POSTURAL PROTEINURIA

Thesis

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Introduction

Introduction

Proteinuria is such a frequent and important sign of renal disease that the recognition of types which are harmless is of very great practical importance. Over a hundred years ago Becquerel (97) described a man who had albuminuria but was otherwise healthy. Since then a vast literature has grown up about the subject of the "Benign proteinurias" but, despite this, there is no unanimity regarding many aspects. On the one hand there are some who deny the existance of benign forms of proteinuria (81,82,83,98) while others consider that they are extremely common (59,63,64). Among those who accept that benign forms do exist, there is considerable difference of opinion regarding their incidence (see later).

It was soon recognised that most of the proteinurias occurring in otherwise healthy persons were intermittent. By the beginning of the twentieth century certain postures, exercise and nervous factors were known to play a part in the production of the proteinuria, but even today, the importance of the various factors remains unsettled (1,2,58,93).

Controversy regarding the pathogenesis of the proteinuria has existed since these cases were first recognised and even today there are several theories to explain the various types. Many of the earlier theories were based on an incomplete knowledge of the clinical picture and on concepts of pathology and physiology that are now outmoded. Hooker (5) reviewed the early work very completely and further references to it are to be found in articles by Fox (4), Nicholson (87) and Fishberg (1). The theories that have survived to recent times can be grouped under four main headings:-

1. The theory that there is an abnormality of the blood.
2. Theories based on a presumed vasomotor instability or alteration in arterial circulation in the kidney.
3. Theories based on a presumed disturbance of the venous return from the kidney.
4. Theories based on presumed congenital or acquired lesions of the kidney and particularly of the glomeruli.

The work reported in this thesis was undertaken to clarify certain of the points at issue, particularly those regarding the incidence and pathogenesis of the postural varieties of benign proteinuria and their relationship to well established types of renal disease, particularly nephritis. In investigating the last factor, one approach to the problem was a detailed study of the urinary sediment. This necessitated the development of a new technique which has more general applications than to the study of the postural proteinurias and is reported in a special section "The Investigation of Methods".

Terminology

The benign proteinurias are a group of conditions in which the dominant feature is the passing of protein in the urine by otherwise normal persons. The term embraces the following types:-

1. Postural proteinuria, occurring only when the subject is placed in certain postures. In the orthostatic variety, the erect posture and in the lordotic variety exaggerated lordosis is associated with proteinuria.

2. Proteinuria occurring only after strenuous exercise.

3. Neurogenic proteinuria occurring with raised emotional tone or accompanying certain diseases of the nervous system.

4. Proteinuria following palpation of the kidneys.

Material

Material

The cases used in this investigation are shown below in Table 1.

Table 1

(E - European: C - Coloured: PP - Postural proteinuria)

Cases	Race	Sex	Age	Remarks
1 - 50	E	♂		The 1944 entry class sea cadets of the South African Training Ship "General Botha". All were healthy youths between 14 and 16 years of age and had been passed previously by their private doctors as fit for life at sea.
51-87	E	♂		The 1945 entry class sea cadets as above.
88-129	E	♂		The 1946 entry class sea cadets as above.
130	C	♂	20	Large gummatous liver.
131	C	♀	50	Hepatic metastaces from carcinoma breast.
132	E	♀	38	Hepatic enlargement of undetermined origin.
133-140				Subjects with acute diffuse glomerulo-nephritis.
141-145				Subjects with chronic glomerulo-nephritis of varying degrees of activity.
146	E	♂		Nephrosis.
147	C	♂		Lysol poisoning.
148	E	♂		Alkalosis from alkali overdosage for a gastric ulcer.
149	C	♂		Lobar pneumonia with constant low Sp.Gr. urine during the illness.
150	E	♀		Renal tuberculosis.
151	E	♂	50	Cirrhosis of the liver.
152	E	♂	38	Hydatids in the liver.
153	E	♂	23	PP. Healthy medical student.
154	E	♂	22	PP. Healthy medical student.
155	C	♀	6	PP. Convalescent 5 weeks after mastoidectomy.
156	C	♀	6	PP. Admitted for tonsillectomy.
157	C	♂	18	PP. Convalescent 4 weeks after mastoidectomy.

Table 1
(Continued)

158	C	♂	14	PP. Convalescent 4 weeks after mastoidectomy.
159	E	♂	27	Non-proteinuric. Healthy medical student.
160	E	♂	31	Non-proteinuric. Healthy doctor.
161	C	♀	5	Non-proteinuric. Convalescent 3 weeks after mastoidectomy.
162	C	♀	6	Non-proteinuric. Admitted for tonsillectomy.
163	C	♀	6	Non-proteinuric. Admitted for tonsillectomy.
164	E	♂	16	PP. Discovered at insurance examination.
165	C	♂	21	Non-proteinuric. Duodenal ulcer.
166	C	♂	18	Non-proteinuric. Convalescent 5 weeks after mastoidectomy.
167	E	♂	19	PP. Discovered at insurance examination.
168	E	♂	16	PP. Discovered at insurance examination.
169	C	♂	12	PP. Admitted for tonsillectomy.
170	E	♂	12	PP. Admitted for tonsillectomy.
171	E	♂	12	PP. Admitted for tonsillectomy.
172	E	♂	14	PP. Admitted for tonsillectomy.
173	E	♂	19	PP. Discovered at army examination.
174	E	♂	17	PP. Bed wetter. No organic cause found.
175	E	♀	27	PP. Had acute nephritis 2 years previously. Complete recovery.
176	E	♂	17	PP. Backache. Horse-shoe kidney discovered during investigation of proteinuria.
177	E	♂	15	PP. Healthy sea cadet. (1945 entry class).
178	E	♂	14	PP. Complained of abdominal pain. PP discovered on routine examination.
179	C	♂	16	PP. Mild bronchitis.
180	C	♂	22	PP. Hysterical weakness of legs.
181	E	♂	29	PP. Loss of weight. No cause found.
182	E	♀	12	PP. ? Filaria loa loa infection.
183	E	♂	9	PP. Migraine.
184	E	♂	16	Continuous proteinuria. No other signs.
185	C	♂	16	PP. Convalescent 5 weeks after mastoidectomy.
186	C	♀	19	PP. Admitted for tonsillectomy.
187	E	♀	12	PP. Admitted for tonsillectomy.
188	E	♀	20	PP. Dysmenorrhoea.
189-192	E			Young adults. PP discovered at army entrance examination.
193	E	♂	18	PP. Discovered at insurance examination.

194	E	♂	25	PP. Had acute nephritis 5 years previously.
195	E	♂	25	Mild rheumatoid arthritis. No gold injections. Continuous proteinuria.
196	E	♂	20	PP. Backache, probably of orthopaedic origin.
197	E	♀	14	PP. Rheumatic fever (inactive). Admitted for tonsillectomy.
198	E	♂	18	PP. Discovered at army entry examination.
199	E	♂	36	PP. Discovered at insurance examination.
200	C	♀	19	PP. Keratitis punctata.
201	C	♂	55	PP. Primary carcinoma of the liver.
202-252				Patients over the age of 50 years at the Conradie chronic sick home, suffering from a variety of non-renal diseases.
253-303	E	♂		Healthy medical students between 20 and 30 years of age.

Many of the postural proteinuric subjects from No. 155 to 200 were discovered by submitting convalescent patients in the Groote Schuur Hospital to tests for the condition. Where postural proteinuria was diagnosed, the cases fulfilled the criteria for the diagnosis of this condition which are laid down later.

Methods

Chemical Methods

Protein estimations

Total serum proteins were estimated by Kagan's (8) falling drop method.

Serum albumin and globulin were estimated by Fine's (9) biuret method, slightly modified for reading on the Pulfrich photometer.

Urine albumin and globulin. Two methods were used:-

A. The same modification of Fine's biuret method as used for serum proteins except that globulin was precipitated by mixing equal volumes of urine and 3.1 molar sodium sulphate solution.

B. The total urinary protein was estimated first by Daley's method (10) except that the final turbidity measurements were made in a simple comparator against standards prepared from serum whose protein content had been estimated by the Kjeldahl procedure. The globulin was precipitated by mixing equal volumes of urine and 3.1 molar sodium sulphate solution and reading the resultant turbidity against the same

standards as for the total urinary protein. The albumin concentration was obtained by subtracting the globulin concentration from the total protein value.

Urea estimations were made by Conway's urease method (11).

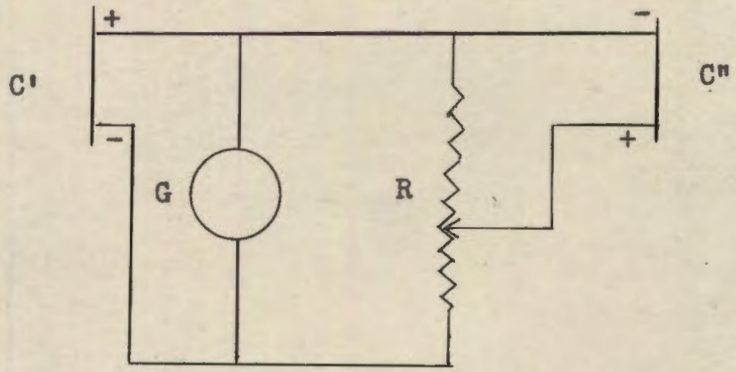
Chloride was estimated by Volhard's titration.

Dietrest was estimated in blood and urine by the method of Alpert (12).

Creatinine estimations were made by the method of Steinitz and Turkand (13) except that the final readings of the colour developed were made on a photo-electric colorimeter which had previously been calibrated with solutions of known creatinine concentration. The colorimeter design was based on that of the twin-cell instrument described by Reeve (14). The following modification in the electrical circuit was made because photo-voltaic cells function best when the external resistance of the circuit is of the same order as the internal resistance of the cells (Figure 1).

Figure 1

Photo-electric Colorimeter Circuit



C' and C" are identical photo-voltaic cells of internal resistance 400 ohms.

G is a 500 ohm "Cambridge" pot galvanometer.

R is a 500 ohm variable resistor.

The instrument was found to give reliable results and was independent of ordinary fluctuations in mains voltage.

Clearance Methods

All urine collections for clearances were made by an indwelling catheter.

Diotrast clearances were carried out by the method of Fos, Woods and Peet (18). Unfortunately diotrast was in short supply and more could not be obtained so that only three subjects could be investigated by this method.

It was necessary to use the endogenous creatinine clearance as an index of the glomerular filtration rate because apyrogenic inulin could not be obtained. Steinitz and Turkand (13) and Miller and Winkler (14) have shown that the endogenous creatinine and inulin clearances are almost identical in normal subjects. However, Smith, Finkelstein and Smith (17) point out that the endogenous creatinine clearance is always higher than the inulin clearance and in disease may be up to 42 % higher. In normal subjects it is usually about 10 % higher. They state that this error is due to the presence of chromogens other than creatinine in the plasma. There is no reason to believe that these chromogens should vary in their concentration over short periods so that while the

absolute figures for the glomerular filtration rate might be in error, comparison of the rates obtained in consecutive periods should provide a reliable index of altering glomerular filtration.

In the present study, only arguments based on altering rates were used, and furthermore, the alterations found were often in excess of 42 %. For these reasons, the deductions drawn from the glomerular filtration rates obtained by using the endogenous creatinine clearance method are valid.

In the case of the filtration fraction calculations, the actual figure obtained for the filtration fraction may be in error for the same reasons but the alterations are almost certainly significant.

Statistical Methods

Differences between means

The significance of the differences between means was obtained by examining the variances of the two distributions with Fisher's "Z" test to determine the applicability of Student's "t" test. After computation of "t" the value for P was obtained from tables (18). P is the probability of obtaining means differing as much as or more than that found, by sampling from a single population. Values for P below 0.05 indicate a significant difference between the means.

Qualitative statistics

The hypothesis is set up that the positives and the negatives do not differ in respect of the characteristics under consideration. The figures are analysed in contingency tables and tested by the "χ^2" test (18). The answer is given in the form of a probability P. If P is less than 0.05 the figures depart significantly from those that would be obtained if the hypothesis was correct.

Correlation coefficients

Correlation coefficients were calculated according to Fisher (18). The answer is given in the form of a probability P. If P is less than 0.05, there is a significant correlation between the factors tested.

Blood Pressure Methods

Blood pressure determinations were made on the right arm by the auscultatory method, using a mercury sphygmomanometer. The diastolic pressure was taken to be the point of abrupt muffling of the Korotkoff sounds as the pressure of the cuff was lowered. Several readings were taken and the lowest recorded to the nearest 5 mm. Hg.

Cold Pressor Test

Hines and Brown's (19) cold pressor test was used.

Methods of Urinary Sediment Examination

In doing urinary sediment counts by Addis' technique (20) on subjects with postural proteinuria it was noted that the cellular deposit differed from that of nephritis and other renal diseases. A study of the literature in English and the available foreign literature failed to assist in the identification of the cells found. Users of the Addis technique, including Addis himself, thought that differentiation of the nucleated elements was impracticable and devised no techniques for their study (20,21,22,23,24). It therefore became necessary to work out a method of studying these cells and to establish criteria for their differentiation. The results of this investigation are reported below and will be dealt with more fully in a future publication.

The Differential Urinary Nucleated Cell Count

The preparation of the sediment for study and the methods of staining

Urinary sediments, obtained by centrifuging urine, were studied microscopically, both wet and after spreading and drying. Wet specimens, unstained or stained in various ways, proved unsatisfactory. It is very difficult to use oil immersion lens systems on such specimens because the act of focussing invariably causes swirling of the liquid bathing the cells. Much detail is lost if lower power dry lens systems are used. Furthermore in wet specimens there is usually insufficient differentiation of the cell components, particularly in the nucleus, and too irregular a depth of staining from cell to cell to allow of certain identification.

Dried smears proved much more satisfactory in all respects. Heat fixation or chemical fixation with ethyl or methyl alcohol or formalin and the following stains and combinations of stains were tried on these smears:-

syl Blue; Methylene Blue; Gentian Violet; Brilliant Cre
Neutral Red; Carbol-Fuschin; Peroxidase; Unna-Pappenheim's and Leishmann's stains; Haematoxylin and Eosin; Methylene Blue and Eosin; Sudan 3 and Methylene Blue.

Leishmann's stain proved by far the most satisfactory. It combined the following advantages:-

1. Preliminary fixation was not necessary.

2. Fine nuclear structure showed up better than with any other stain.

3. Excellent cytoplasmic differentiation was usually found despite wide variations in urine pH.

4. Staining times and stain concentrations were not as critical as with some of the other stains used.

This stain has now been adopted as a routine in doing differential counts on the nucleated cells in the urine.

The routine method used for examination of the urinary sediment.

This examination is carried out at any time of day. The patient is allowed no excess fluid for 12 hours before the test but his fluid intake is not restricted. He empties his bladder and the urine is discarded. At some fixed time, usually one or two hours later, he again empties his bladder into a cleaned urinal. In the case of females, the urine is collected by catheter. No formalin or other preservative is added because it was found to interfere with the staining of the cells. The urine volume is measured immediately and a known fraction of it taken directly to the laboratory for counting, or, if this is not practicable, placed in the icebox.

As soon as possible after the urine is passed, and not more than one hour later, the urine is examined as follows:-

A Fuchs-Rosenthal counting slide of depth 2 mm. is prepared by allowing a tiny drop of saturated alcoholic solution of Brilliant Cresyl Blue to dry on the edge of the counting chamber. The urine is well mixed and a drop is transferred to the slide. There it is mixed with the stain and then allowed to flow under the

18 coverglass. With the high dry objective of the microscope the numbers of casts, red cells and nucleated cells are counted. Approximately 50 red cells and 50 nucleated cells are counted, always ending the count by completing the square in which the 50 th. cell lies. All the casts in one complete counting chamber are counted. From the number of cells and the number of squares counted, the concentration of cells per cc. is calculated and the figure so obtained is used to compute the number of formed elements passed per 12 hours. These calculations take little time if a slide rule is used. Where the cell counts are very low, as in normals, it is sometimes necessary to refill the counting chamber one or more times. This is seldom necessary in pathological urines.

Ten cc. of the urine are transferred to a centrifuge tube and spun at about 1000 revolutions per minute for approximately 15 minutes. The supernatent fluid is decanted. It is essential to obtain a very concentrated sediment. The sediment is mixed by shaking and part of it is transferred to a microscope slide where it is spread in the same way as a blood film. The slide is then air-dried in an incubator and stained with Leishmann's stain as used for blood films. Urine sediments usually stain more darkly than blood under similar circumstances so

suitable corrections in staining time or dilution must be made. One should aim to slightly overstain and then wash out the excess blue dye with distilled water under visual control with the microscope. The prepared film can now be examined or stored for study when convenient.

The remainder of the sediment is placed on another slide and covered with a coverslip. This must be examined immediately for doubly refractile fat, using a polarising microscope. A sheet of "Polaroid" or one of the lenses of a pair of polaroid sunglasses placed over the light source and another, at right angles to the first, over the eyepiece of the microscope makes an efficient polarising microscope. Polaroid is actually preferable to Nicol prisms because some of the red light is not polarised and this allows one to keep the sediment in focus as the fields are moved. Refractile material shows up white on a red background.

The error of the total counts

Berkson (25) found that the percentage error of counting white blood cells in a counting chamber was:-

$$\% E = \sqrt{\frac{100^2}{N} + \frac{4.6^2}{C} + \frac{4.7^2}{P}}$$

Where N is the number of cells counted, C the number of counting chambers used and P the number of diluting pipettes used.

The method used here is the same except that the urine is not diluted. The percentage error therefore becomes:-

$$\% E = \sqrt{\frac{100^2}{N} + \frac{4.6^2}{1}}$$

where one counting chamber is used. The percentage error calculated for various levels of N are shown below:-

No. of cells counted	Percentage error
10	± 32 %
50	± 15 %
60	± 14 %
70	± 13 %
80	± 12 %
100	± 11 %
200	± 8 %
300	± 7 %

In practice, the error is probably slightly more than these figures indicate because of uneven mixing of the urine before sampling. However, even an error of ± 50 to 100 % in the counting is not of practical significance because, in pathological counts, the concentration of cells may be anything from 4 to 1000 times the maximum normal.

Mc Kay, using a similar technique of short urine collection periods, found variation in the counts according to time of day. The rate of excretion of erythrocytes and nucleated cells was relatively constant during the late afternoon and night, fell during the morning and rose to a peak in the mid-afternoon. The counts varied up to five times the lowest figure (22)

Table 2 shows the normal ranges of formed elements passed per 12 hours.

Table 2

Normal Ranges of Formed Elements Passed in the Urine

Author	RBCs Mils./ 12 hrs.	Nucl. Cells Mils./12 hours	Casts Mils./12hrs.
Addis (20)	0 - 0.425	0.0324 - 1.635	0 - 0.00427
Beerse (21)	0 - 1.1	0.048 - 4.0	0 - 0.0087
Goldring (23)	0 - 1.55	0.024 - 5.4	0 - 0.0078
Lyttle (26)*	0 - 0.00129	0.009 - 2.622	0 - 0.0129
Author **	0	0 - 0.7	0 - 0.02

* Children 4 to 12 years old.

