | 7.5 | 15 | 22.5 | 28 | 34 | 26 | 12 | 18 | 25 | 30 | 40 |
| 2 | 10 | 17 | 27 | 35 | 45 | 27 | 12.5 | 19 | 30 | 35 | 45 |
| 3 | 8 | 15 | 23.5 | 31 | 35 | 28 | 17.5 | 25 | 31 | 41 | 53.5 |
| 4 | 20 | 28 | 39 | 48 | 65 | 29 | 15 | 20 | 26 | 38 | 46 |
| 5 | 11 | 17 | 29 | 31 | 49 | 30 | 13 | 20 | 25 | 30 | 34 |
| 6 | 8 | 15 | 23.5 | 32 | 38 | 31 | 13 | 20 | 30 | 34 | 36 |
| 7 | 10 | 15.5 | 25 | 31 | 37.5 | 32 | 13.5 | 20.5 | 31 | 37 | 46 |
| 8 | 15 | 21 | 29 | 35 | 40 | 33 | 21 | 28 | 37 | 49 | 58 |
| 9 | 17.5 | 24 | 32.5 | 40 | 48 | 34 | 20 | 30 | 42 | 47 | 60 |
| 10 | 21 | 26 | 35 | 45 | 62 | 35 | 15.5 | 23 | 32.5 | 42 | 50 |
| 11 | 8 | 16 | 27 | 35 | 42 | 36 | 16 | 24 | 33 | 42 | 55 |
| 12 | 14.5 | 20 | 30 | 40 | 50 | 37 | 16 | 22 | 32.5 | 40 | 55 |
| 13 | 8.5 | 16 | 24 | 33 | 40 | 38 | 8 | 17 | 24 | 29 | 35 |
| 14 | 9 | 18 | 26 | 34 | 38 | 39 | 17.5 | 23 | 34 | 44 | 61 |
| 15 | 8 | 16.5 | 26 | 30 | 36 | 40 | 23 | 32 | 50 | 62 | 70 |
| 16 | 12 | 17.5 | 28 | 32 | 37 | 41 | 22.5 | 34 | 45 | 55 | 67.5 |
| 17 | 8.5 | 17 | 23.5 | 29 | 34.5 | 42 | 22 | 31 | 42 | 46 | 60 |
| 18 | 16.5 | 22 | 27 | 37 | 45 | 43 | 20 | 30 | 42 | 45 | 60 |
| 19 | 22 | 32.5 | 43 | 52.5 | 69 | 44 | 19 | 27 | 40 | 44 | 57.5 |
| 20 | 12 | 22 | 30 | 40 | 51.5 | 45 | 18.5 | 26 | 38 | 43 | 57.5 |
| 21 | 8.5 | 18 | 27.5 | 36 | 47 | 46 | 18.5 | 29 | 39 | 43 | 56 |
| 22 | 14 | 19 | 32 | 39 | 46 | 47 | 18.5 | 25 | 32 | 43 | 55 |
| 23 | 19 | 29 | 40 | 50 | 62 | 48 | 17 | 30 | 36 | 39 | 50 |
| 24 | 15 | 23 | 35 | 42 | 51.5 | 49 | 8 | 18 | 26 | 36 | 43 |
| 25 | 13 | 21 | 28 | 38 | 53.5 | 50 | 8 | 20 | 24 | 30 | 35 |

until the first formation of fibrin strands was noted. The resultant time was the erythrocytin prothrombin consumption time.

No difference was observed in the AHG activity in test plasma of normal subjects, hemophiliac patients, or carriers when the plasma was used either immediately or after rapid freezing, storage, and later thawing.

## Results

The normal range of erythrocytin prothrombin consumption time was determined on 30 male and 20 female subjects. These results are shown in Figure 1 and Table 1. As increasing amounts of normal plasma were added to the test substrate of erythrocytin, hemophiliac plasma, and aged serum, the prothrombin consumption in seconds steadily rose. The average time at 0.0001 ml., 0.0005 ml., 0.0008 ml. and 0.001 ml. was 14.4 secs., 31.6 secs., 38.4 secs., and 48.7 secs., respectively. This rise was presumed to be due to the increasing amounts of AHG added. No difference was observed between the range and average of normal male and female patients.

In addition, the variations of 21 hemophiliac patients are shown in Figure 1 and Table 2. In contrast to the results obtained when normal plasma was used, increasing amounts of hemophiliac plasma (AHG deficient) did not increase the prothrombin consumption. This was presumably due to the absence of AHG in the tested hemophiliac plasma.

Thus, it seems evident this test system is actually measuring AHG activity. The test is sensitive enough to determine the difference in the AHG activity between a dilution of 0.0005 ml. and of 0.0008 ml. of normal test plasma.

In Figure 1 and Table 2, the prothrombin consumption activity produced by plasma of female carriers is recorded. Figure 2 shows the specific differences obtained using 0.0008 ml. of test plasma. All except three of the carriers fall in the area between the normal range and the range of hemophiliac patients. These differences are statistically significant, as shown in Table 3. At the dilutions of 0.0005 ml., 0.0008 ml., and 0.001 ml., the differences between carriers and normals and the differences between carriers and hemophiliacs show a "p" value of less than 0.0001.

Figure 3 and Table 4 show the AHG levels for three generations in one family. Notice that the son and the grandson have identical AHG assay levels, and the mother and the daughter have almost identical amounts. This was the only instance in which we were able to assay three generations in the same family. The constancy of AHG levels in families, however, is

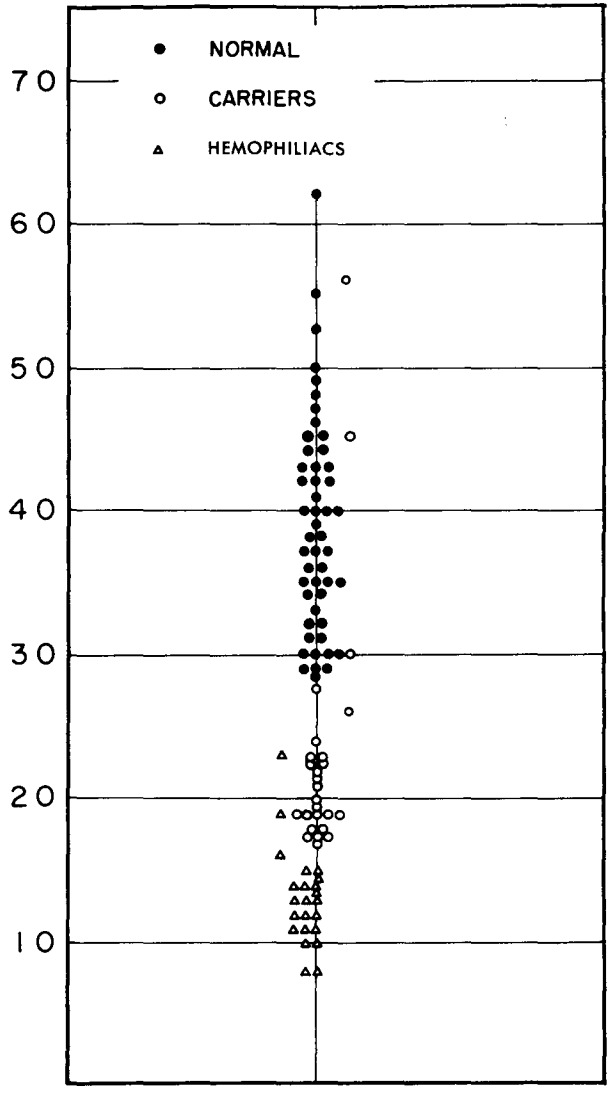


Fig. 2. Demonstration of the erythrocytin prothrombin consumption time in seconds at 0.0008 ml. dilution of normal, AHG hemophiliac, and female carrier plasmas

further shown in Table 5. In family number 1, all the sisters have the same prothrombin consumption values; their three affected hemophiliac offspring have erythrocytin prothrombin consumption values of 11, 8, and 9 seconds, respectively. The remaining two families demonstrate that the erythrocytin prothrombin consumption values of hemophiliac offspring born of the same carriers are identical (family 2—10 and 11 seconds; family 3—14 seconds).