** Data from Experiment 11.

The Differential Nucleated Cell Count

The following cell types are recognisable in urinary sediments:-

1. Renal parenchymal cells.
2. Renal tract cells.
3. Polymorphs.
4. Eosinophils.
5. Mononuclear cells of blood origin.
6. Small cells, possibly of glomerular origin.
7. Unclassifiable cells.

In order to distinguish between these cell types, scrapings of cut sections of normal kidney, renal pelvis and ureters and blood cells were examined both directly and after suspension in urines of different pH and concentration for different periods. In this way, the stages of degeneration of the different cells could be followed under controlled conditions. Further knowledge of the cell types was obtained from the examination of urinary sediments from patients with various diseases.

Investigation of Method

The Differentiation of the Nucleated Cells in Urine

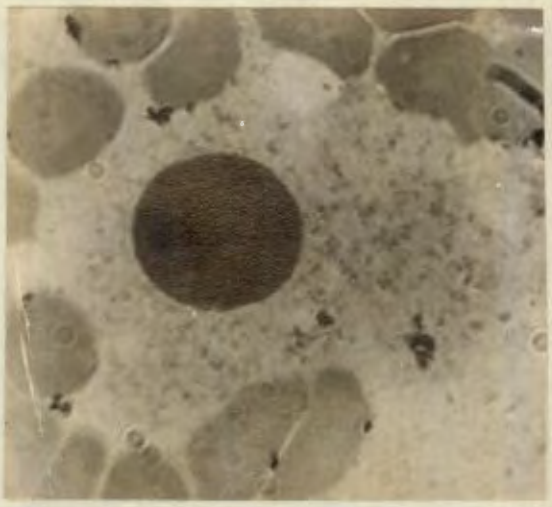
The Renal Parenchymal Cell

Fresh smears of kidney stained with Leishmann's stain show the parenchymal cells to be about 30 by 20 μ with an eccentric oval nucleus and greyish-purple, granular cytoplasm. After incubation in urine, the cell and its nucleus become rounder and much of the cytoplasm is lost, with the result that cell size and cytoplasmic characters lose some of their value in differentiating this cell from others. Fortunately, the nucleus is very characteristic, and throughout, serves as the best criterion for the recognition of renal cells.

The nucleus. The nuclear chromatin in fresh and incubated renal cells is condensed into small nodes which give the nucleus a stippled appearance which persists even after the nuclear membrane has burst and the nucleus has commenced to disintegrate (Figs. 2,3 and 4). When normal renal cells are examined, one or two nucleoli are usually seen and these often persist as vacuoles even after commencing nuclear disruption.

In urine from subjects with renal diseases, many cells are seen which show the characteristic stippled nucleus and are obviously the same as those

Figure 2



Fresh, smeared, normal renal cell. Note the stippling of the nucleus and the nucleoli.

Figure 3

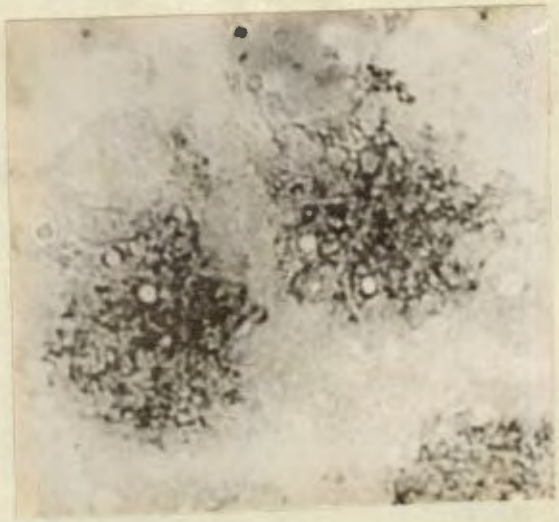
Normal renal cells incubated in urine of pH 7 for 2 hours. Note the persistance of the nuclear stippling.

produced by artificial incubation (Figures 5 and 6). However, in disease and particularly in glomerulonephritis, one frequently sees cells with nuclei which differ from these in that the nuclear chromatin is more condensed and sometimes hyalinised. It is probable that this type of nuclear alteration and those types mentioned below, occur before the cells are shed into the urine and represent varieties of necrobiotic change. Similar changes have been seen in other cells (95). More frequently than not, round holes form in these probably necrobiotic nuclei (Figures 7 and 12). That these cells are of renal origin is shown by the fact that types intermediate between them and the stippled variety are often seen (Figures 6,8 and 9). Other variants such as those shown in Figures 9,10,11 and 12 occur much less frequently. None of these variations from the stippled appearance are seen in smears from normal kidneys and cannot be produced by incubation of normal renal cells in urine.

Other variations in appearance

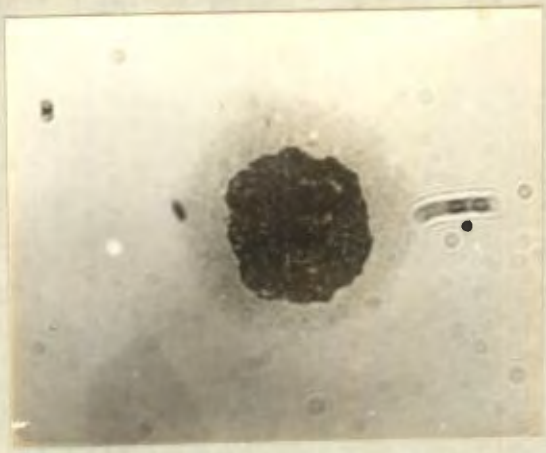
In very acid urine, the cytoplasm tends to stain a clear pink colour while the nucleus often does not take on the usual purple colour and can only be

Figure 4



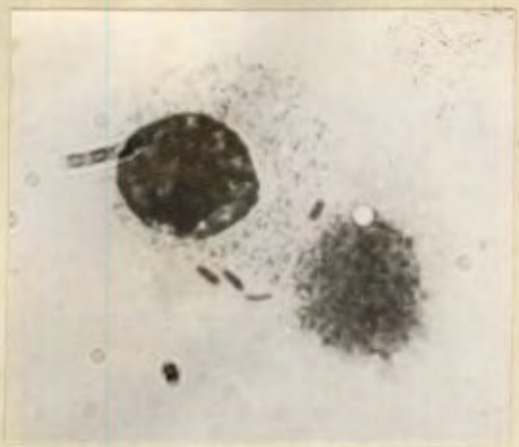
Normal renal cells incubated in urine of pH 7 for 4 hours.

Figure 5



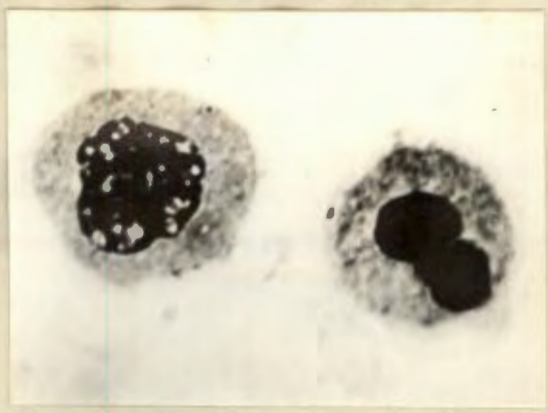
Renal cell in urine from a case of acute nephritis.
Note the characteristic stippling of the nucleus.

Figure 6



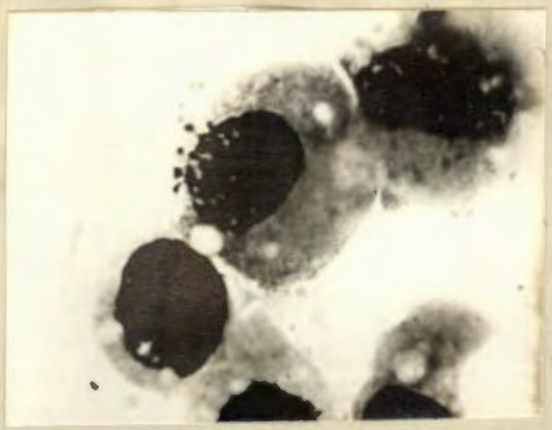
Two renal cells in urine from a case of acute nephritis.

Figure 7



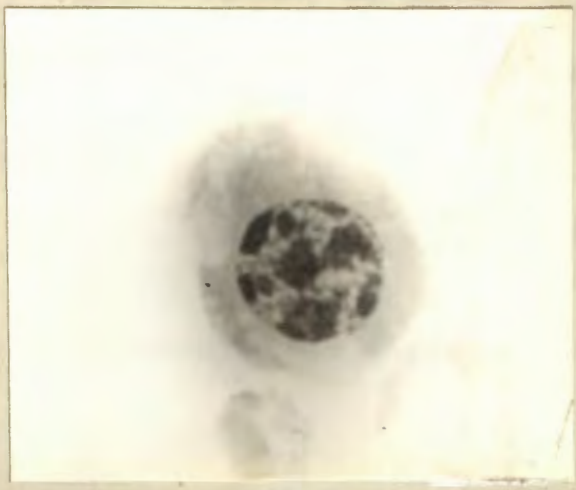
A renal cell and a polymorph in urine from a case of acute nephritis. The renal cell nucleus shows necrobiotic change.

Figure 8



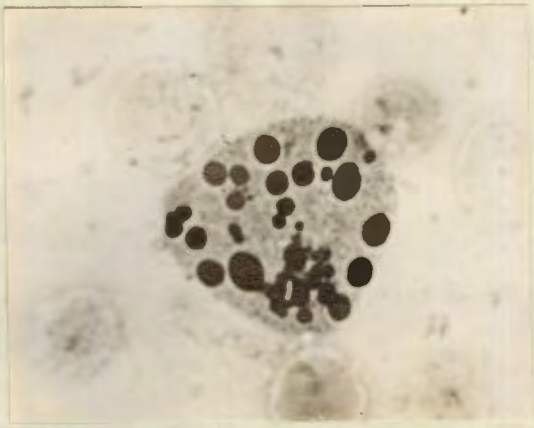
Renal cells from a case of acute nephritis. Note the commencing round vacuolation of the nucleus of the central cell and the stippled nature of the nuclear chromatin.

Figure 9



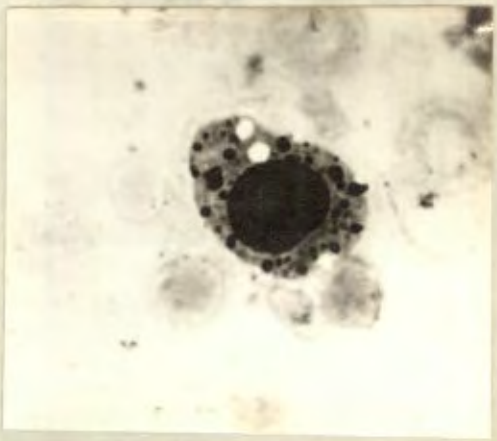
A renal cell from a case of acute nephritis.

Figure 10



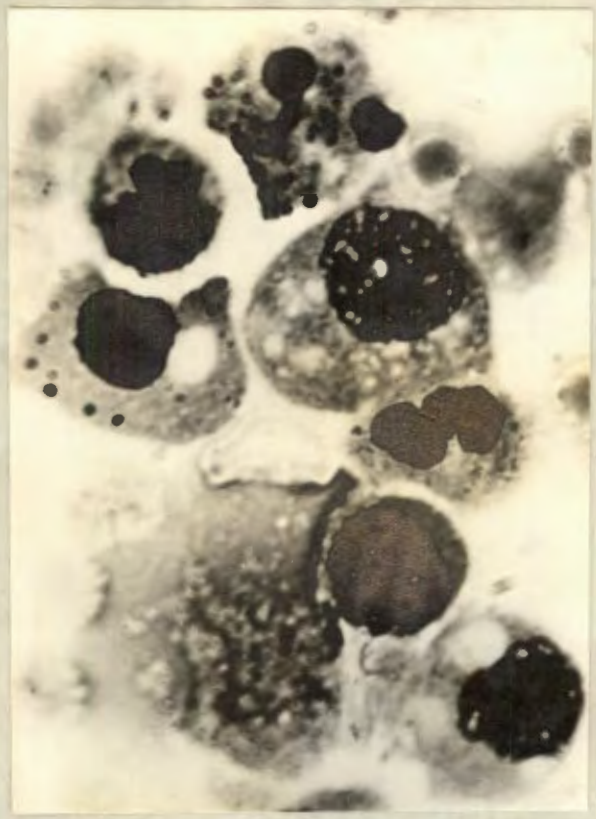
A renal cell of the fragmented nuclear type from a case of acute nephritis.

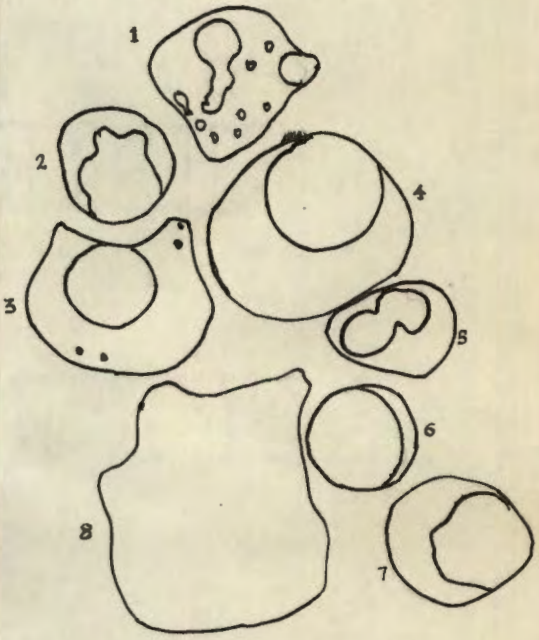
Figure 11



A renal cell showing an unusual type of necrobiotic change.

Figure 12





A typical microscopic field of urinary sediment from a subject with an acute exascerbation of chronic nephritis

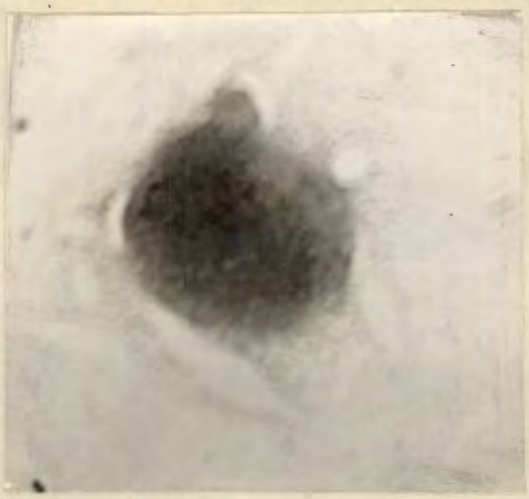
1. Necrobiotic renal cell with fragmented nucleus.
2 and 5. Polymorphs.
3,4,6 and 7. Necrobiotic renal cells.
8. Smeared renal cell nucleus.

recognised by a red stippling. Sometimes, only a few of the chromatin nodes stain purple (Figure 13).

In urine above pH 7, cell disintegration is rapid and all that may remain of a cell may be a purple blob in which one can often see the characteristic chromatin nodes (Figure 6).

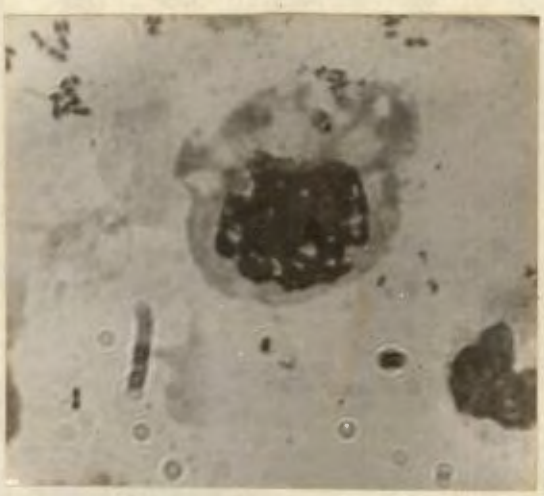
Necrobiotic changes in the nuclei of renal parenchymal cells are often accompanied by vacuolation of the cytoplasm (Figure 14). The vacuoles must often contain fat because vacuolated cells are much more common in urines which show intracelluler doubly refractile fat on examination with the polarising microscope.

Figure 13



Renal cell in acid urine.

Figure 14



Necrobiotic renal cell with vacuolated cytoplasm. The vacuoles probably contained fat because this urine contained much doubly refractile lipoid material when examined with the polarising microscope.

Renal Tract Cells

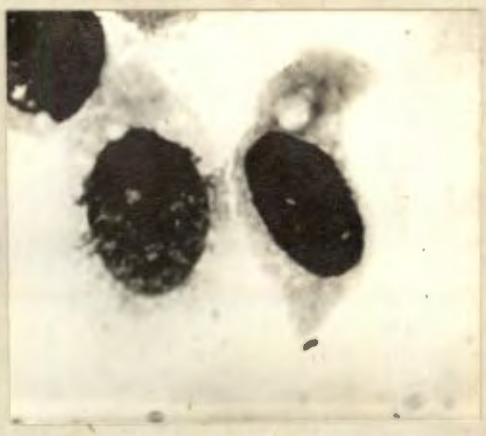
These vary considerably in size and may be very large as in the familiar squamous epithelial cell. Other large types occur in the renal pelvis (Figure 15). The smaller varieties are of about the same size as renal parenchymal cells.

The nucleus has the same stippled appearance as in renal parenchymal cells but tends to maintain an oval shape. The main differentiating features are, however, in the cytoplasm. The cell tends to be pointed at one or both ends or be oval and it degenerates much more slowly than do parenchymal cells. Most important of all, the cytoplasm is hyaline and stains more darkly than all other cells in the urinary sediment. The colour of the cytoplasm varies from a deep blue to purple or red, depending on the urinary pH. Alkalinity favours blueness. Cells with nuclei showing necrobiotic change occur. Figures 16 and 17 illustrate three cells.

Figure 15

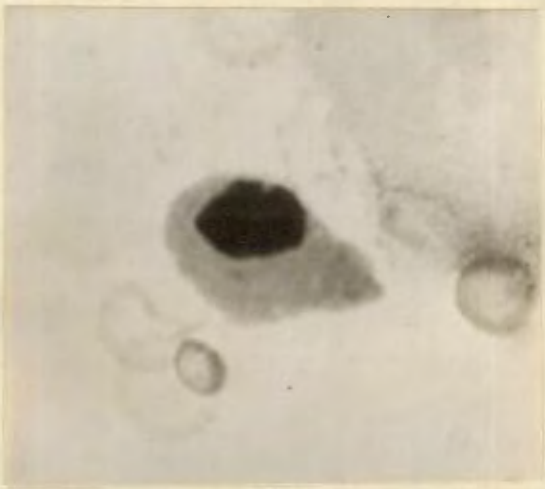
A large cell from the renal pelvis.

Figure 16



Two renal tract cells. Note the oval nucleus and elongated shape of the cells.

Figure 17



A renal tract cell.