Table 6 records the clinical manifestations of the hemorrhagic tendencies for these carriers. All but six of the carriers had a subjective history of very easy bruising. One mother had a severe hemorrhage following an operation and required two pints of blood. Following tonsillectomies, two mothers had profuse bleeding lasting three days in both instances. Two mothers had histories of prolonged bleeding after tooth extractions. None

TABLE 2

MODIFIED ERYTHROCYTIN TEST

| Carriers | Prothrombin Consumption in Seconds .01 | .025 | .05 | .08 | .1 | Family Hemophiliacs | Prothrombin Consumption in Seconds .01 | .025 | .05 | .08 | .1 | Plain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Mrs. | 13 | 14 | 17 | 18 | 24 | 1. P.C. | 9 | 9 | 11 | 11 | 12 | 8 |
| 2. Mrs. | 22 | 24 | 22 | 22.5 | 24 | 2. D.L. | 10 | 12 | 11 | 12 | 12 | 10 |
| 3. Mrs. | 12 | 14 | 15 | 19 | 23 | 3. M.S. | 11 | 15 | 14 | 14 | 14 | 11 |
| 4. Mrs. | 16 | 17.5 | 20 | 28 | 30 | 4. L.H. | 11 | 12 | 13 | 15 | 15 | 16 |
| 5. Mrs. | 8 | 12 | 12 | 18 | 24 | 5. D.N. | 8 | 8 | 9 | 12 | 12 | 8 |
| 6. Mrs. | 25 | 26 | 29 | 45 | 57 | 6. J.Q. | 11 | 11 | 10 | 10 | 10 | 10 |
| | | | | | | D.Q. | 8 | 9 | 11 | 11 | 11 | 9 |
| 7. Mrs. | 13 | 14 | 16 | 17.5 | 17 | 7. B.M. | 14 | 14 | 16 | 14 | 14 | 16 |
| | | | | | | J.M. | 14 | 14 | 15 | 15 | 14 | 14 |
| 8. Mrs. | 14 | 15 | 15 | 18 | 24 | 8. M.D. | 8 | 8 | 8 | 8 | 8 | 8 |
| | | | | | | J.D. | 8 | 9 | 9 | 9 | 9 | 9 |
| 9. Mrs. | 15 | 20 | 18 | 17 | 23 | 9. | | | | | | |
| 10. Mrs. | 12 | 16.5 | 18.5 | 20 | 22.5 | 10. D.A. | 13 | 13 | 13 | 13 | 13 | 13 |
| 11. Mrs. | 14 | 17 | 21 | 22 | 26 | 11. C.M. | 14 | 14 | 14 | 14 | 14 | 14 |
| 12. Mrs. | 15 | 18 | 20 | 19 | 24 | 12. R.B. | 8 | 8 | 8 | 8 | 8 | 8 |
| 13. Mrs. | 14 | 16 | 20 | 21 | 28 | 13. | | | | | | |
| 14. Mrs. | 22.5 | 17.5 | 22.5 | 30 | 42.5 | 14. A.A. | 9 | 9 | 9 | 9 | 9 | 9 |
| 15. Mrs. | 12 | 13 | 15 | 17.5 | 22 | 15. G.N. | 13 | 13 | 13 | 13 | 13 | 13 |
| 16. Mrs. | 14 | 15.5 | 17 | 17 | 23 | 16. M.F. | 12 | 12 | 12 | 12 | 12 | 12 |
| 17. Mrs. | 18 | 20.5 | 21 | 21.5 | 25 | 17. | | | | | | |
| 18. Mrs. | 17 | 20.5 | 22 | 23 | 25.5 | 18. | | | | | | |
| 19. Mrs. | 17 | 19 | 21 | 19 | 19.5 | 19. A.N. | | 17 | 18.5 | 19 | 22 | 19 |
| 20. Mrs. | 16 | 17 | 18 | 19 | 20 | 20. D.O. | | 11 | 11 | 11 | 11 | 11 |
| 21. Mrs. | 14 | 17 | 18 | 23 | 20.5 | 21. R.B. | | 13 | 13 | 13 | 13 | 15 |
| 22. Mrs. | 14 | 15 | 15.5 | 23 | 27 | 22. J.D. | | 11.5 | 12 | 12 | 12 | 14 |
| 23. Mrs. | 17.5 | 17.8 | 18.8 | 19.2 | 21 | 23. I.H. | 12 | 13 | 13 | 13 | 13 | 12 |
| 24. Miss | 19 | 21 | 22 | 24 | 26 | 24. W.W. | 8 | 8 | 8 | 8 | 8 | 8 |

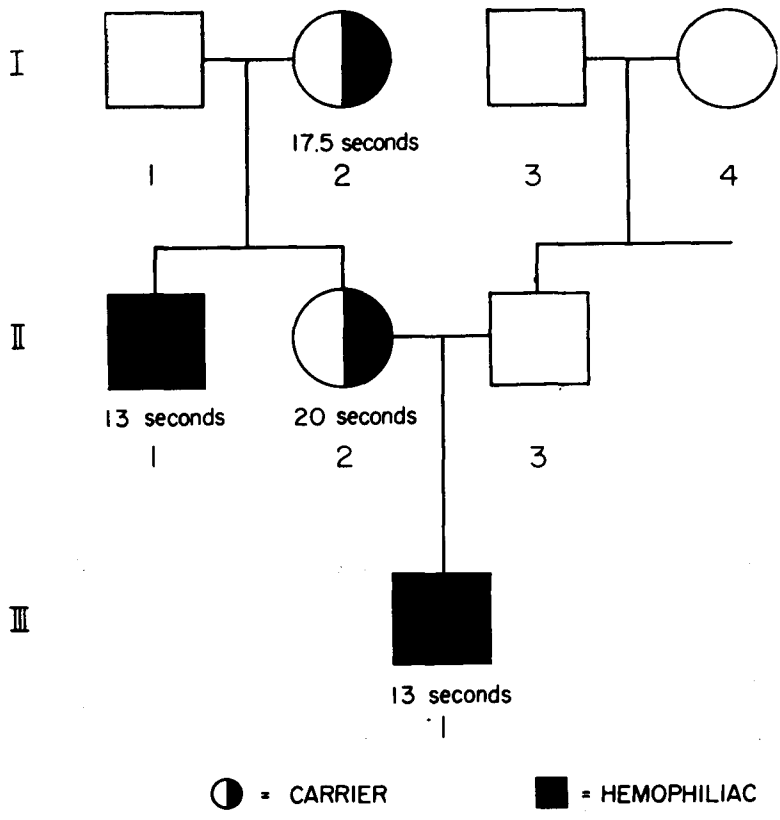


Fig. 3. Family tree showing heritage and prothrombin consumption at 0.0008 ml. plasma dilution. Lower range of normal, 29 seconds

had any bleeding difficulties associated with delivery of their children. The three carriers who showed normal AHG levels had no evidence of hemorrhagic tendency.

In Table 7 these carriers are divided into "definite" and "probable" categories by the definitions previously established. Of the three women who had normal AHG levels on this test, two were definite carriers and the third was a probable carrier.

## Discussion

The possibility of AHG deficiency in the female has only gradually been accepted, probably because in the classic description, hemophilia occurs only in the male. Now, however,

TABLE 3

STATISTICAL EVALUATION OF MEANS AND STANDARD DEVIATIONS OF EACH GROUP

| Amount of Plasma from Patient Added to Substrate | Group | Prothrombin Consumption Time in Seconds N | X | S.D. | k | P |
|---|---|---|---|---|---|---|
| .0005 cc. | Controls | 50 | 32.28 | 6.48 | 9.27 | $< 0.0001$ |
| | Carriers | 26 | 19.86 | 5. | 7.30 | $< 0.0001$ |
| | Hemophiliacs | 25 | 11.9 | 2.35 | | |
| .0008 cc. | Controls | 50 | 38.88 | 7.37 | 8.6 | $< 0.0001$ |
| | Carriers | 26 | 22.97 | 7.8 | 6.7 | $< 0.0001$ |
| | Hemophiliacs | 25 | 12.12 | 2.65 | | |
| .001 cc. | Controls | 50 | 49.12 | 11.13 | 7.8 | $< 0.0001$ |
| | Carriers | 26 | 27.63 | 11.5 | 6.7 | $< 0.0001$ |
| | Hemophiliacs | 25 | 12.24 | 2.65 | | |

TABLE 4

PROTHROMBIN CONSUMPTION IN THREE GENERATIONS OF ONE FAMILY

| Generation | Patient | Prothrombin Consumption at 0.008 ml. in seconds |
|---|---|---|
| I | Grandmother | 17.5 |
| II | Daughter | 20 |
| | Son | 13 |
| III | Daughter's son | 13 |

there appear to be three distinct entities in which the female shows lowered levels of antihemophiliac globulin:

1) *Classic AHG deficiency* in the human female occurs rarely, but it has been described by several investigators.[14–17] This condition results from the mating of a hemophiliac male and a carrier female, with the female offspring receiving an affected gene from each parent.