Cells of Blood Origin

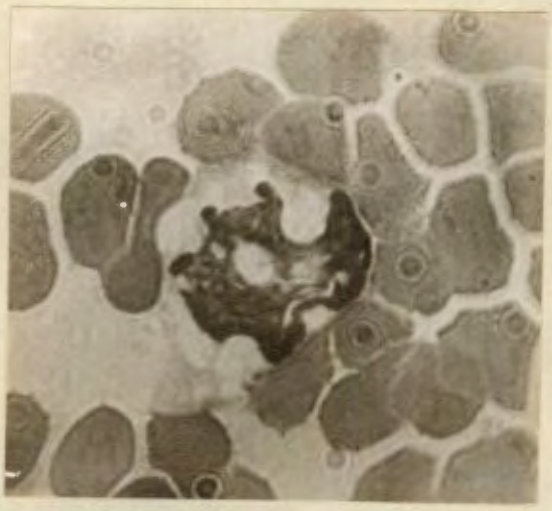
The appearance of fresh blood cells stained with Leishmann's stain requires no description. In degenerating cells, however, the appearances change. The nucleus is of most value in differentiating blood cells from cells of kidney or renal tract origin. In the former, the stippled appearance of the nucleus is never seen, and in degeneration, there is a tendency to streakiness of the nuclear chromatin. This often leaves gaps between the chromatin bands which are, however, quite different from the round holes in necrobiotic renal cells (Figures 18 and 19). The end result of disintegration is an interlacing web of coarse purple bands (Figure 20) or an appearance like that seen in "smear cells" in blood films.

When the cells are reasonably well preserved there is no difficulty in distinguishing between eosinophils (Figure 21), polymorphs and mononuclear cells of blood origin. In the late stages of disintegration, however, they may be indistinguishable from one another yet still recognisably of blood origin. For example, the cell shown in Figure 20 may be either a polymorph or a lymphocyte or monocyte.

Figure 18

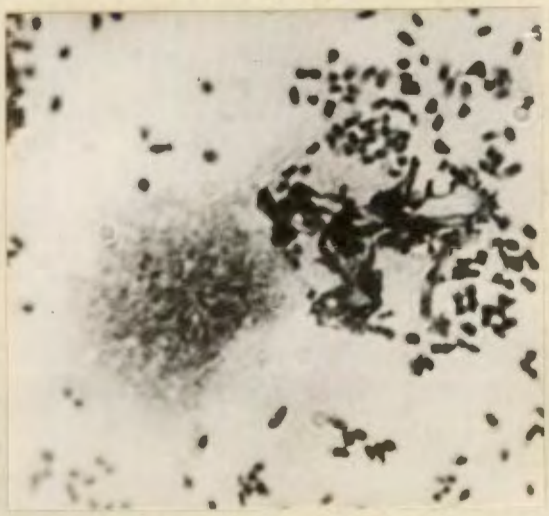
Lymphocyte incubated for 2 hours in neutral isotonic urine.

Figure 19



Lymphocyte incubated for 3 hours in neutral isotonic urine.

Figure 20



Late stages of degeneration of a renal cell and a cell of blood origin. The urine contains many organisms.

Figure 21

An eosinophil in the urine from an acute nephritic.

Variations in appearance

In acid urines, the cytoplasm of all cells of blood origin becomes pink with the method of staining used. The nuclei of polymorphs tend to become round and the fine chromatin bridges between the parts of the nucleus tend to break leaving a cell with two or three dense purple blobs (Figures 22 and 23). These can be distinguished from the somewhat similar necrobiotic renal cells by the smaller number of nuclear fragments and their tendency to uniformity in size. Furthermore, necrobiotic renal cells are generally larger.

In acid urine, lymphocytic nuclei tend to condense, obscuring the strand-like nature of the chromatin (Figure 23). In these circumstances, they may be very difficult to distinguish from renal parenchymal cells with pyknotic nuclei. Fortunately in renal cells, pyknosis is usually accompanied by a round vacuolation of the nucleus or nuclear fragmentation as in Figure 7.

Figure 22

Two polymorphs.

Figure 23

Two polymorphs and a lymphocyte. The fourth cell is probably also a lymphocyte..

The Small Cell

These cells are very easily recognised as they are only about 4 to 5 μ in diameter, are flat, and have a round nucleus about 1½ to 2 μ in diameter (Fig.24). Their origin is uncertain but their small size suggests that they come from the glomeruli. There is some support for this suggestion in the fact that they have been seen most frequently in acute diffuse glomerulo-nephritis. Attempts at picking off cells from normal glomeruli for study have failed.

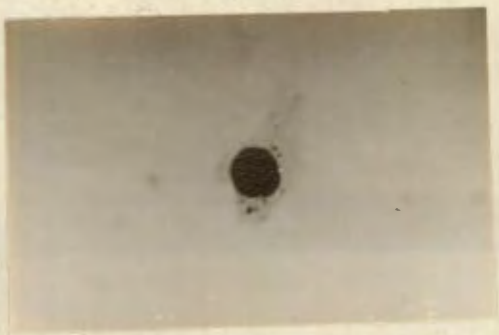
Unclassifiable cells

In almost every count, a varying and often large percentage of the cells or cell nuclei will be unclassifiable. Long periods of urine collection favour high percentages of unclassifiable cells because of cell disintegration. The optimum period of urine collection is about one hour. Often, despite all precautions regarding freshness of urine and rapid examination, the unclassifiable cell percentage may be as high as 80 %.

Very acid or very alkaline urines bring attendant changes in the cells and cause difficulties in their recognition.

Variations in urine concentration do not materially alter the appearances of the cells.

Figure 24



A small cell.

Illustrative counts

Tables 5 to 8 illustrate the type of finding that is to be expected when the full technique of urinary sediment counts is applied to urine from normal subjects and from those with various diseases. The data for Table 5 are derived from Table 27.

Table 5

The Differential Nucleated Cell Count in Normal Subjects

Polymorphs	6 %
Lymphocytes	4 %
Renal Tract Cells	66 %
Renal Parenchymal Cells	2 %
Small Cells	10 %
Unclassifiable Cells	12 %

The methods of arriving at these figures will be dealt with later in connection with Table 27.

Table 4

The Urinary Sediment in Acute Diffuse Glomerulo-nephritis

No.	Pr	RBCs	NCs	E	P	L	RP	RT	Sm	?s	DRF	Remarks
133	6.7	2090	425	0	35	12	23	0	11	21	-	?s probably blood origin. Necrobiosis +++
134	0.7	557	66	0	20	2	38	1	0	39	-	?s probably blood origin. Necrobiosis +++
135	0.5	595	655	1	31	5	13	0	0	50	-	?s probably blood origin. Necrobiosis +
136	0.2	195	466	2	19	0	36	0	0	43	-	?s probably blood origin. Necrobiosis ++
137	0.2	420	48	2	10	1	49	0	0	35	-	?s probably blood origin. Necrobiosis +
138	1.5	1480	11	1	32	30	14	0	0	22	-	?s probably blood origin. Necrobiosis ++
139	3.2	725	99	0	15	3	34	0	0	48	-	?s probably blood origin. Necrobiosis ++
140	8.9	5950	1025	2	56	5	32	0	0	5	-	?s probably blood origin. Necrobiosis +

No. Case number
Pr Protein in gm. passed per 12 hrs.
RBCs Erythrocytes passed per 12 hrs. in millions
NCs Nucleated cells passed per 12 hrs. in millions.
E Eosinophils % .
P Polymorphs % .
L Mononuclear cells % .
RP Renal parenchymal cells % .
RT Renal tract cells % .
Sm Small cells.
?s Unclassifiable cells % .
DRF Doubly refractile fat.

Table 5

The Urinary Sediment in Chronic Diffuse Glomerulo-nephritis

No.	Pr.	RBCs	NCs	E	P	L	RP	RT	Sm	?s	DRF	Remarks
141	++	2390	299	1	57	4	13	0	0	25	+	Acute exascerbation
142	1.2	51	128	0	16	0	37	0	0	47	+	Active stage. Most ?s blood origin. Necrobiosis ++.
143	4.8	53	125	0	78	6	8	0	0	7	++	Continued moderate activity. 2 weeks between counts. Necrobiosis ++.
	4.7	58	140	0	72	1	9	0	0	18	+	
	4.5	62	130	0	52	0	7	0	0	41	+	
144	3.7	96	126	0	28	5	32	0	0	35	+++	3 weeks between counts. High protein diet begun after first count.
	14	28	9	0	27	15	45	0	0	13	+++	
145	2.6	15	15	1	49	9	16	0	0	25	+	Inactive stage.

Table 6

The Urinary Sediment in Nephrosis

No.	Pr.	RBCs	NCs	E	P	L	RP	RT	Sm	?s	DRF	Remarks
146	6.3	3	13	0	0	0	63	0	0	37	++++	Most of ?s renal. Vacuolated forms +++. Necrobiosis +.
	14	12	65	0	0	0	95	0	0	5	++++	On high protein diet after last count.

Table 7

The Urinary Sediment in Carbolic Acid Poisoning

No.	Pr	RBCs	NCs	E	P	L	RP	RT	Sm	?s	DRF	Remarks
147	0.2	18	107	0	1	0	99	0	0	0	-	46 hrs. after ingestion of lysol.
	0.1	180	118	0	94	4	2	0	0	1	-	± 30 hours.
	0	23	10	0	88	6	2	0	0	4	-	4 th. day.

(The nucleated cells on the first count all had a dirty brown-purple colour. This continued in diminishing intensity while the urine remained dark and disappeared on the second day.)

Table 8

The Urinary Sediment in Miscellaneous Diseases

No.	Pr	RBCs	NCs	E	P	L	RP	RT	Sm	?s	DRF	Remarks
148	0.1	1.4	32	0	3	0	82	0	0	15	-	Alkalosis - renal failure. Necrobiosis ++++.
149	0	1.1	4.2	0	1	0	30	60	0	6	-	Pneumonia with low Sp.Gr. Urine.
150	1.3	0	56	0	97	3	0	0	0	0	-	Renal tuberculosis.

Experimental Results

Figure 25

Erect Lordosis.[1]

Experiment 1

The Incidence of Proteinuria and its Relation to Posture and Age

A. 14 to 16 year age group

The 1943, 1944 and 1946 classes of sea cadets, in all 129 subjects, were investigated as follows:-

On arrival at the ship's shore depot, the boys were fed and then remained sitting until they were called for medical examination. After completion of a full medical examination they were told that they had been accepted as cadets. This reassurance removed all anxiety. They were then instructed to empty their bladders and report for kit issue. For the next hour they sat marking kit or walking about quietly and were then called for urine examinations. A specimen of urine (Specimen 1) was collected. It will be noted that this specimen had been secreted during a period in which there had been no control of posture and during which no strenuous exercise had been undertaken. Then the cadets were made to stand immobile in a position of extreme lordosis (Figure 25) until a second specimen of urine could be passed (Specimen 2). This usually took about 15 minutes. Specimens 1 and 2 were examined quantitatively

for protein by the turbidimetric method. In all subjects in whom both Specimens 1 and 2 contained detectable quantities of protein, a third specimen of urine was obtained before rising next morning. (Specimen 3). The night had been spent in a posture of recumbent kyphosis in hammocks. Specimen 3 was also tested for protein.

Results

The results are shown in Tables 9 and 10 and in Figures 26 and 29 and are derived from Protocol

Table 9

The Numbers of Cadets with Detectible Proteinuria in three postures

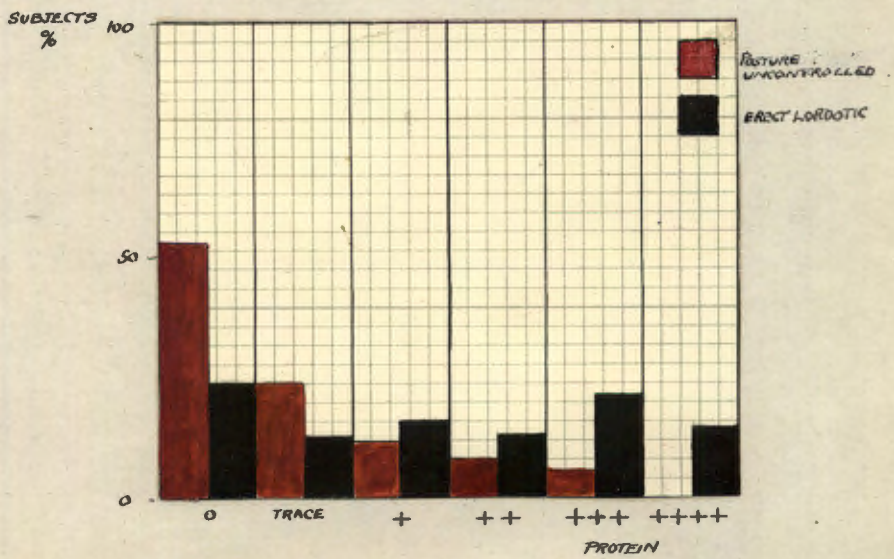
Class	Total	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic		Specimen 3 Recumbent
1943	37	15	55 %	30	81 %	0
1944	50	19	38 %	34	68 %	0
1946	42	26	62 %	35	84 %	0
Total	129	60	46.5%	99	77 %	0%

Table 10 and Figure 26

The Number of Cadets of All Years Divided into Groups According to the Amount of Protein Found in the Urine

Protein Conc.	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic		Specimen 3 Recumbent	
0	68	52.7%	51	24 %	99	100%
Trace	30	23.3%	15	11.6%	0	0 %
+	14	10.8%	20	15.5%	0	0 %
++	10	7.7%	17	13.2%	0	0 %
+++	7	5.5%	27	21.0%	0	0 %
++++	0	0 %	19	14.7%	0	0 %

Trace up to 9 mg./100cc.
\+ 10 to 29 mg./100cc.
++ 30 to 99 mg./100cc.
+++ 100 to 499 mg./100cc.
++++ above 500 mg./100cc.



B. 20 to 30 year age group

Fifty healthy male medical students between the ages of 20 and 30 years were used for this study.

After a period of uncontrolled posture, usually spent in sitting at lectures or walking about the wards, the students passed urine Specimen 1. They then stood in a posture of erect lordosis until they could pass another specimen of urine - Specimen 2. This usually required about 10 minutes. Specimens 1 and 2 were tested for protein.

Results

The maximum degree of lordosis obtained by this group was less than in the younger subjects but more than in the older. Tables 11 and 12 and Figures 27 and 29 show the results of the investigation. The data are derived from Protocol

Table 11

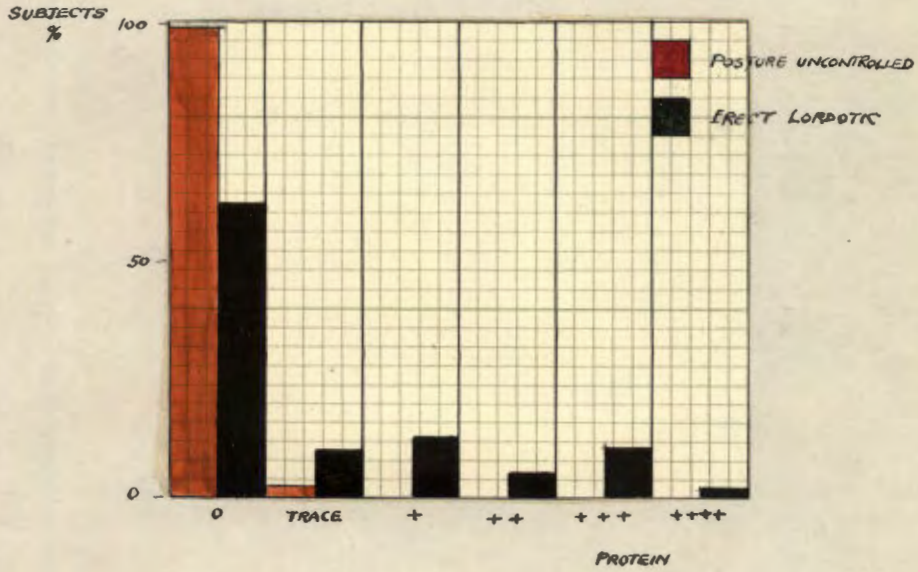
The Number of Students Between 20 and 30 Years of Age who Passed Protein in the Urine under Two Conditions of Posture

Total	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic	
50	1	2 %	18	36 %

Table 12 and Figure 27

The Number of Students Between 20 and 30 years of Age Divided into Groups According to the Amount of Protein in Specimens 1 and 2

Protein Conc.	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic	
0	49	98 %	32	64 %
Trace	1	2 %	4	8 %
+	0	0 %	6	12 %
++	0	0 %	2	4 %
+++	0	0 %	5	10 %
++++	0	0 %	1	2 %



C. 50 years and over age group

Fifty ambulant male patients above the age of 50 years and mostly suffering from isolated neurological lesions were examined.

A urine specimen was obtained after a period of uncontrolled posture (Specimen 1) and tested for protein. The men were then placed in a position of as great a degree of lordosis as they could attain until they could pass a further specimen of urine (Specimen 2). This specimen was also tested for protein.