2) *Vascular hemophilia*—characterized by a prolonged bleeding time with normal platelets, usually a positive Rumple-Leede test, anatomically abnormal capillaries, and a low level of plasma AHG—has been well documented in women.[18–25] The impor-

TABLE 5

FAMILY STUDIES OF HEMOPHILIACS AND CARRIERS

| Family | Relation | AHG Status | Case Number in Table 1 | Prothrombin Consumption at 0.008 ml. in Seconds |
|---|---|---|---|---|
| 1 | Sisters | Carriers | 1 | 18 |
| | | | 8 | 18 |
| | | | 9 | 17 |
| | Cousins | Hemophilia | 1 | 11 |
| | | | 8(a) | 8 |
| | | | (b) | 9 |
| 2 | Brothers | Hemophilia | 6(a) | 10 |
| | | | (b) | 11 |
| 3 | Brothers | Hemophilia | 7(a) | 14 |
| | | | (b) | 14 |

TABLE 6

HEMORRHAGIC TENDENCIES IN CARRIERS

| | |
|---|---|
| Total number of carriers | 26 |
| Bleeding following surgery | 3 |
| Bleeding from tooth extractions | 2 |
| Personal history of easy bruising | 20 |

TABLE 7

AHG LEVELS IN CARRIERS

| Type | Number | Number with Normal AHG Levels |
|---|---|---|
| Carrier | 21 | 2 |
| Probable carrier | 5 | 1 |

tance of careful differential diagnosis has recently been stressed by Graham.[26]

3) *Partial deficiency of AHG in carriers* is a subject of debate. Some authors have found that these women have no bleeding tendencies which are evident clinically,[5,6] while others have described definite bleeding tendencies as evidencd by severe and prolonged bleeding after tooth extractions[8,27,28] and tonsillectomies,[27,28] easy bruising,[27,29] and menorrhagia.[29] Twenty of our 26 carriers gave subjective histories of bruising easily, while

three had prolonged bleeding after surgery and two after tooth extractions.

Until recently, the only carriers with proved low AHG levels have been isolated patients whose AHG levels were actually low enough to cause bleeding tendencies and to be demonstrable with the laboratory techniques available.[27,28,30] Otherwise, studies of carriers of severe hemophilia have produced normal results.[4,5,8,10] An occasional abnormal subject has appeared with enough regularity, however, that the search to demonstrate a significant difference from the normal has continued. Margolius and Ratnoff[6] found that four carriers out of 27 had prolonged silicone clotting times. Also, one carrier had an abnormal modified thromboplastin generation time and a prolonged recalcification time when the patient's plasma was added to hemophiliac plasma. Merskey and MacFarlane[8] described three carriers out of 33 who had slightly prolonged clotting times and abnormally low prothrombin consumption values. In addition, Stefanini and Dameshek[31] have described the presence of the alpha X globulin in the plasma electrophoretic pattern of hemophiliac patients and of many carriers.

Recently there have been two major contributions in the endeavor to test for carrier states. Pitney and Arnold[7] demonstrated abnormally low AHG levels in 10 carriers and four possible carriers of AHG deficiency among 25 patients tested by a modified thromboplastin generation test. Our findings strongly support these observations. The carrier state in another type of hemophilia was demonstrated by Bond and co-workers,[32] who discovered a definite deficiency of PTC in carriers of PTC deficiency by using a new substitute for the platelet factor in the thromboplastin generation test.

These previous positive studies have utilized methods other than the erythrocytin test for determining AHG levels. The extreme sensitivity of this erythrocytin test is shown by the ease with which it detects the addition of 0.0008 ml. of normal plasma to 1 ml. of hemophiliac plasma. Although the mechanism of this reaction is not known, the observation remains that as increasing minute amounts of normal plasma are added to the test substrate, the prothrombin consumption values increase. Conversely, the prothrombin consumption values do not change with the addition of AHG-deficient hemophiliac plasma.

The reproducibility of results with this test is shown by the similar prothrombin consumption values noted in the family studies. The data thus obtained in Figure 3 and Table 4 indicate almost identical levels throughout three generations in one family. The similarity of results in siblings and their offspring are

shown in Table 5. Reproducibility is also indicated by virtue of the same prothrombin consumption values appearing in replicate determinations performed for any given subject without identification as to prior clinical diagnosis.

These studies indicate that the female carriers manifest an abnormal X chromosome by a lowered plasma AHG activity. The exact content is probably determined by an abnormal gene that is transmitted from generation to generation.

## Summary

Twenty-one definite carriers and five probable carriers of AHG deficiency were assayed for the AHG plasma levels using a modification of the erythrocytin method of Quick. Twenty-three of the subjects showed abnormally low AHG levels in the range between the normal and hemophiliac levels.

Five of the mothers had hemorrhagic difficulties associated with surgical procedures while twenty gave a personal subjective history of easy bruising.

The similarity in levels of AHG which has been illustrated in siblings and in different generations of the same family suggests that the exact plasma level of AHG is evidently a genetically controlled factor.

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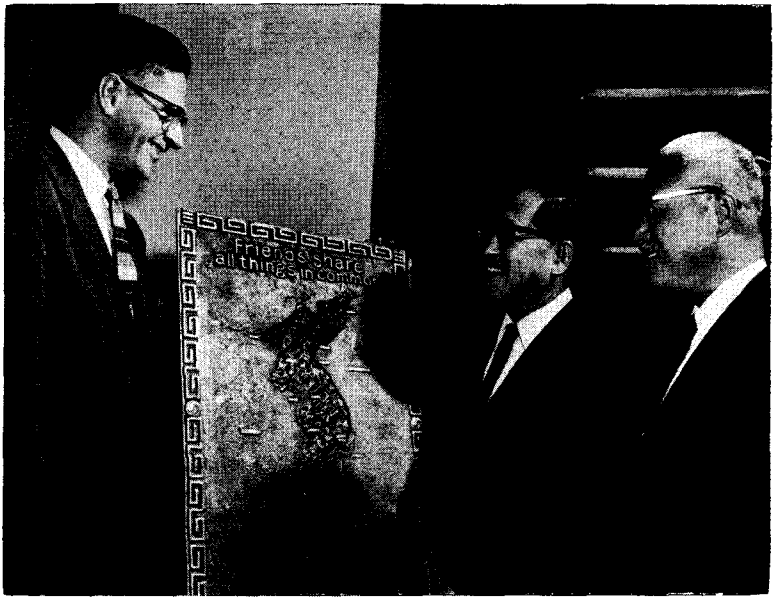
# Medical School News



## "FRIENDS SHARE ALL THINGS IN COMMON"

Those simple words are inscribed on a bronze plaque which represents a bond of lasting friendship between two medical schools located half a world apart. The plaque was given recently to the University of Minnesota Medical School by Seoul National University in Korea. It expresses Korean appreciation for the successful educational exchange program conducted by the two institutions during the past five years.

The presentation was made Nov. 13 at the University of Minnesota Medical Center. Dr. Robert B. Howard (left), Dean of Medical Sciences, accepted the 60-lb. plaque from Dr. Choo Wan Myung (center), Dean of Seoul University's College of Medicine, and Dr. Dong Ik Kim (right), superintendent of its affiliated hospital. The Korean educators have since returned to their own nation.

Since 1954, some 60 Korean and American educators and administrators have exchanged assignments. Minnesotans have

contributed much to the rehabilitation of war torn Seoul University medical school, and received rewarding faculty experience.

Koreans, said Dr. Myung in his presentation remarks, have learned the newest methods of medical education and practice during their visits to Minnesota.

"I am sure," he said, "that these faculty exchanges will continue to hold the two colleges together in friendship and respect long after our formal association has ended."

The original three year exchange contract has been extended twice, and will now run until September, 1961.

## Memorials

Recent memorial contributions to the Minnesota Medical Foundation have been received in memory of:

**Frank A. Janes, Minneapolis**

Memorial gifts are a practical means of honoring the memory of a friend or loved one while providing needed assistance for the University of Minnesota Medical School. Dignified acknowledgments are made by the Foundation to both the donor and to the family of the deceased.

# Departmental News

## SURGERY

Dr. Owen H. Wangensteen, Professor and Chairman of the Department, attend the 5th Assamblea Medica de Occidenta at the University of Guadalajara, Mexico, Nov. 9-13, where he lectured on "Studies of Local Gastric Hypothermia as Related to Peptic Ulcer."

On Dec. 2, Dr. Wangensteen delivered the 4th annual Rose Liebowitz Memorial Lecture at Long Island Jewish Hospital in New York. His topic was "Surgical Facets of the Peptic Ulcer Problem."