Results

The maximum degree of lordosis obtained by this group was considerably less than in the younger subjects. Tables 13 and 14 and Figures 28 and 29 show the results of the investigation. The data are derived from Protocol

Table 13

The Number of Subjects Over 50 Years with Proteinuria

Total	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic	
50	1	2 %	6	12 %

Table 14 and Figure 28

The Number of Subjects Over 50 Years Old Divided into Groups According to the Amount of Protein Found in Specimens 1 and 2

Protein	Specimen 1 Posture Uncontrolled		Specimen 2 Erect Lordotic	
0	48	96 %	44	88 %
Trace	1	2 %	4	8 %
+	1	2 %	1	2 %
++	0	0 %	1	2 %
+++	0	0 %	0	0 %
++++	0	0 %	0	0 %

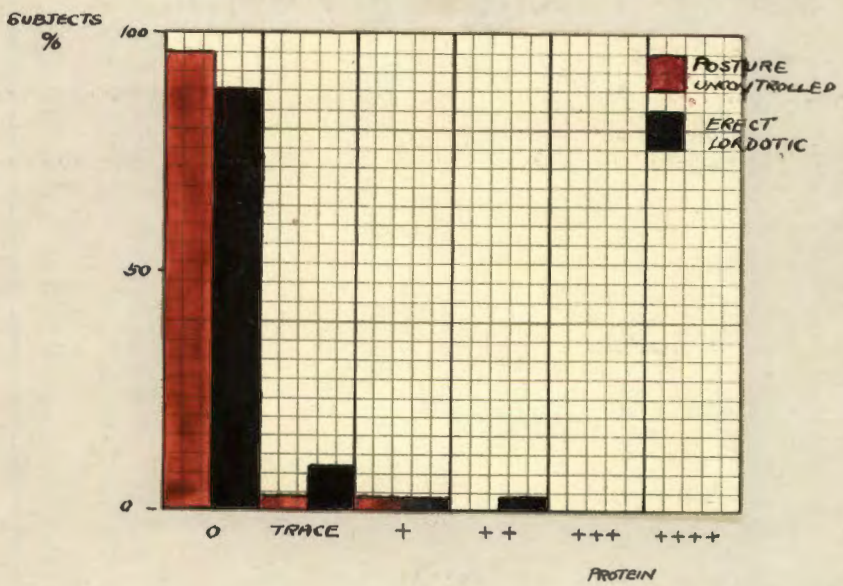
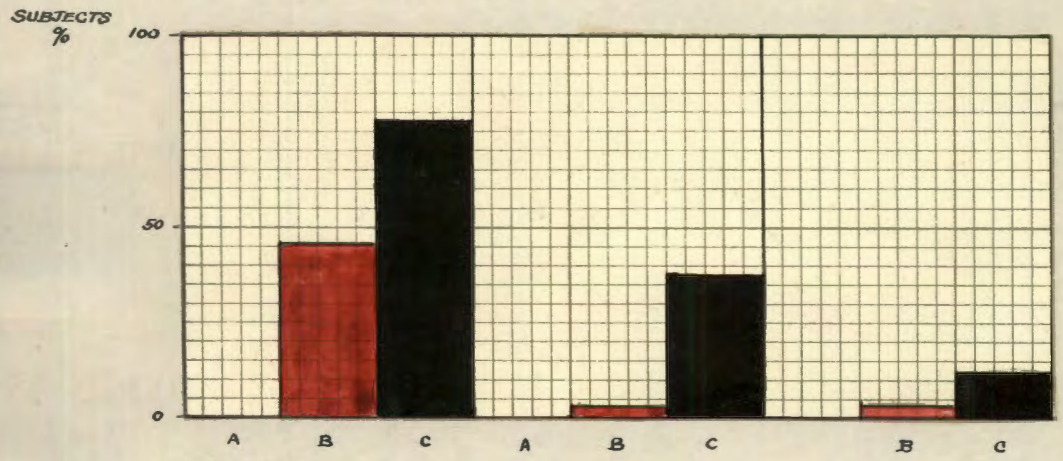


Figure 29

The Percentages of Subjects in all Age Groups Having Protein in the Urine in Various Postures



A. Recumbent kyphotic.

B. Posture uncontrolled.

C. Erect lordotic.

Comment

Tables 9,10,11,12,13 and 14 show that proteinuria was induced in the greatest number of subjects and in greatest concentration when the subjects were placed in a posture of extreme lordosis. Tables 9 and 10 show that in all the subjects examined no proteinuria occured when they were in a recumbent kyphotic posture.

Tables 9,10,11,12,13 and 14 show that a variable and smaller percentage of subjects secreted protein when their posture was uncontrolled than when they were in a posture of erect lordosis. Furthermore, they demonstrate that the degree of proteinuria was less when the subjects' postures were uncontrolled than when they were in erect lordosis.

Therefore, in the subjects examined, the proteinuria was manifestly related to posture and particularly to the erect lordotic posture.

Table 9 shows that approximately 3/4 of youths in the age group 14 to 16 years passed protein when they were in an erect lordotic posture. Table 11 shows that approximately 1/3 of the subjects in the age group 20 to 30 years and Table 13 shows that

approximately 1/10 of the subjects in the age group 80 years and above, passed protein under the same conditions. The relationship of proteinuria to age is shown also in Figure 29. The incidence of postural proteinuria, therefore, diminishes with age.

Tables 10 and 12 and Figures 26 and 27 show that the concentration of protein in the urine secreted in erect lordosis may be very considerable in a large proportion of cases. This is particularly the case in the younger subjects.

Conclusions

1. A postural mechanism was demonstrated to be responsible for the proteinuria in all the subjects examined.

2. The erect lordotic posture induced the greatest proteinuria.

3. No proteinuria occured in the recumbent kyphotic posture.

4. Postural proteinuria occurs in approximately 3/4 of youths about the age of 15 years, 1/3 of young men and 1/10 of men over the age of 50 years.

Figure 30

Recumbent Lordosis

Figure 31

Erect Kyphosis

Experiment 2

The Effect of Posture and Abdominal Support on Proteinuria

For this study, subjects numbers 4,6,11,15,20, 21 and 32 were taken at random from the proteinuric group of the 1944 class of cadets. In addition cases 168 to 175 were submitted to the same tests. These tests were designed to show in greater detail than had been done in Experiment 1, the effect of various postures on the passage of protein. In addition, the effect of application of a tight abdominal binder on the proteinuria was tested.

The procedure was as follows:-

After a period of uncontrolled posture, the subject presented himself and was instructed to empty his bladder. The urine was saved (Specimen A). He was now placed in various postures in turn and at the end of each period in a new posture (usually about half an hour) he emptied his bladder and the urine was tested for protein. The following postures were used in the order listed:-

Recumbent kyphosis (Specimen B).

Recumbent lordosis produced by placing pillows under the lumbar spine (Figure 30) (Specimen C).

Erect kyphosis produced by standing with one foot on a chair (Figure 31)(Specimen D).

Erect lordosis with a firm abdominal binder applied.

The binder was a many tailed bandage tightened from below upwards and was applied with the subject recumbent (Specimen E).

Erect lordosis without the abdominal binder. (Specimen F).

Results

The results are shown in Table 15.

Table 15

The Effect of Posture and the Application of a Tight Abdominal Binder on Postural Proteinuria

		Protein in mg. per 100 cc.												
No.	4	6	11	15	20	21	52	168	169	171	172	173	174	175
A	0	0	5	40	5	10	0	0	100	0	0	10	0	0
B	0	0	0	5	0	0	0		0	0	0	0	0	0
C	0	0	5	60	0	50	15		60	0	0	10	0	0
D	0	0	0	0	0	0	0		0	0	0	0	0	0
E	0	0	0	40	0	0	15	0	0	60	80	70	0	300
F	40	60	40	280	120	180	15	55	100	80	600	200	70	200

A Uncontrolled posture.
B Recumbent kyphotic posture.
C Recumbent lordotic posture.
D Erect kyphotic posture.
E Erect lordotic + binder.
F Erect lordotic without binder.

Comment

It will be noted that:-

1. The maximum proteinuria occured when the subjects were in erect lordosis.
2. Six of the subjects who secreted protein in erect lordosis also did so in recumbent lordosis.
3. With the exception of case 175, the proteinuria induced by the erect lordotic posture was lessened or abolished by the application of an abdominal binder.
4. In case 175, the application of an abdominal binder increased the proteinuria.
5. With the exception of case 15, all subjects secreted protein-free urine when in a kyphotic posture even when kyphosis was combined with standing.

In case 15, the small amount of protein found in the urine secreted in recumbent kyphosis was probably due to incomplete emptying of the bladder before lying down, resulting in admixture of protein-containing urine with the protein-free urine secreted in recumbent kyphosis. This was demonstrated to be the cause in several other cases in which the same phenomenon was found. In every case, a further period in this posture caused the urine to become protein-free.

Conclusions

1. Postural proteinuria is maximal in erect lordosis but can be induced in some subjects in recumbent lordosis.

2. The application of a firm abdominal binder usually prevents or diminishes the proteinuria induced by the erect lordotic posture but may increase it.

3. Proteinuria does not occur in recumbent or erect kyphosis.

Experiment 5

The Relationships of Blood Pressure, Posture and Proteinuria

Amongst the current theories of the pathogenesis of postural proteinuria are those relating the condition to vasomotor instability and renal disease. Experiment 5 was therefore carried out in conjunction with Experiment 1 in order to test these hypotheses. All 50 of the 1944 class of sea cadets were used.

Twenty minutes before passing urine Specimen 1, the cadets were placed in the dorsal decubitus position and 15 minutes later, while they remained in this position, estimations of the blood pressure were made on the right arm. Several readings were taken over the course of two minutes and further readings if the blood pressure continues to fall after 1½ minutes. If this occured, estimations were continued until two readings were the same. The lowest constant reading was recorded.

The subjects then passed urine Specimen 1 and stood in a position of extreme lordosis for about 8 minutes. They then stood in a normal erect posture for a few minutes while further recordings of the blood pressure were made by the same method.

Figure 32

The Systolic Pressure in Recumbency

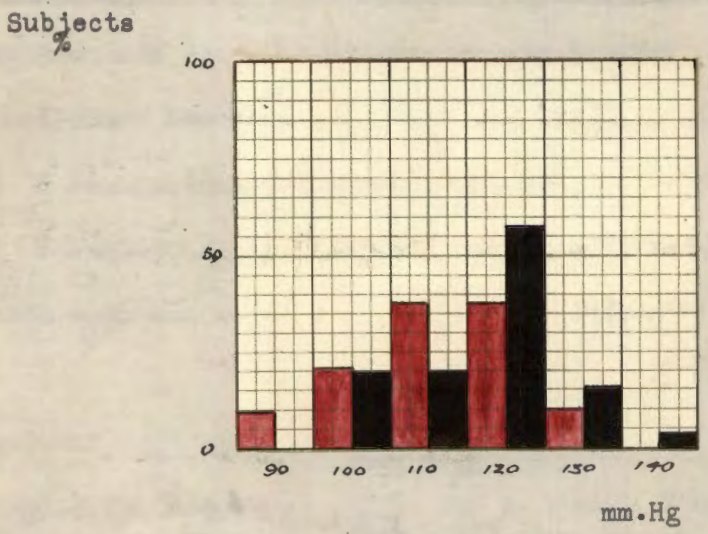
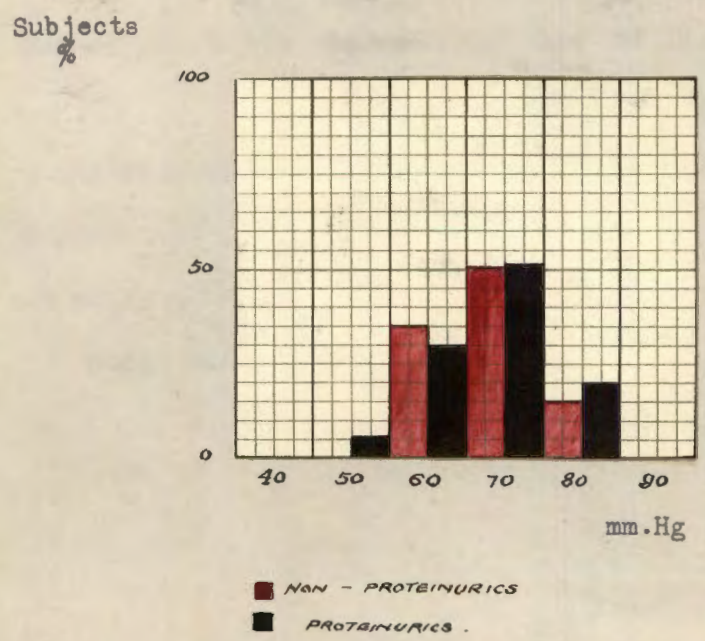


Figure 33

The Diastolic Pressure in Recumbency



Results

The results are shown in Tables 16,17,18 & 19 and in Figures 52,53,54 and 55. The data are derived from Protocol . The proteinuric group includes all subjects who passed a detectable quantity of protein when standing in lordosis.

Table 16

The Blood Pressure in Recumbency

	Mean Systolic Pressure		Mean Diastolic Pressure	
	mm.Hg	No.	mm.Hg	No.
Proteinuric group	116.9	33	66.0	33
Non Proteinuric group	110.5	14	66.8	14
Differences of the means	6.4		0.8	

For Systolic Pressure $0.05 < P < 0.1$

For Diastolic Pressure $0.7 < P < 0.8$

Figure 34

Changes in Pulse Pressure accompanying Change in Posture

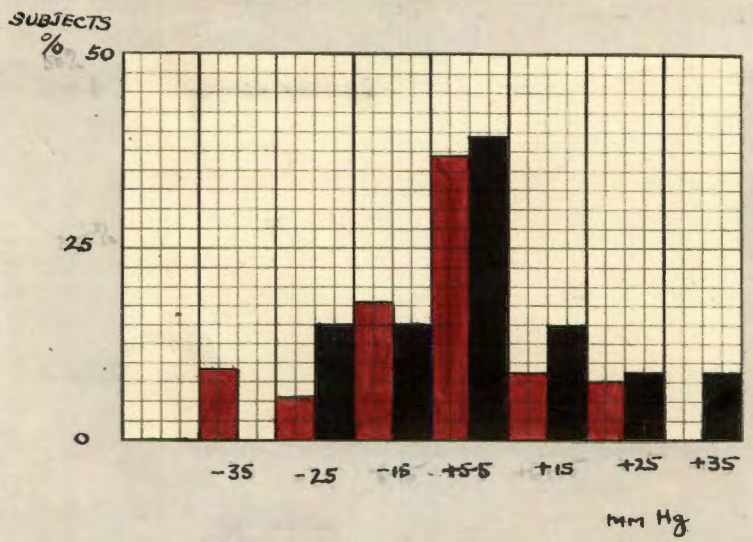


Table 17

Changes in Pulse Pressure with Change of Posture

The number of subjects in the proteinuric and non-proteinuric groups who showed a rise, no change or a fall in pulse pressure on assuming the erect posture.

Pulse Pressure	Proteinurics	Non-proteinurics
Rise	13	5
No Change	6	1
Fall	14	7

$0.2 < P < 0.5$

Table 18

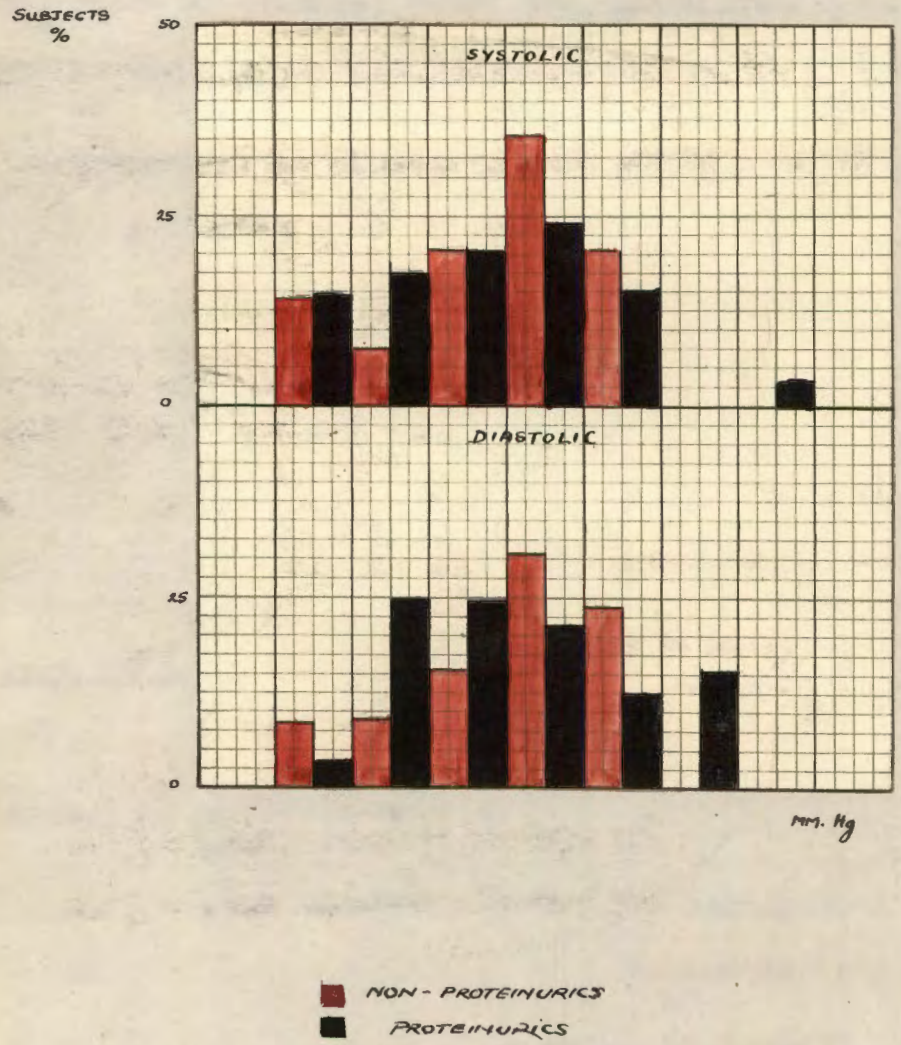
The Mean Fall in Pulse Pressure on Assuming the Erect Posture

	Mean Pulse Pressure Fall in mm. Hg.	No. Subjects
Proteinurics	1.8	33
Non Proteinurics	0.4	13
Differences of the means	1.4	

$0.7 < P < 0.8$

Figure 35

The Change in Blood Pressure on Assuming the Erect Posture



54

Table 19

The Change in Blood Pressure on Assuming the Erect Posture

The means of the rises in systolic and diastolic pressures on assuming the erect posture.

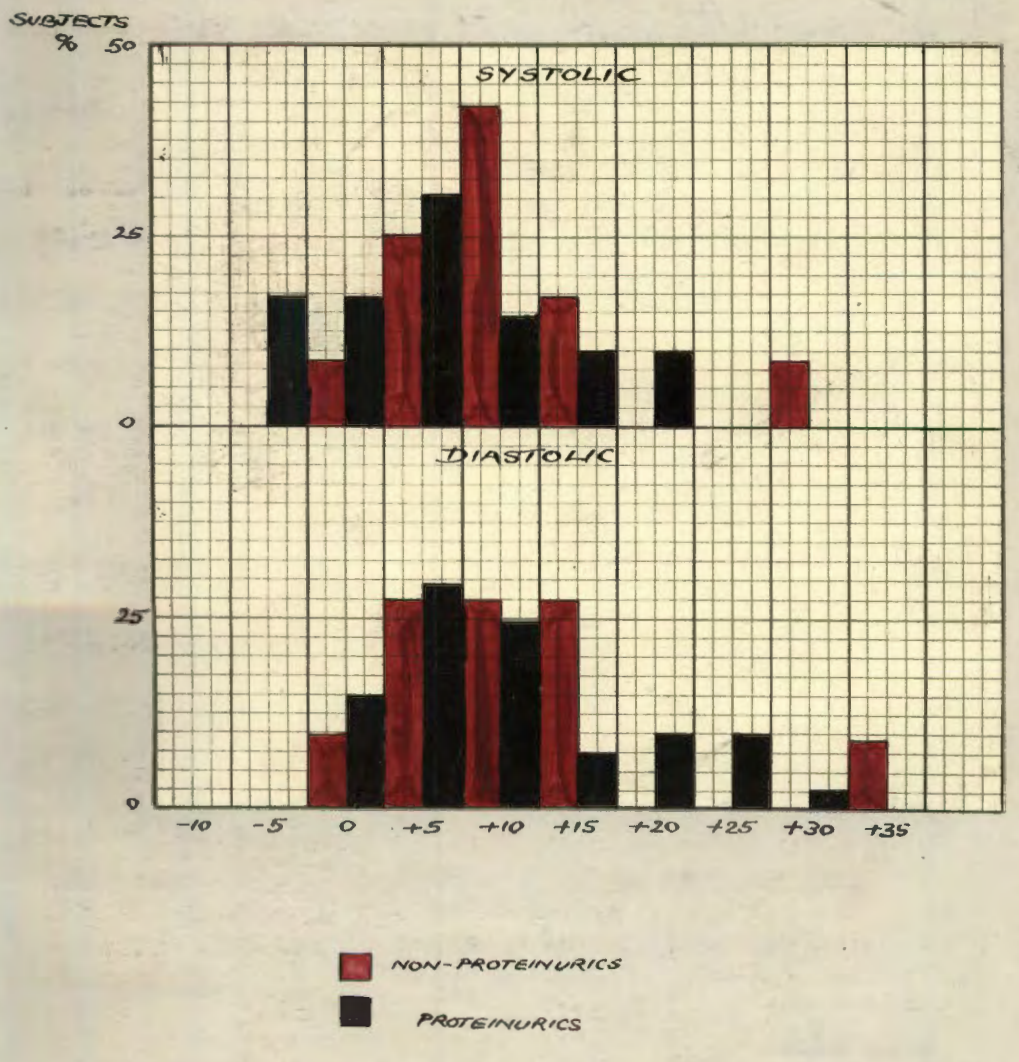
	Mean Systolic Rise		Mean Diastolic Rise	
	mm.Hg	Subjects	mm.Hg	Subjects
Proteinurics	2.8	33	5.8	33
Non-proteinurics	3.6	14	4.6	13
Differences of means	0.8		1.2	

For Systolic Pressure $0.8 < P < 0.9$

For Diastolic Pressure $0.7 < P < 0.8$

Figure 36

The Changes in Blood Pressure on Application of the Cold Pressor Stimulus



Comment

The values for P are consistently high and indicate that not only is there no detectable significant difference between the proteinuric and non-proteinuric groups in respect of the characteristics examined but also that they show a high degree of similarity. In particular it will be noted that:-

1. The systolic and diastolic blood pressures of subjects with postural proteinuria do not differ significantly from those without proteinuria (Table 16 and Figs.32 & 33).
2. Proteinuria may occur with rising or falling pulse pressures and the incidence of rising and falling pulse pressures is not significantly different in the proteinuric and non-proteinuric groups (Table 17).
3. The degree of fall of pulse pressure is not significantly greater in subjects with postural proteinuria than in non-proteinurics (Table 18 and Figure 34).
4. There is no difference in lability of the systolic or diastolic blood pressures on change of posture in subjects with postural proteinuria as compared with non-proteinurics (Table 19 and Figure 35).

Conclusions

Postural proteinurics do not differ from non-proteinurics in respect of their resting blood pressures or in the responses of their blood pressures to changes in posture.

Experiment 4

The Cold Pressor Test

This experiment was designed to disclose any differences in lability of the blood pressure between postural proteinuric and non-proteinuric subjects. Fortyone of the 1944 class cadets were used. Half an hour after they had retired to their hammocks in the evening, a cold pressor test was performed.

Results

The results are shown in Table 20 and Figure 36 and are derived from Protocol

Table 20

The Cold Pressor Test in Proteinuric and Non-proteinuric Cadets

This table shows the mean, maximum rise of systolic and diastolic pressures in the proteinuric and non-proteinuric groups. As the pressure in all cases returned to the basic level within 2 minutes or less of the application of the cold stimulus, the time factor has not been analysed.

	Mean Systolic Rise		Mean Diastolic Rise	
	mm.Hg	Subjects	mm.Hg	Subjects
Proteinurics	5.7	29	10.7	29
Non-proteinurics	10.4	12	11.4	11
Differences of means	4.7		0.7	

For Systolic Pressure $0.05 < P < 0.1$

For Diastolic Pressure $0.8 < P < 0.9$

Comment

The results show that the response to the cold pressor stimulus was less in the proteinuric group than in the non-proteinuric but that the difference in the means is not statistically significant. Furthermore it will be seen from Figure 36 that the variations in response are similar in the two groups.

Conclusion

There is no significant difference between the behaviour of subjects with postural proteinuria and non-proteinurics towards the cold pressor stimulus.

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Experiment 5

Past Illnesses of the 1944 Class Sea Cadets

In order to obtain information for the purpose of testing the theory that postural proteinuria is related to certain diseases, particularly nephritis, a medical history was taken from 46 of the 1944 class of sea cadets. Results. The results are shown in Table 21 and are derived from Protocol

Table 21

The Frequency of Occurrence of Diseases from the Past Histories of Proteinuric and non-proteinuric Cadets

	Proteinuric Group 32 Subjects		Non-proteinuric Group 14 Subjects	
	Number	%	Number	%
Chicken Pox	21	65 %	10	71 %
Whooping Cough	17	53 %	7	50 %
Measles	25	78 %	12	86 %
Mumps	10	31 %	7	50 %
"Tonsillitis" *	13	40 %	7	50 %
German Measles	3	9 %	1	7 %
Scarlet Fever	3	9 %	2	14 %
Appendicitis	3	9 %	0	0 %

* Under "Tonsillitis" are grouped all subjects giving a history of tonsillitis or who had had their tonsils removed.

Osteitis, intussusception, enteric fever, broncho-pneumonia, malta fever, influenza, jaundice, migraine, asthma and diphtheria each occured once in the proteinuric group. Malaria occured twice and pneumonia and jaundice once each in the non-proteinuric group. No case in either group gave a history of renal disease.

Comment

It will be noted that there is no disproportionate occurrence of any disease in either group. Tonsillitis, which might be expected to predispose to nephritis, occured less often in the proteinuric group than in the non-proteinuric but the difference is small and not significant. Scarlet fever, which also predisposes to nephritis, occured very infrequently in both groups and again there is no significant difference in incidence.

Conclusions

1. Postural proteinuria can occur without a past history of renal disease or scarlet fever or tonsillitis which might predispose to renal disease.

2. There is no significant difference between the proteinuric and non-proteinuric groups in the incidence of past disease.

Experiment 6

General Examination

In order to obtain information for the purpose of testing the theory that postural proteinuria is related to certain diseases, particularly nephritis, a routine clinical examination was carried out on all 129 cadets.

Results. None of the cadets showed signs of oedema, cardiac enlargement or of arteriosclerotic or other changes in the fundi.

One subject in the 1944 class and one in the 1946 class each had a small varicocoele.

The blood Wassermann reaction was done on all the cadets in the 1944 class and was negative in every instance.

The test for cold agglutinins in the sera of all the cadets of the 1944 class showed titres of agglutinin below 1 in 20 in every case.

For the rest, apart from the proteinuria, general examination of all the cadets revealed no abnormalities.

Conclusion

None of the physical signs that characterise obvious nephritis accompany the proteinuria in postural proteinurics.

Experiment 7

Follow-up Study

In order to obtain information for the purpose of testing the theory that postural proteinuria is related to certain diseases, particularly nephritis, the 1943 and 1944 classes of cadets were followed for two years and the 1946 class for 6 months.

None of the cadets examined subsequently developed symptoms or signs suggestive of nephritis.

Approximately half of the 1943 and 1944 classes developed German measles during 1944. Cases occurred in both the proteinuric and non-proteinuric groups.

Five of the 1943 and four of the 1944 class developed appendicitis during their two years' training.

One subject in the 1945 class developed pulmonary tuberculosis.

For the rest, apart from injuries and minor ailments such as colds, the cadets have remained in good health.

Conclusion

Six to twentyfour-month follow up study reveals no tendency for postural proteinurics to develop patent nephritis or other renal disease.

Experiment 8

Correlation of Proteinuria with Body Build

The view has been expressed that postural proteinuria occurs more readily in persons of a certain build. The hypothesis was tested in this experiment, using the 1944 class of sea cadets. The following data were obtained by questioning or measurement:-

1. The concentration of protein in the urine secreted in erect lordosis (Data from Experiment 1).
2. The age to the nearest month.
3. The weight in pounds.
4. The height to the nearest half inch.
5. The ratio weight / height.
6. The ratio of the circumference at the nipple line in inspiration to the circumference at the umbilicus.

The weight / height ratio was used as an index of body build. In sthenic individuals the ratio should be high and in asthenics low. The ratio of the circumference at the nipple to the circumference at the umbilicus was used as an index of abdominal obesity.

Results

The results are shown in Table 22 and are derived from Protocol . Figures 37,38,39 and 40 show examples of proteinuric and non-proteinuric cadets.

Table 22

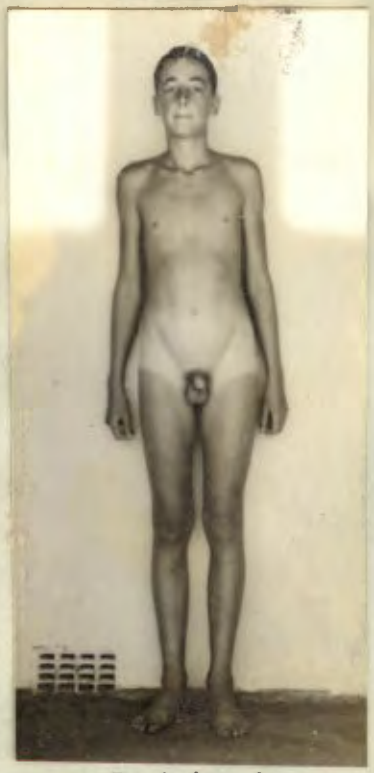
Correlations of Proteinuria with Body Build

Correlations	Coefficients	Probabilities
r 12	+ 0.15180	0.1 $\angle$ P
r 13	+ 0.27537	0.05 $\angle$ P (P is very near 0.05)
r 14	+ 0.16951	0.1 $\angle$ P
r 15	+ 0.30955	0.02 $\angle$ P $\angle$ 0.05
r 16	+ 0.17716	0.1 $\angle$ P
r 23	+ 0.50074	
r 24	+ 0.49924	
r 25	+ 0.49368	
r 26	+ 0.15007	
r 34	+ 0.68590	
r 35	+ 0.90071	
r 36	+ 0.57816	
r 45	+ 0.56495	
r 46	+ 0.39642	
r 56	+ 0.56833	
r 13.2	+ 0.2495	P is nearly 0.1
r 15.2	+ 0.2836	0.05 $\angle$ P $\angle$ 0.1

Figure 37

Proteinuric
Height/weight ratio

Figure 38



Proteinuric
Height/weight ratio

Figure 39

Non-proteinuric
Height/weight ratio

Figure 40

Non-proteinuric
Height/weight ratio

Comment

It will be noted that with the exception of the correlation coefficient r 15 which related proteinuria to the ratio weight/height, none of the correlations is significant. r 15 suggests that proteinuria is commoner in subjects with high weight/height ratios i.e. sthenics. However, the partial correlation coefficient r 15.2 relating proteinuria to the weight/height ratio but correcting for age, shows that this ratio is not significantly related to proteinuria.

r 13 relating proteinuria to weight borders on significance but if this is similarly corrected for age (r 13.2) it becomes definitely non-significant.

The correlation r 12 or proteinuria with age is not significant but in view of the limited age group of 14 to 16 years used in this study, it does not mean that there might not have been a significant correlation if a wider age group had been used.

Conclusions

Postural proteinuria is not related to height or weight or the degree of abdominal obesity. It does not occur more commonly in sthenic or asthenic persons.

Figure 41

Lumbar Curve
Normal

Figure 42

Lumbar Curve
Plus

Experiment 9

The Relationship of Lumbar Lordotic Build to Postural Proteinuria

The view has been expressed that postural proteinuria is more common in subjects with marked lumbar lordosis. In order to test this hypothesis, the degree of lumbar lordosis in 47 of the 1944 class sea cadets was classified on an arbitrary scale as normal or more than normal. Figures 41 and 42 illustrate the types.

Results

The results are shown in Table 23, derived from Protocol

Table 23

The Lumbar Curve in Postural proteinurics and Non-proteinurics

	Lumbar Curve	
	Normal	Above Normal
Proteinurics	24	7
Non-proteinurics	15	3

Comment

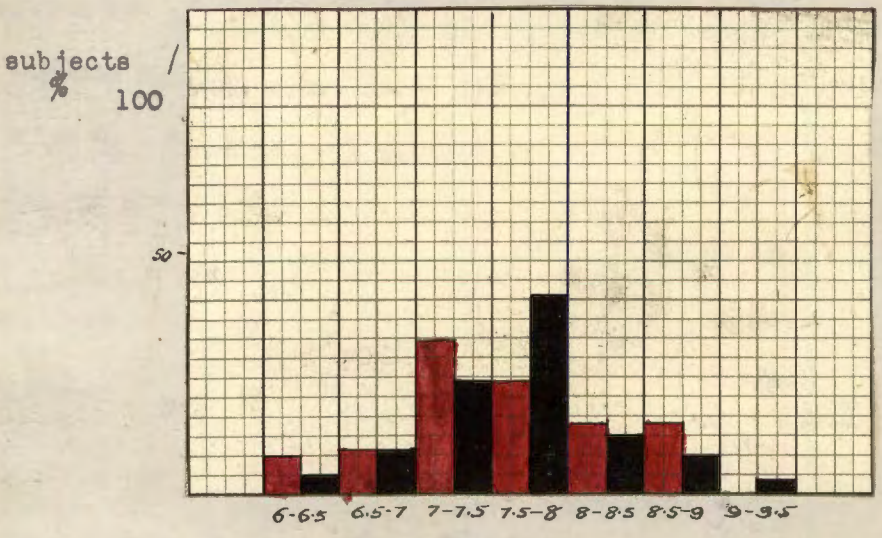
The degree of lumbar lordosis is very similar in the two groups. This confirms an impression obtained from all the cases of postural proteinuria examined.

Conclusion

Subjects with postural proteinuria do not have a tendency to undue lumbar lordosis.

Figure 43

The Serum Protein Concentrations of the 1944 Class Cadets



Protein concentration
Gms. / 100 cc.

Non-proteinurics

Proteinurics

Experiment 10

Serum Protein Determinations

The object of this experiment was to determine whether postural proteinurics had low serum protein concentrations which might indicate that they were suffering from nephritis. 39 of the 1944 class of sea cadets were used for this experiment. The total serum protein concentrations were determined by the falling drop method.

Results. The results are shown in Table 24 and Figure 43 and are derived from Protocol

Table 24

The Serum Protein Concentrations of the 1944 Class of Cadets

	Mean Concentration Serum Proteins Gm. / 100 cc.	No. of Subjects
Proteinurics	7.7	26
Non-proteinurics	7.7	13

Differences of the variances: 0.300

Error of the difference of the variances: 1.309

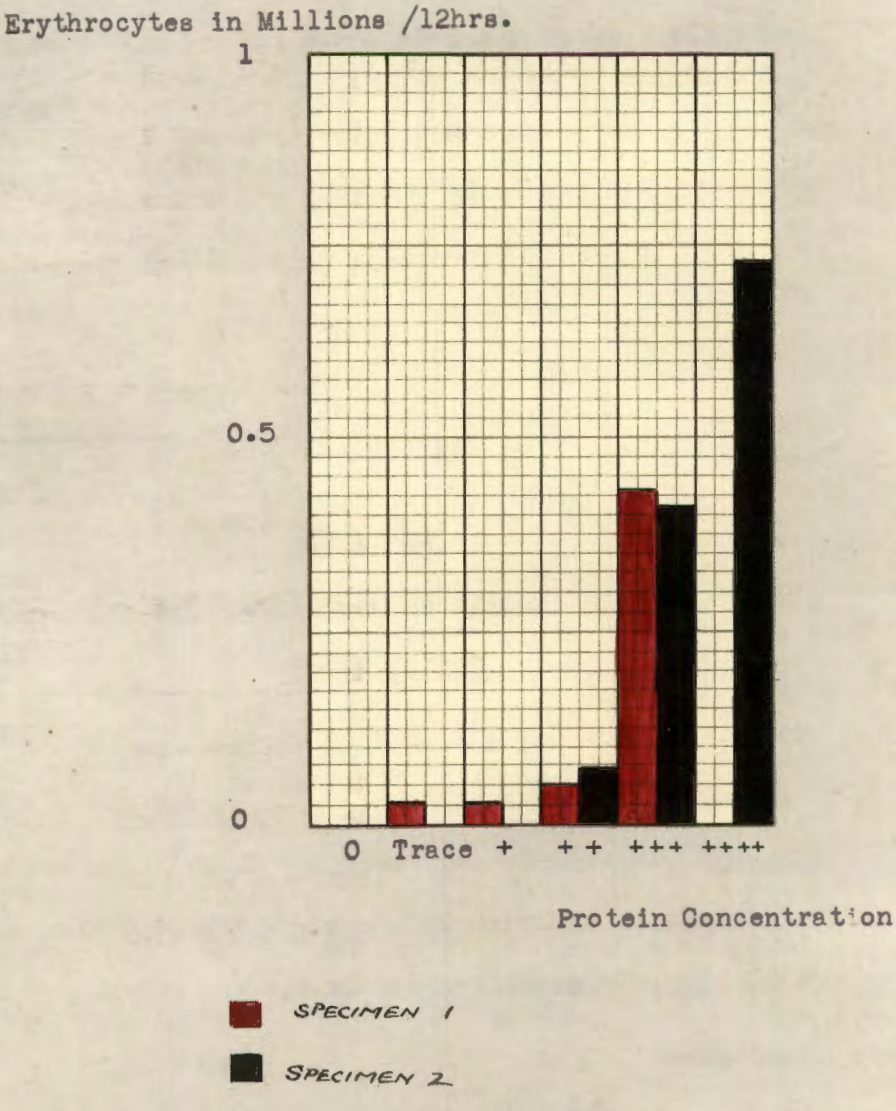
Comment. It will be seen that not only is the mean protein concentration the same in the two groups but also that there is no significant difference in the variances.

Conclusion

The serum protein concentrations of postural proteinurics are within normal limits and within these limits do not differ from those of non-proteinurics.

Figure 44.

The erythrocytes in the urinary sediment related to proteinuria



Experiment 11

Microscopic Examination of the Urine

This study was undertaken to establish the urine sediment picture in postural proteinurics and normal subjects. All 42 members of the 1946 class of sea cadets were used for the study. Urine specimen 1 of Experiment 1 which was secreted under uncontrolled conditions of posture and urine specimen 2 secreted in lordosis were collected and examined microscopically. Total and differential counts were made on the sediment.