## PATHOLOGY

Dr. Mitchell Rosenholtz presented a paper by invitation before the American Association for the Study of Liver Disease on Nov. 5 in Chicago. The title was "Use of the Histochemical Demonstration of Aminopeptidase to Distinguish Small Bile Ducts and Hepatic Parenchymal Cells." He was accompanied to the meeting by Dr. Richard L. Davis, Medical Fellow.

## INTERNAL MEDICINE

Dr. Cecil J. Watson, Professor and Head, was elected Vice President of the American Clinical and Climatological Association at its November meeting in Hot Springs, Ark.

Dr. Yang Wang, Minnesota Heart Association Research Fellow, became an Instructor in the department on Oct. 1.

Dr. Frederick W. Hoffbauer, Professor, assumed duties as Chief of Medicine at Minneapolis General Hospital Oct. 1.

Dr. Charles N. Ballentine resigned from the department Nov. 1 to enter private practice.

## DERMATOLOGY

Dr. Francis W. Lynch, Professor and Director, has been elected President of the American Academy of Dermatology at the group's annual meeting Dec. 9 in Chicago. He is the first faculty member so honored.

## UNIVAC MAY SOLVE A.P.S. PROGRAM PROBLEM

Can Univac outthink a committee of scientists in organizing a major scientific meeting?

The answer may come in 1960, according to Dr. Horace Davenport, Head of the Department of Physiology at the University of Michigan, who visited the University of Minnesota Oct. 27-28. He lectured on "Metabolic Aspects of Gastric Acid Secretion," and devoted a dinner speech in part to the prospects of an electronic brain as "program chairman" for the American Physiological Society, which will meet April 11-15, 1960 in Chicago, Illinois. He heads the Society's Committee on Education.

The sheer weight of scheduling scientific sessions for six federated societies in simultaneous session is becoming impossible to handle, Dr. Davenport said. A.P.S. directors are struggling to relieve the confusion surrounding 10,000 scientists attempting to benefit from 60 simultaneous meetings.

Next year for the first time the Societies will attempt to utilize Univac in organizing a more integrated program. Dr. Davenport said that they will feed into the machine about 100 items of information on each paper offered for presentation. At the same time, a program set up in the usual way by secretaries of the Societies will be matched with Univac's results, and judgment will be made as to which side produces the more sophisticated grouping of papers on particular topics.

"It will be interesting," Dr. Davenport said, "to see whether the electronic brain arranges a better program than the Committee. If so, Univac may become a kind of organizational genie which could spare the Society's officers a great deal of work in the future."

—Contributed by MAURICE B. VISSCHER, M.D.
Head, Department of Physiology

# Coming Events

## University of Minnesota Medical School

COURSES IN CONTINUATION MEDICAL EDUCATION
DURING 1960

| | |
|---|---|
| January 11–13 . . . | Ophthalmology for Specialists |
| January 21–23 . . . | Surgery for Surgeons |
| February 8–10 . . . | Cardiovascular Diseases for General Physicians and Specialists |
| February 15–19 . . . | Pediatric Neurology for Specialists |
| February 29–March 2 | Pediatrics for General Physicians |
| March 14–16 . . . . | Internal Medicine for Internists |
| March 19 . . . . . | Trauma for General Physicians |
| March 28–April 1 . | Endocrinology for General Physicians |
| April 7–9 . . . . . | Emergency Surgery for Surgeons |
| April 11–13 . . . . | Radiology for General Physicians |
| April 21–23 . . . . | Otolaryngology for General Physicians |
| May 2–6 . . . . . | Intermediate Electrocardigoraphy for General Physicians and Specialists |
| May 16–18 . . . . | Office Psychotherapy for General Physicians |
| May 23–27 . . . . | Proctology for General Physicians |
| June 13–15 . . . . | Gynecology for Specialists |
| Continuous in 1960 . | Cancer Detection for General Physicians |

Courses are held at the Center for Continuation Study or at the Mayo Memorial Auditorium on the campus of the University of Minnesota. Usual tuition fees are $10 for a one-day course, $40 for a three-day course, and $65 for a one-week course. These are subject to change under certain circumstances.

Register early. For further information write to:

DIRECTOR
DEPT. OF CONTINUATION MEDICAL EDUCATION
1342 Mayo Memorial — University of Minnesota
Minneapolis 14, Minnesota

THE

MEDICAL BULLETIN

extends best wishes

to its readers

for a

JOYOUS CHRISTMAS

and

BOUNTIFUL NEW YEAR

May your New Year be blessed

with life's most precious gift—

good health

. . . THE EDITORS