Results

The results are shown in Tables 25,26 and 27 and in Figures 44 and 45 and are derived from Protocol

Table 25

Urinary Sediment Counts of Cadets when the Posture was Uncontrolled

Protein	No.	Formed elements in millions per 12 hrs.					
		RBCs		Nucl. Cells		Casts	
		Mean	Range	Mean	Range	Mean	Range
0	14	0	-	0.116	0 - 0.7	0.001	0-0.02
Trace	10	0.03	0 - 0.2	0.196	0 - 0.7	0.01	0-0.1
+	6	0.03	0 - 0.1	0.308	0 - 0.9	0.016	0-0.1
++	4	0.05	0 - 0.2	0.2	0 - 0.4	0.025	0-0.1
+++	8	0.43	0 - 1.6	1.44	0 - 3.1	0.062	0-0.3

Figure 45

The nucleated cells in the urinary sediment related to proteinuria

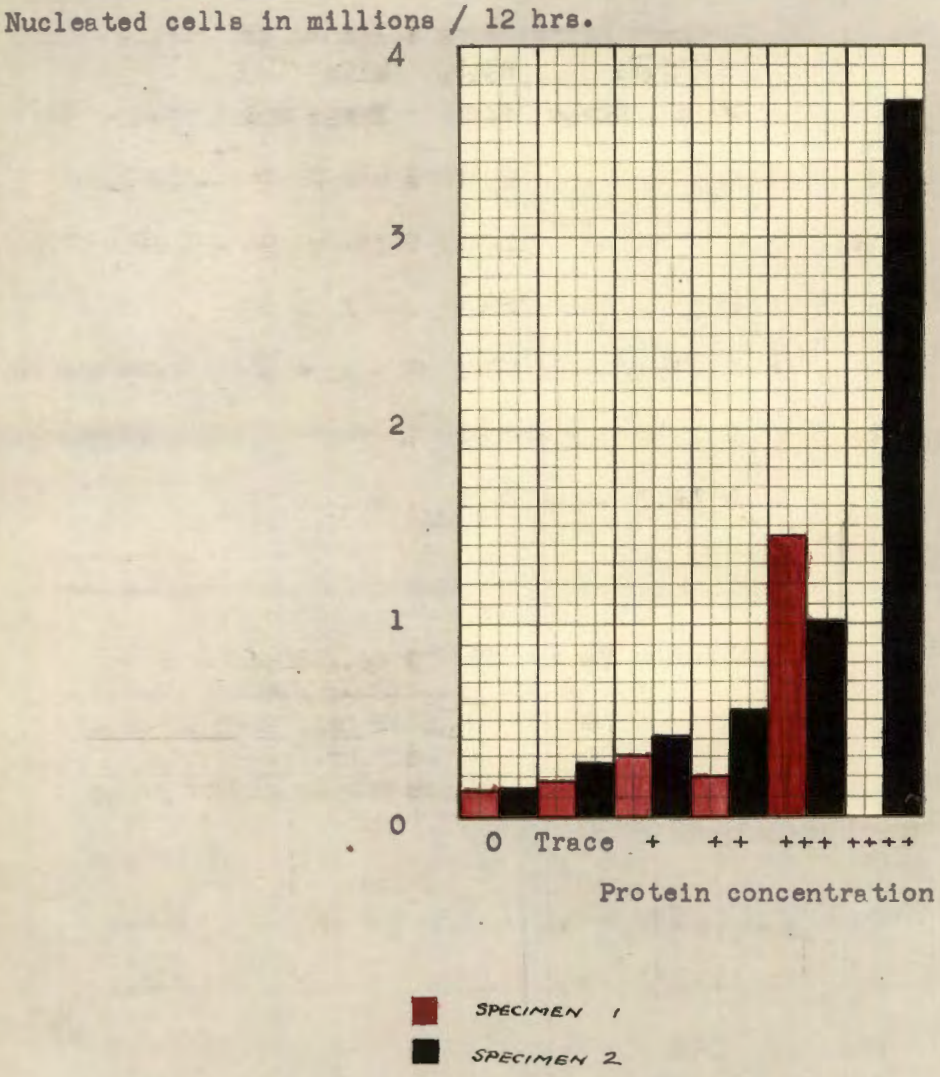


Table 26

Urinary Sediment Counts of Cadets when in the Erect Lordotic Posture

Protein	No.	Formed elements in millions per 12 hrs.					
		RBCs		Nucl. Cells		Casts*	
		Mean	Range	Mean	Range	Mean	Range
0	7	0	-	0.14	0 - 0.5	0	-
Trace	5	0	-	0.287	0.19-0.7	0	-
+	7	0	-	0.419	0 - 1.58	0.04	0 - 0.3
++	7	0.073	0 -0.51	0.557	0 - 2.04	0	-
+++	8	0.41	0 - 2.6	1.066	0.2-5.2	0.35	0 - 2.6
++++	7	0.73	0 - 2.4	3.715	0 - 10.8	0.49	0 - 1.5

Trace	1 - 9 mg./100cc.
+	10 - 29 mg./100cc.
++	30 - 99 mg./100cc.
+++	100-499 mg./100cc.
++++	above 499 mg./100cc.

* All casts were granular or hyaline.

Table 27

Differential Nucleated Cell Counts in the Urine

	Proteinurics %	Non-proteinurics %
Polymorphs	10	6
lymphocytes	16	4
Renal Tract Cells	52	66
Renal Parenchymal Cells	1	2
Small cells	13	10
Unclassifiable Cells	8	12

These figures show the mean percentages of the various types of cell making up the total nucleated cell count in Specimen 2. As the cells were so scanty, these percentages had to be calculated from the sum of all the cells seen, instead of from the mean percentages of the individual cases.

Comment

Comparison of the results in Tables 25 and 26 show that when subjects change from an uncontrolled posture to one of extreme lordosis the following occur:-

1. There is an increase in the number of subjects secreting protein in the urine.
2. The concentration of protein in the urine of subjects already secreting it rises.
3. Parallel to these increases is an increase in the output of all the formed elements in the urine and particularly of the nucleated cells.

Figures 44 and 45 illustrate the increased output of cells.

Table 27 shows that the types of nucleated cells passed and their distribution is very similar in proteinurics and non-proteinurics. The greater proportion of lymphocytes found in the urine of proteinurics is probably not significant because of the difficulty in differentiating these from renal parenchymal cells in some urines.

Conclusions

1. Postural proteinuria is accompanied by an increase in the output of all formed elements in the urine.

2. Differential nucleated cell counts show that the types and proportions of cells passed by proteinurics are similar to those found in non-proteinurics.

Experiment 12

Clearance Studies

This experiment was undertaken to establish the dynamics of kidney function in postural proteinurics. Clearances were done on nine subjects.

Results

The results are shown in Table 28.

Table 28

The Clearances of Various Substances in Postural Proteinurics in Different Postures

Case	Recumbent kyphosis cc./min.					Erect kyphosis cc./min.					Erect lordosis cc./min.				
	Urine flow	Endogenous creatinine clearance	Urea clearance	Plasma diotrast clearance	Plasma chloride clearance	Urine flow	Endogenous creatinine clearance	Urea clearance	Plasma diotrast clearance	Plasma chloride clearance	Urine flow	Endogenous creatinine clearance	Urea clearance	Plasma diotrast clearance	Plasma chloride clearance
171	7.1	-	84	-	-	3.3	-	45	-	-	0.55	-	35	-	-
170	1.2	-	57	-	-	-	-	-	-	-	1.2	-	28	-	-
179	11.6	186	-	-	-	7.4	200	-	-	-	0.55	13	-	-	-
	8.7	128	-	-	-	0.77	118	-	-	-	0.23	69	-	-	-
180	10.35	92	78	449	1.7	16.15	103	85.5	498	1.68	2.09	77	27	396	0.78
185	17.7	148	-	545	-	-	-	-	-	-	11.0	98.5	-	396	-
186	17.30	-	106	660	-	14.6	-	129	859	-	3.21	-	67	610	-
187	4.1	-	68	-	-	-	-	-	-	-	1.3	-	25	-	-
199	2.9	218	193	-	-	1.95	125	116	-	-	0.66	156	140	-	-
200	0.65	-	-	-	-	-	-	-	-	-	0.41	84	-	-	-

The results shown in Table 27 are analysed below in Tables 29 and 30.

Table 29

Urine Flow Related to Glomerular Filtration Rate

Case		Recumbent (cc./min.)	Erect Lordotic (cc./min.)	Erect/Recumbent %
179	Urine flow	11.6	0.55	4.75
	Glomerular filtration	186	13	7
	Urine flow	0.7	0.23	33
	Glomerular filtration	120	60	50
180	Urine flow	16.4	2.09	12.3
	Glomerular filtration	92	77	78.5
185	Urine flow	17.7	11	62
	Glomerular filtration	146	98.5	62
199	Urine flow	7.9	0.68	8.7
	Glomerular filtration	210	156	74.5
200	Urine flow	0.65	0.41	63
	Glomerular filtration	89	84	94

The last column shows the rates of urine flow and the glomerular filtration rate in lordosis expressed as a percentage of those in recumbency.

Table 30

Renal Plasma Flow in Relation to Glomerular Filtration Rate, Urine Flow and Urea Clearance

Case	Posture	Urine flow	Renal plasma flow	Glomerular filtration	Urea Clearance	Filtration fraction
180	Recumbent kyphotic	16.35	449	92	70	20.05
	Erect kyphotic	16.15	490	103	65.5	21.0
	Erect lordotic	2.09	326	77	27	25.6
185	Recumbent kyphotic	17.7	545	146	-	26.8
	Erect lordotic	11.0	306	98	-	32.2
186	Recumbent kyphotic	17.36	860	-	108	-
	Erect kyphotic	14.6	859	-	120	-
	Erect lordotic	3.21	610	-	67	-

Comment

It will be seen from Table 28 that there is little difference between the clearances in recumbent kyphosis and erect kyphosis.

Tables 28 and 29 shos that the urine flow in the erect lordotic posture may drop to as little as 5 % of that in the recumbent posture and Table 29 shows that this drop in urine flow is usually considerably more than can be accounted for by the drop in glomerular filtration rate that accompanies it.

Table 30 shows that when the subject changes from recumbent kyphosis to the erect lordotic posture, a drop in effective renal plasma flow occurs.

Tables 28 and 30 show that the urea clearance is less in the erect lordotic than in the recumbent kyphotic posture and that the diminution is more than can be accounted for by the parallel drop in renal plasma flow and glomerular filtration rate. This indicates that there is a greater tubular reabsorption of urea in erect lordosis. It will be noted that there is a comparable increase in water reabsorption under the same conditions.

Table 30 shows that on changing posture from recumbent kyphosis to erect lordosis there is a rise in the filtration fraction.

Conclusions

In subjects with postural proteinuria, changing the posture from recumbent kyphosis to erect kyphosis produces no significant alteration in renal dynamics. However, on assuming the erect lordotic posture, there is a drop in renal plasma flow and in glomerular filtration rate. This drop in glomerular filtration rate is less than would be expected from the diminution in plasma flow, which indicates that a greater proportion of the plasma is filtered at the glomerulus under these conditions.

The rate of water and urea excretion is less in erect lordosis than in recumbent kyphosis and this is in part due to a drop in glomerular filtration but mostly due to greater tubular reabsorption of these substances.

Experiment 13

The Urinary Proteins in Postural Proteinuria

It has previously been reported that low albumin/globulin ratios occur in the urine of postural proteinurics. This experiment was designed not only to test this statement but also to attempt to discover under what conditions high and low albumin/globulin ratios occur in the urine. The quantities of albumin and globulin in the urine and the ratio of albumin to globulin were determined 32 times in 17 subjects by the turbidimetric method and 26 times in 12 subjects by the Biuret method. In two cases, the subjects were placed in a lordotic posture on a tilting table and the urine collected by catheter after periods in varying degrees of tilt from the horizontal.

Results

The results are shown in Tables 31, 32, 33 and 34.

Table 51

Urinary Proteins in Postural Proteinuria by the Turbidimetric Method

Case No.	Albumin mg./100cc.	Globulin mg./100cc.	Albumin/Globulin Ratio
1	20	0	
2	20	0	
3	5	0	
	3	0	
	80	0	
4	40	0	
6	60	30	2
11	5	0	
	3	0	
	40	0	
15	40	+	
	180	++	
20	5	0	
	5	0	
	110	10	11
21	10	0	
	50	0	
	160	20	8
32	15	0	
173	90	10	9
	10	0	
	190	10	19
	70	10	7
	10	0	
176	460	40	11
182	660	60	11
185	60	5	12
	170	30	6
188	40	10	4
191	10	0	
	65	15	4
193	760	40	19
	40	5	8

Table 52

Urinary Proteins in Postural Proteinuria by the Biuret Method

Case No.	Total Protein mg./100cc.	Albumin mg/100c	Globulin mg/100cc	Albumin/globulin Ratio
168	65	40	15	2.7
172	790	478	312	1.5
174	70	40	30	1.3
178	104	86	18	4.8
179	780	555	245	2.2
	485	302	183	1.9
	1131	692	439	1.6
	603	535	68	7.9
	1445	1020	425	2.4
	465	414	51	8.1
180	603	535	68	7.9
	291	261	30	8.7
	551	446	145	2.1
180	840	300	540	0.6
184	160	140	20	7.0
199	120	61	59	1.0

Table 35

The Effect Of Tilting a Postural Proteinuric Subject from the Horizontal to the Erect Posture on the Urine Flow Output of Albumin and Globulin and on the Creatinine Clearance

(Case No.200)

°T	V/mn	Vol.	T	TP	A	G	A/mn	G/mn	A/G	Cr.Cl.
15	0.65	6.5	10	0	0	0	0	0	-	89
30	1.01	10.1	10	0	0	0	0	0	-	116
45	0.8	8.0	10	0	0	0	0	0	-	125
60	0.65	6.5	10	57	57	0	0.24	0	/1	99
75	0.41	6.2	15	167	153	14	0.68	0.06	10.9/1	64.5
90	0.41	6.2	15	242	121	121	0.50	0.50	1/1	63.5
75	0.40	6.0	15	207	151	66	0.55	0.26	2/1	66
60	0.38	5.8	15	268	125	143	0.48	0.55	0.87/1	91
45	0.40	6.0	15	207	168	39	0.67	0.16	4.3/1	88.5
30	-	-	15	199	99	100	-	-	1/1	-

°T - Degrees of tilt from horizontal.
V/mn - Urine flow in cc./min.
Vol. - Volume of urine passed per period.
T - Duration of period in minutes.
TP - Total protein in mg. per 100 cc.
A - Albumin concentration in mg. per 100cc.
G - Globulin concentration in mg. per 100cc.
A/mn - Albumin passed in mg. per minute.
G/mn - Globulin passed in mg. per minute.
A/G - Albumin/Globulin ratio.
Cr.Cl. - Creatinine clearance in cc./min.

Table 34

The Effect of Tilting a Subject with Postural Proteinuria from the Horizontal to the Erect Posture on the Concentration of Albumin and Globulin in the Urine (Case No. 186)

°Tilt	Total Protein mg./100cc.	Albumin mg/100cc	Globulin mg/100cc	Albumin/Globulin Ratio
0	0	0	0	-
15	0	0	0	-
30	0	0	0	-
45	0	0	0	-
60	0	0	0	-
75	49	46	3	15/1
90	76	63	13	5/1

Comment

The results show that there is considerable variation in the output of albumin and globulin and in the albumin / globulin ratio from case to case and in individual cases. For example, in Case 200, the ratio of albumin / globulin varied from infinity/1 to 0.87/1. Tables 31 and 32 show that there is a tendency for the albumin / globulin ratio to be high when small amounts of protein are being passed and to be lower when the concentrations of protein are high. In every case where multiple determinations revealed a rising concentration of protein in the urine, the first protein to appear was albumin.

Conclusions

There is considerable individual and case to case variation in the ratio of albumin to globulin in the urine of postural proteinurics. At low concentrations of total protein and when subjects pass increasing amounts of protein, albumin is the first protein to appear in the urine.

Experiment 14

Ureteric Catheterisation

This experiment was designed to determine whether one or both kidneys secrete protein during postural proteinuria. Three subjects with this condition, Cases 164,187 and 190 were used for the experiment. Mr.Goldschmidt kindly inserted catheters into the ureters of these patients under local anaesthesia. After urine flow had commenced through the catheters, the subjects were made to stand in forced lordosis and the urine secreted from the right and left kidneys collected separately and tested for protein.

Results

The results are shown in Table 55. In cases 164 and 187, it was fortunate that no blood contaminated the specimens but in case 190, on assuming the erect posture, both catheters commenced to discharge slightly blood-stained urine. The urine from the right side contained more blood than that from the left.

Table 55

Concentration of Protein in Urine from the Right and Left Kidneys

Case No.	Right Kidney mg./100 cc.	Left Kidney mg./100cc.
164	93	87
187	37	19
190	22	70

Comment

In cases 184 and 187, the results clearly demonstrate that both kidneys secreted protein. In case 190, owing to contamination of the urine with blood, one cannot be certain whether the right kidney secreted protein at all. One can, however, see that the left secreted protein because the urine from the left side contained more protein and less blood than that from the right.

Conclusion

In postural proteinuria, both kidneys may secrete protein.

Experiment 15

Foot-to-tongue Circulation Times in Proteinuric Subjects and Non-proteinuric Controls

This experiment was designed to show any possible delay in venous return from the lower extremities which would indicate inferior vena cava obstruction. In preliminary experiments, it was found that satisfactory end points were difficult to obtain when the subjects were in the erect posture, so subjects were chosen for this experiment on the basis of their having proteinuria in recumbent lordosis. Cases 155 to 163 and 165 and 166 were used. It will be noted that Cases 155,156,161,162 and 163 were all 5 or 6 years old.

As insufficient Decholin could be obtained for the whole series, 10 % calcium gluconate solution had to be substituted in some of the cases. Where calcium gluconate was used, only those subjects who gave distinct end points were included.

The results are shown in Tables 56 and 57.

Table 56

The Foot-to-tongue Circulation Times in Postural Proteinurics in the Recumbent Kyphotic and the Recumbent Lordotic Postures

Case	Recumbent Kyphosis		Recumbent Lordosis		Method
	Circ.Time Secs.	Protein mg./100cc.	Circ.Time Secs.	Protein mg./100cc.	
153	32	0	70	320	Ca
154	26	0	*	500	Ca
155	10	0	15	50	D
156	10	0	17	50	D
157	29	0	125	400	D
158	23	0	35	300	D

* No end point.

Table 57

The Foot-to-tongue Circulation Times in Non-proteinuric Subjects in the Recumbent Kyphotic and Recumbent Lordotic Postures

Case	Recumbent Kyphosis		Recumbent Lordosis		Method
	Circ.Time Secs.	Protein mg./100cc	Circ.Time Secs	Protein mg./100cc.	
159	31	0	27	0	Ca
160	24	0	27	0	Ca
161	8	0	9	0	Ca
162	10	0	11	0	Ca
163	9	0	8	0	Ca
164	19	0	25	0	D
165	35	0	39	0	D

Comment

It will be noted that in the proteinuric group, the foot-to-tongue circulation times in recumbent lordosis are considerably greater than in recumbent kyphosis and that in this they differ from the non-proteinuric controls.

The short circulation times obtained in some of the subjects are explained by their youth and small size combined with fear of the test which increased the circulation rate.

Conclusion

Subjects in whom proteinuria can be induced by the recumbent lordotic posture have longer foot-to-tongue circulation times when in this posture than when they are in recumbent kyphosis. Subjects in whom proteinuria cannot be induced by the same manoeuvre do not show this increase in circulation time under the same conditions.

Experiment 16

In view of the results of the previous experiment, it is obvious that there is a delay in the circulation in the inferior vena cava during the proteinuric phase. To establish the cause and the site of the obstruction to the venous flow, anatomical dissections were undertaken.

Twenty-eight adult cadavers were examined in the Anatomy Department of the University of Cape Town to determine the relationship of the liver to the upper part of the inferior vena cava. In each case the liver was removed intact and that portion of the inferior vena cava which runs posterior to it was removed with it.

Results

Four specimens are shown in Figures 46, 47, 48 and 49 and were chosen to illustrate the great variability of the anatomy at this level. Further variations are shown in figures in Protocol

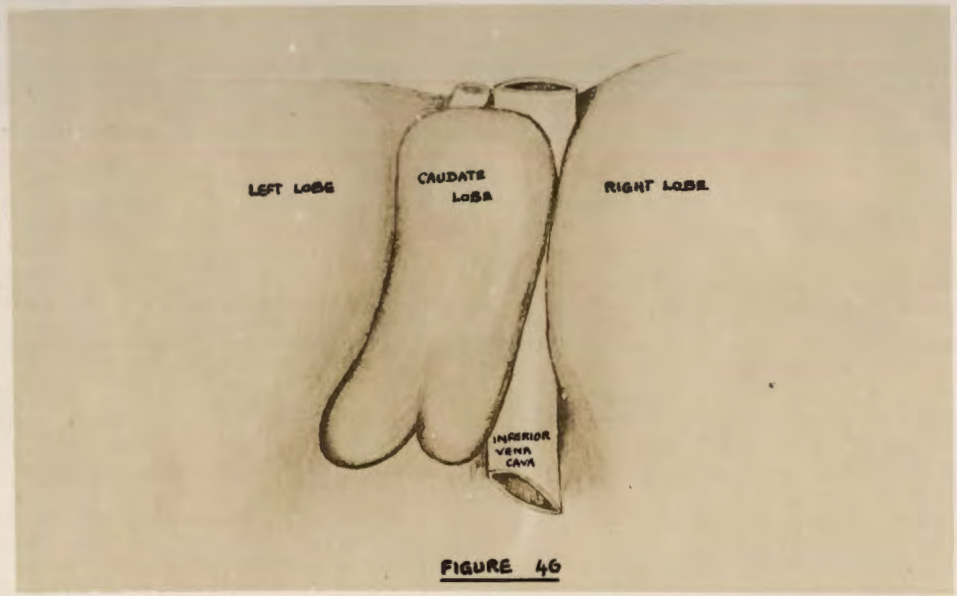


FIGURE 46

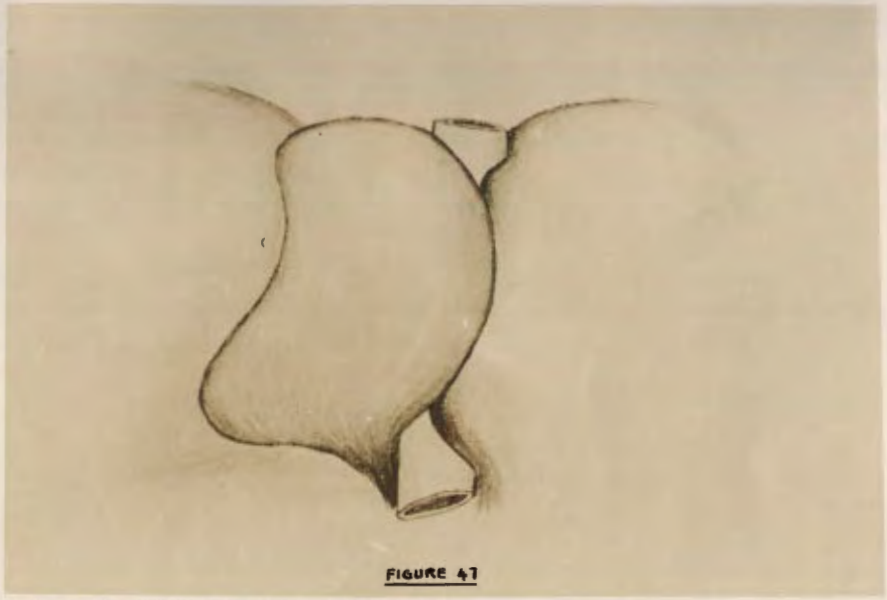


FIGURE 47

FOUR LIVERS VIEWED FROM BEHIND WITH THE INFERIOR VENA CAVA IN POSITION

FIGURE 48

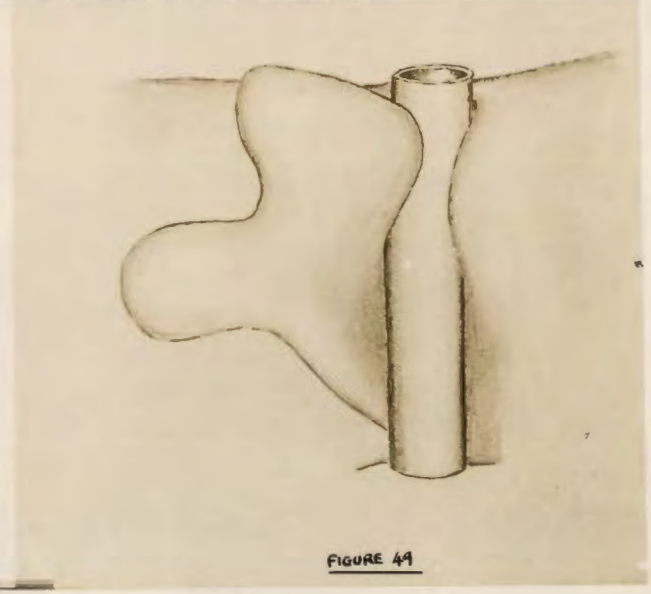


FIGURE 49

Comment

It will be noted that the inferior vena cava is surrounded to a variable degree by liver substance. In those subjects in whom the liver encases the inferior vena cava as in Figures 46 and 47, the intrahepatic portion of the vessel must follow the liver when this organ rotates. In other subjects such as those shown in Figures 48 and 49, a wide range of rotation of the liver could not affect it.

Conclusion

The relationship of the inferior vena cava to the liver is very variable.

Experiment 17

The Effect of the Position of the Liver on Proteinuria

This experiment was undertaken to determine whether proteinuria could be induced by rotating the liver into different positions. Adult subjects were chosen for this investigation on the basis of their having easily palpable livers which could be manually rotated through the intact abdominal wall. After a period of uncontrolled posture, the subjects emptied their bladders and the urine was saved (Specimen A). Then the following manoeuvres were undertaken for 10 minutes each in the order listed. At the end of each period a specimen of urine was collected and tested for protein.

1. The subjects were placed in a posture of recumbent kyphosis. (Urine Specimen B).
2. They then remained in the same posture but manual pressure was applied to the liver in an attempt to rotate its anterior surface inferiorly. (Urine Specimen C).
3. They were then placed in a posture of recumbent lordosis and at the same time, the lower edge of the liver was pushed upwards causing the anterior part of the liver to rotate upwards. (Urine Specimen D).

4. The liver was then released but the subjects remained in recumbent lordosis. (Urine Specimen E).

5. Finally, pressure was applied to rotate the anterior surface of the liver inferiorly, the subject remaining in the posture of recumbent lordosis.

After completion of these manoeuvres, certain of them were repeated and foot-to-tongue circulation times done while the subjects were maintained in two of the positions.

Results

The results are shown in Table 38.

Table 38

The Effect of Rotation of the Liver on the Urinary Protein and the Foot-to-tongue Circulation Time

	A Uncontrolled posture	B Recumbent kyphosis	C Recumbent kyphosis plus inferior rotation liver	D Recumbent lordosis plus upward rotation liver	E Recumbent lordosis. No manipulation of liver	F Recumbent lordosis plus inferior rotation liver	Case
Total protein mg./100cc.	5	5	10	0	20	720	201
Globulin mg./100cc.	0	0	0	0	0	80	
Total protein mg./100cc.	0	-	-	0	10	330	
Total protein mg./100cc.	0	-	-	0	-	60	
Circulation time secs.				38		61	
Total protein mg./100cc.	0	0	0	0	0	100	130
Total protein mg./100cc.	0	0	0	0	0	10	131
Circulation time secs.		33				†	
Total protein mg./100cc.	0	0	0	0	10	30	132
Circulation time secs.		22				51	
Total protein mg./100cc.	5	0	-	0	30	560	305
Total protein mg./100cc.	0	0	-	-	-	300	
Circulation time secs.		17				65	
Total protein mg./100cc.	10	10	-	10	10	30	304
Circulation time secs.		35				130	

† No end point.
At the times indicated, both subjects tasted the Decholin. The liver was then released and about 5 seconds later a much stronger taste was observed.
The continuous proteinuria was caused by pyelitis.

Comment

It will be noted that in each of the subjects, a position of recumbent lordosis with inferior rotation of the liver produced varying degrees of proteinuria. In 3 of the subjects, recumbent lordosis alone was sufficient to induce the proteinuria and, in these, upward rotation of the liver abolished it.

Comparison of the results of this experiment with those of Experiment 2 reveals a close similarity. Here, as in Experiment 2, lordosis was a necessary factor but in most of the cases was insufficient by itself to induce the proteinuria. When lordosis was combined with an inferior rotation of the liver, the proteinuria was maximal.

It will be seen also that the same lengthening of the circulation time occurred in strict association with the proteinuria as was seen in Experiment 15. This suggests that inferior vena cava compression was responsible.

Conclusion

Subjects whose livers could be rotated through the intact abdominal wall could be caused to pass protein in the urine by inferior rotation of the anterior part of the liver when they were in a lordotic posture. In some of these subjects, proteinuria occurred with the assumption of the recumbent lordotic posture alone and in these, the proteinuria could be abolished by upward rotation of the anterior part of the liver.

Accompanying the proteinuria induced by lordosis plus downward rotation of the liver and in strict association with the manoeuvre, was a lengthening of the foot-to-tongue circulation time.

Discussion

The Type of Proteinuria

Experiments 1 and 2 demonstrate that all of the proteinuric subjects in the present series of cases fall into the group of postural proteinurias. The proteinuria could always be abolished by the assumption of a posture of kyphosis and induced by lordosis, either alone, or combined with other factors.

Exercise can be dismissed as a factor in these cases because the proteinuria occurred under conditions of rest or after mild exertion. Barach (26,27), Collier (28), Hellebrandt (29) and Hellebrandt, Brogden and Kelso (30) all showed that violent exercise is necessary to induce proteinuria.

Similarly, neurogenic causes can be excluded because the cases showed no extreme emotional disturbances or signs of such organic nervous diseases as meningitis, cerebral haemorrhage or tumours as may be associated with proteinuria. Reno-palpatory proteinuria can be dismissed because the proteinuria occurred independently of manipulation of the kidneys.

Pathogenesis of Postural Proteinuria

The theories of the pathogenesis of postural proteinuria can be grouped as follows:-

1. The theory of an abnormality of the serum proteins.

2. Theories based on a presumed vasomotor instability or alteration in the arterial circulation to the kidney.

3. Theories based on a presumed disturbance of the venous return from the kidney.

4. Theories based on presumed congenital or acquired lesions of the kidney and particularly of the glomeruli.

The Theory of an Abnormality of the Serum Proteins

In 1905, Wright and Ross (100) found what they believed to be a hypocoagulability of the blood in two cases of "physiological albuminuria". They postulated that an increased hydrostatic pressure, combined with the abnormality of the blood was responsible for the condition. To test this hypothesis, they administered Calcium salts to the patients because of the then current belief that the coagulability of the blood could be increased by this means. The albuminuria disappeared. Fox (102,4) confirmed the effect of Calcium therapy and subscribed to Wright and Ross' theory of the pathogenesis of postural proteinuria.

Post and Thomas (2) believed that it was not Calcium as such that was responsible for the abolition of the proteinuria but that it acted by virtue of its basic properties. They stated that they could regularly abolish the proteinuria by neutralisation or mild alkalisation of the urine and suggested that the administration of alkali "restored the normal physico-chemical state of the proteins" and prevented their escape into the urine. They admitted, however, that some circulatory factor must also play a part.

In the papers by Wright, Fox and Post and Thomas, no mention is made of any control investigations

and these workers do not appear to have realised the great importance of accurate control of posture in any study of this condition. Nicholson (87) in a well controlled investigation was unable to confirm Wright and Ross' suggestion that the administration of calcium abolished the proteinuria. Harrison (101) similarly found calcium administration to have no effect on the proteinuria and rightly pointed out that careful control must be undertaken before deciding on the efficacy of any treatment.

The suggestion of Post and Thomas that alkalisation of the urine abolishes the proteinuria was not substantiated in the present investigation. Although no deliberate attempt was made at investigating this point, several subjects spontaneously passed alkaline urine containing protein.

A final decision on the question of the effect of alkali administration must rest on more complete study, but any effect that calcium or alkali may have, must be of minor importance, for circulatory factors must be present to account for the postural nature of the proteinuria.

Theories Based on Disturbances of the Arterial Circulation to the Kidney

Among the earliest suggestions for the pathogenesis of postural proteinuria was one that vasomotor instability caused circulatory changes in the kidney and these in turn were responsible for the proteinuria (31,32, 33). The first experimental attempt at proving this theory was that of Erlanger and Hooker (34). They examined one subject with postural proteinuria and one control subject and noted that in the proteinuric, the proteinuria was accompanied by a fall in pulse pressure. Certain manoeuvres such as immersion of the body in water or the application of a pneumatic suit, prevented both the proteinuria and the fall in pulse pressure. In three of their experiments (numbers 11,59 and 67) the association of fall of pulse pressure and proteinuria did not occur. Later, Hooker, Hegemann and Zartman (35) published a brief report of another case in which there was the same association of a fall in pulse pressure with the proteinuria. All these authors concluded that the fall in pulse pressure caused the proteinuria.

Hooker (36) in certain perfusion experiments on isolated kidneys found that the amount of urine passed varied directly and the amount of protein inversely with the magnitude of the pulse pressure. This was taken as further evidence favouring the theory. Mason and Erickson (7) quoted further indirect evidence to show that renal metabolism was altered by lowered pulse pressure and described four cases of postural proteinuria in whom the proteinuria was accompanied by a fall in pulse pressure. As controls, they determined the blood pressures of certain other subjects, some of whom were nephritics. In their subjects with postural proteinuria, the pulse pressures in the erect posture were 14,32,40 and 55 mm.Hg while in their four non-nephritic control cases, the pulse pressures under the same circumstances were, 58, 49,50 and 50 mm.Hg. Despite the fact that all of these controls had lower pulse pressures than one of their postural proteinurics, their work has been extensively quoted in favour of the pulse pressure theory. It appears that the 6 cases quoted form the basis on which the pulse pressure theory has been carried through the literature (1,2,4,37,38).

Investigation of the present larger series of 48 cases revealed that the behaviour of the pulse

pressure in postural proteinurics is the same as in non-proteinurics. On the assumption of the erect posture, proteinuria can occur whether the pulse pressure rises or falls. Furthermore, there is no tendency for proteinurics' blood pressures to be more labile than non-proteinurics as suggested by Lee (39).

In support of the present findings is the work of Bass and Kessler (40) and Diehl and Mc Kinley (41). These investigators similarly found no relationship between the pulse pressure and the occurrence of proteinuria. The former studied a younger group of children and the latter a group about 10 years older than the present series.

The Increased Venous Pressure Theory

The effect of increased venous pressure on the renal dynamics

Posnor (42) induced proteinuria in animals by compression of the renal veins. This has been confirmed many times since then. Winton (43) working on dogs' heart-lung-kidney preparations induced proteinuria by raising the venous pressure and noted that accompanying the proteinuria was an oliguria and decrease in renal blood flow. He quoted certain histological evidence by Ludwig (44) to show that the rise in venous pressure dilated the peritubular venules and compressed the tubules with a consequent rise in intratubular pressure. This suggestion was confirmed by his work because he found that a rise in ureteric pressure which ordinarly reduced urine flow did not do so when the venous pressure was increased. This apparently paradoxical result is explained by the fact that the ureteric pressure is communicated to the tubules and prevents their compression by the dilated venules. Furthermore, when the ureteric pressure was raised first and the venous pressure later, it was possible to induce an increase in urine flow with the rising venous pressure. The interpretation of this was that the venous pressure was communicated back to the glomerulus and caused an increase in the filtration pressure.

Theobald (45) working on dogs, showed that the normal pressure in the inferior vena cava was 4 to 8 mm. Hg and when this pressure was raised to 8 to 10 mm.Hg, oliguria resulted. Between 10 and 15 mm.Hg pressure, oliguria, albuminuria and retention of chloride, phosphorus and nitrogen occurred and between 15 and 20 mm.Hg pressure, haematuria occurred as well. If the pressure rose above 20 mm.Hg, anuria resulted.

There is, therefore, sufficient evidence that an increase in venous pressure will cause proteinuria and certain other manifestations in animals. Theobald (46) was able to induce proteinuria in man by pressure on the epigastrium, presumably compressing the inferior vena cava. The author has seen a case of Hodgkin's disease with proteinuria. At autopsy, both renal veins were surrounded by masses of glands and compressed. No renal lesion was found to account for the proteinuria so that venous compression by the glands was probably responsible. Cardiac failure is often accompanied by a raised venous pressure. Under these conditions there is frequently proteinuria, and water and salt retention is a feature of the condition (47). The picture is, however somewhat complicated and will be discussed later in the section on plans for further study. Therefore, despite the lack

of direct evidence, it is almost certain that an increased venous pressure does produce similar effects in man and animals.

By inference from Winton's work, we should expect to find a rise in the filtration fraction because the venous pressure is probably conducted back to the glomerulus and tends to raise the filtration pressure. This rise in the filtration fraction is not likely to be large because of the parallel increase in intratubular pressure. The effect of the increased intratubular pressure and decreased renal blood flow on the glomerular filtration rate would, therefore, only partly be compensated for by the rise in filtration fraction and a decrease in glomerular filtration rate should result.

Therefore, if postural proteinuria is due to an increased venous pressure mechanism we should find:-

1. Proteinuria.
2. Oliguria.
3. Diminution of chloride excretion.
4. Diminution of urea excretion.
5. Haematuria if the rise in venous pressure is sufficient.
6. Decreased renal blood flow.
7. Increase in the filtration fraction.
8. Lowering of the glomerular filtration rate.

1. Proteinuria, of course, occurs by definition.
2. Oliguria. Experiment 12 shows that there is a drop in urine flow during the stage of proteinuria and that it may be considerable. This feature has been noted before (46).
3. Diminution in chloride excretion. In Case 180, the clearance of chloride dropped considerably with the occurrence of proteinuria. This has been noted before to be a regular feature of postural proteinuria (34,46).
4. Diminution in urea excretion. Experiment 12 demonstrates lowered urea clearances accompanying the proteinuria. The urine flow is also lowered; therefore there is a diminution in the output of urea as well as lowering of the clearance. This has been noted previously (34,49).
5. Haematuria. Experiment 11 demonstrates that there is an increased passage of erythrocytes in the urine and that this parallels the degree of proteinuria. Case No. 202 with a high grade postural proteinuria actually passed very scanty red cell casts. Rytand (48) also found an increase in the numbers of red cells in the urine of 5 patients during the phase of proteinuria.

6. The renal blood flow. Experiment 12 shows that there is a decrease in renal blood flow accompanying the proteinuria.

7. The filtration fraction Experiment 12 demonstrates that there is a rise in the filtration fraction accompanying the proteinuria.

8. The glomerular filtration rate. Experiment 12 demonstrates that there is a fall in glomerular filtration rate accompanying the proteinuria. This change has been noted before and shown to be characteristic of postural proteinuria (50).

Therefore, the renal dynamics in postural proteinuria are consistent with the theory that the proteinuria is due to an increase in venous pressure.

Possible causes of increased venous pressure

Three possible mechanisms might give rise to increased pressure in the renal veins.

1. A general increase in venous pressure.
2. The renal veins may be compressed unilaterally or bilaterally.
3. The inferior vena cava may be compressed.

1. A general increase in venous pressure

This possibility can be ruled out immediately because there is no distension of the veins in the neck or other evidence of congestive cardiac failure in postural proteinurics.

2. Compression of the renal veins

A. Left renal vein compression

Kelling (51) suggested that compression of the left renal vein by the superior mesenteric artery was responsible for postural proteinuria. This would explain why lordosis alone can produce proteinuria in some individuals and why lordosis plus the erect posture does so even more effectively. The erect posture, by causing visceroptosis, would close the angle between the

aorta and the superior mesenteric artery. Support for Kelling's suggestion came from Somne (54) who catheterised the ureters of 6 subjects and found that the urine from the right ureter contained no protein while on the left there was anuria or proteinuria. One of his subjects had bilateral anuria. Rieser and Rieser (55) found that the application of an abdominal binder, correcting visceroptosis, prevented the proteinuria and this was taken as further evidence favouring the theory that the "aorta-mesenteric pincers" obstructed the left renal vein. The present study confirms Rieser and Rieser's findings (Experiment 2). Finally, Rytand (49) showed radiologically that an increase in the size of the left kidney occurred during the period of proteinuria in two out of 5 subjects. This suggested that it was distended by the increase in venous pressure on that side.

However, there are certain objections to this theory of left renal vein compression:-

(a) <u>The proteinuria may be bilateral</u>

Table 39 shows the results of ureteric catheterisation of subjects with postural proteinuria

derived from the literature and from Experiment 14.

Table 39

Protein Content of the Urine from Right and Left Kidneys in Postural Proteinuria

Author	No. of cases	Protein in the urine	
		Right kidney	Left kidney
Sonne (54)	1	Anuria	Anuria
	3	0	Anuria
	1	0	+
	1	0	++++
Beer (55)	2	0	+
Prince (58)	1	+	+
	1	+	Trace
Theobald (56)	4	+	+
Ekehorn (67)	1	+	0
Expt. 14	1	+	++
	1	++	++
	1	?	+

It will be noted that 8 of the 18 cases passed protein bilaterally and a ninth had right and left sided anuria. One case had unilateral right sided proteinuria.

(b) The renal functions are altered to a degree greater than would be expected from a unilateral disturbance.

Experiment 12 shows that when the subject is in an erect lordotic posture, the urine flow, urea clearance and creatinine clearance may drop to levels

considerably below 50 % of those in the kyphotic posture. If only the left kidney was affected, these functions should not be depressed by more than a half.

(c) The foot-to-tongue circulation time is prolonged.

Experiment 15 shows that accompanying the proteinuria there is a delay in the foot-to-tongue circulation time. This cannot be explained by a renal vein mechanism alone and suggests inferior vena cava compression.

Because of these facts, the left renal vein theory does not explain the whole picture.

B. Double renal vein compression

There is no obvious explanation on an anatomical basis to explain why the application of a binder to the abdomen should prevent compression of the right renal vein. This vein takes a short and direct course from the inferior vena cava to the kidney and is not enclosed in a pincer as is the left. A neural reflex from the left kidney to the right in response to the left sided venous distension might be postulated but is difficult to prove. However, this theory can also be excluded on the basis of the prolonged foot-to-tongue circulation time.

5. Inferior vena cava compression

Jehle (57) suggested that the upper lumbar spine in lordosis, kinked and compressed the upper part of the inferior vena cava. This explains very well the fact that lordosis causes proteinuria and overcomes the objections to the renal vein theories. The erect posture favours lordosis and this explains why it can induce proteinuria. It does not explain, however, why the proteinuria in the erect posture is greater than in the recumbent lordotic posture (Experiment 2) nor why the application of a binder to the abdomen abolishes the proteinuria.

All the facts are best explained on the basis of a new theory which is elaborated below.

Figure 50

The Relationship of Inferior Vena Cava to Liver and Spine in Kyphosis

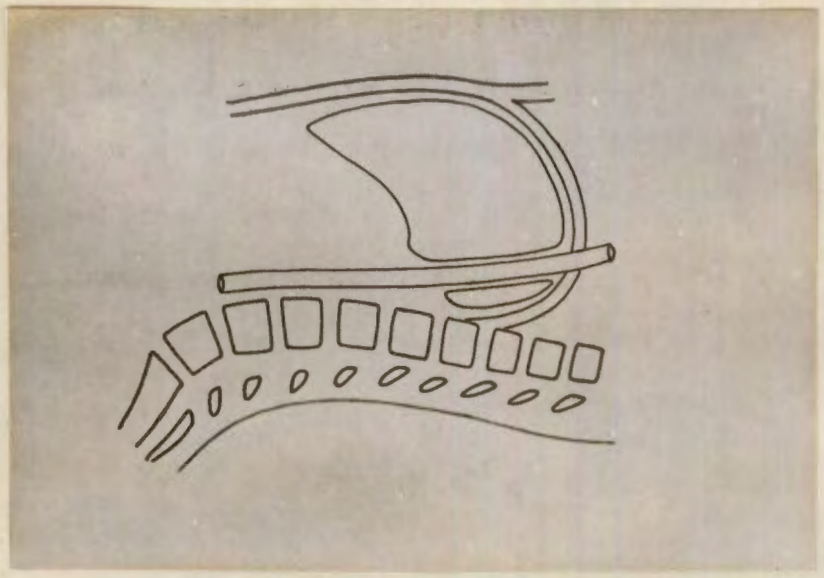
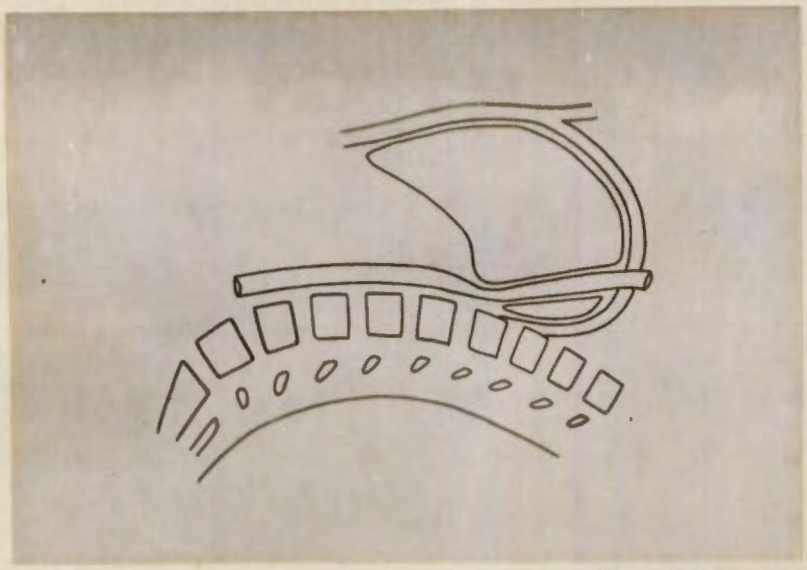


Figure 51

The Relationship of Inferior Vena Cava to Liver and Spine in Lordosis



The liver and inferior vena cava theory of postural proteinuria

It is suggested that the mechanism of postural proteinuria is as follows. When the subject is in a kyphotic posture, the distance between the diaphragmatic opening of the inferior vena cava and its origin at the junction of the common iliac veins is least and the inferior vena cava is relatively lax. If the subject is now placed in a lordotic posture it is tensed and the part behind the liver is brought into close apposition with the spine. Now the upper end of the inferior vena cava is surrounded to a variable degree by liver substance (Experiment 16) and any rotation of the liver about the axis of its area of fixation to the posterior part of the diaphragm will tend to rotate the inferior vena cava with it and compress it against the spine. The degree of rotatation and the extent of compression will depend on its relation and degree of fixation to the inferior vena cava. Some rotation of the liver may occur in recumbent lordosis because its anterior aspect is less fixed than its posterior, but the erect posture will favour this rotation much more because the liver's centre of gravity lies in front of the centre of rotation. This theory is illustrated in Figures 50 and 51.

This theory explains why lordosis is necessary for the production of proteinuria and why erect lordosis is more effective than recumbent lordosis. It explains bilateral proteinuria and the considerable lowering of renal function that can occur. The fact that one kidney may secrete more protein than the other is explained by local differences in venous return from the two sides such as might be caused by the "aorta-mesenteric pincers".

The theory also explains the increased foot-to-tongue circulation time and the response to the application of an abdominal binder. If the binder supports and elevates the liver, preventing its inferior rotation, proteinuria will not result even in the erect lordotic posture, but if it catches the lower end of the liver and rotates it inferiorly, it may increase the proteinuria. In case 175 in Experiment 2, the liver was probably caught under the binder. The great anatomical variations in the relations of the inferior vena cava to the liver explain why subjects respond to posture with varying degrees of proteinuria from 0 to ++++.

Immobility in lordosis is more effective in inducing proteinuria than is lordosis with movement (65) because it is not possible to maintain continuously the same degree of lordosis when moving.

Further evidence favouring this theory was obtained in Experiment 17 on patients whose livers were artificially rotated. It will be noted that these subjects were postural proteinurics in that certain postures were necessary for the production of proteinuria. In some cases it could be induced by lordosis alone and increased by further manual rotation of the liver. Furthermore, where proteinuria occurred spontaneously, upward rotation of the liver entirely removed it. The same delay in the foot-to-tongue circulation time occurred as had been found in the postural proteinurics. These cases therefore only differed from the usual postural proteinurics in having livers that could be artificially rotated.

Figures 52 and 53 show reproductions of two X-ray photographs of one of the cases used in Experiment 17. In the inferior vena cava is a catheter from which is issuing radio-opaque diotrast. Figure 52 was taken with the subject in a recumbent lordotic posture alone and Figure 53 in the same posture with the liver rotated inferiorly. The change in direction of the catheter is obvious. Figure 54 from a tracing of the two plates superimposed shows this change of direction more clearly. Unfortunately there is insufficient diotrast in the inferior vena cava to outline it sufficiently to demonstrate

Figure 52

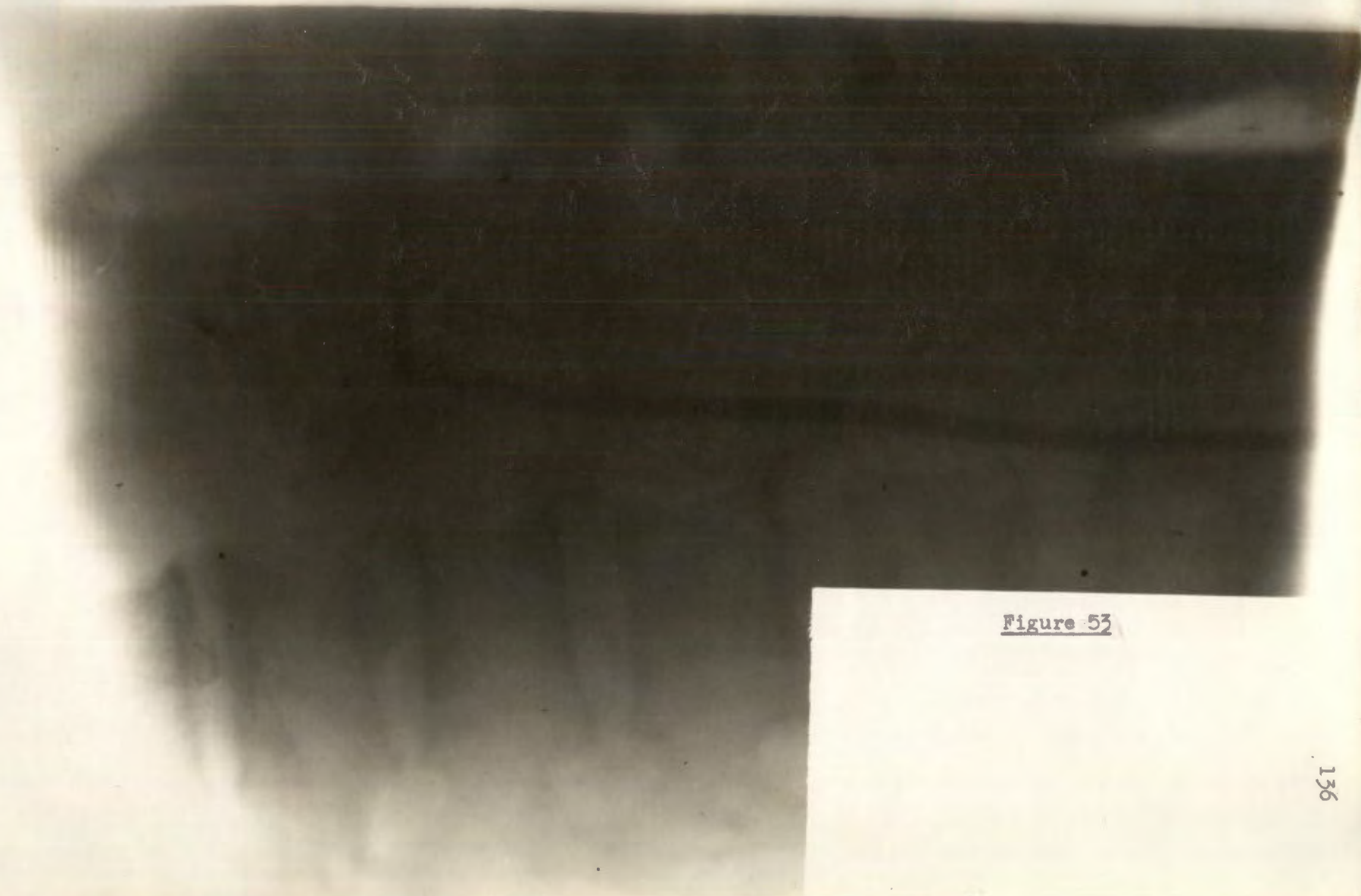


Figure 53

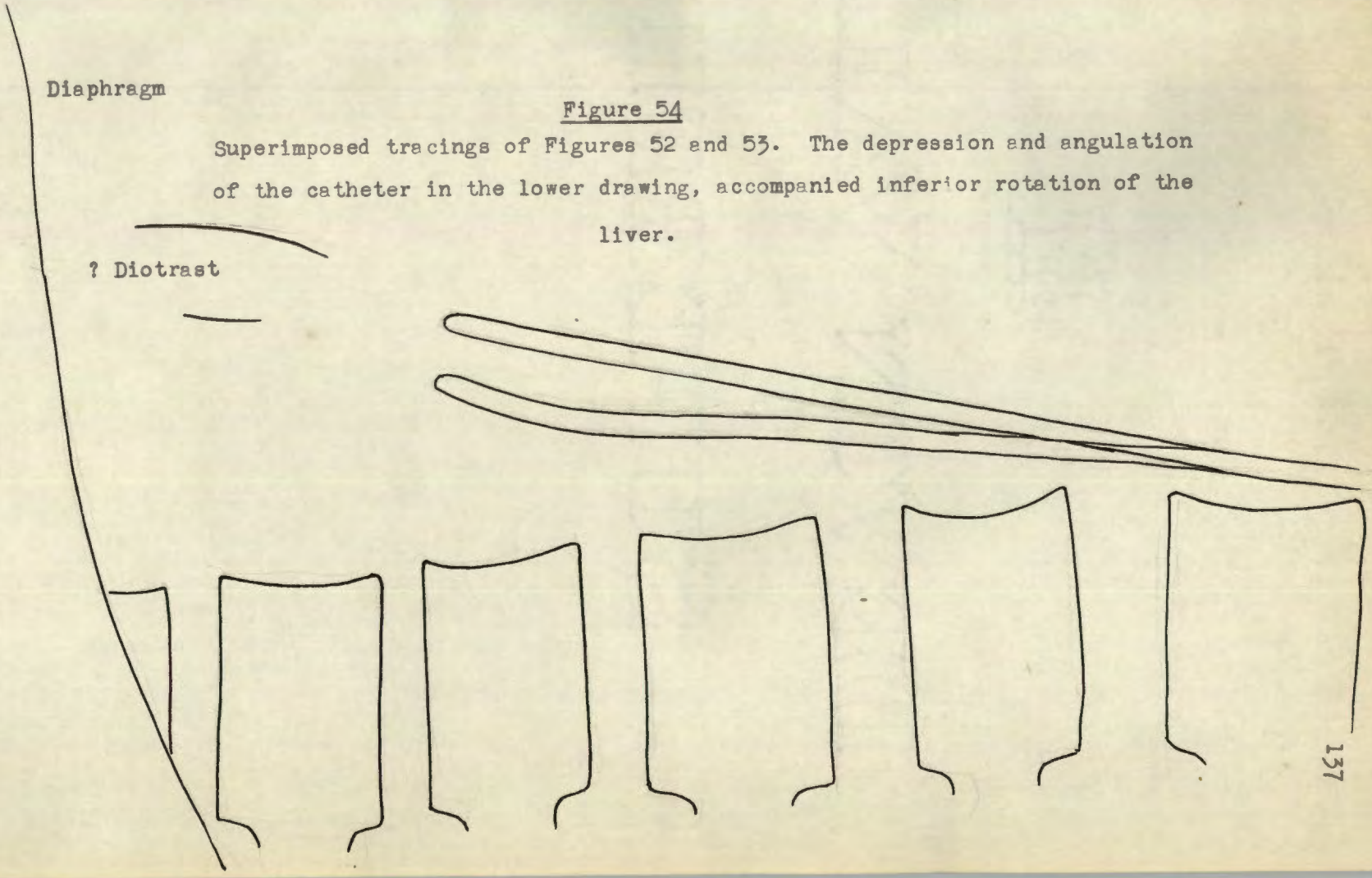


Figure 54

Superimposed tracings of Figures 52 and 53. The depression and angulation of the catheter in the lower drawing, accompanied inferior rotation of the liver.

any compression.

Compression of the vessel, however, is shown in Figures 55,56 and 57. These figures are copies of radiographs of the inferior vena cava and its branches obtained by injecting barium sulphate emulsion into the venous system of a cadaver and taking X-ray photographs.

Legend to Figures 55,56 and 57

Figure 55 is an antero-posterior X-ray of the abdomen and shows the inferior vena cava and its branches filled with Barium Sulphate. Note the levels of the various major branches to enable them to be identified in Figures 56 and 57.

Figure 56 is a lateral X-ray of the abdomen and lower part of the thorax. The cadaver is recumbent and the spine kyphotic. Note the width of the inferior vena cava at the point indicated by an arrow.

Figure 57 is another lateral X-ray of the abdomen and lower part of the thorax. Here the cadaver is recumbent and the spine is lordotic. The liver has been rotated inferiorly and this is shown by the narrowing of the angle between the right hepatic vein and the inferior vena cava. Note that part of the inferior vena cava indicated by the arrow which corresponds to the same area in Figure 56. It will be seen that the inferior vena cava is compressed in an antero-posterior direction.

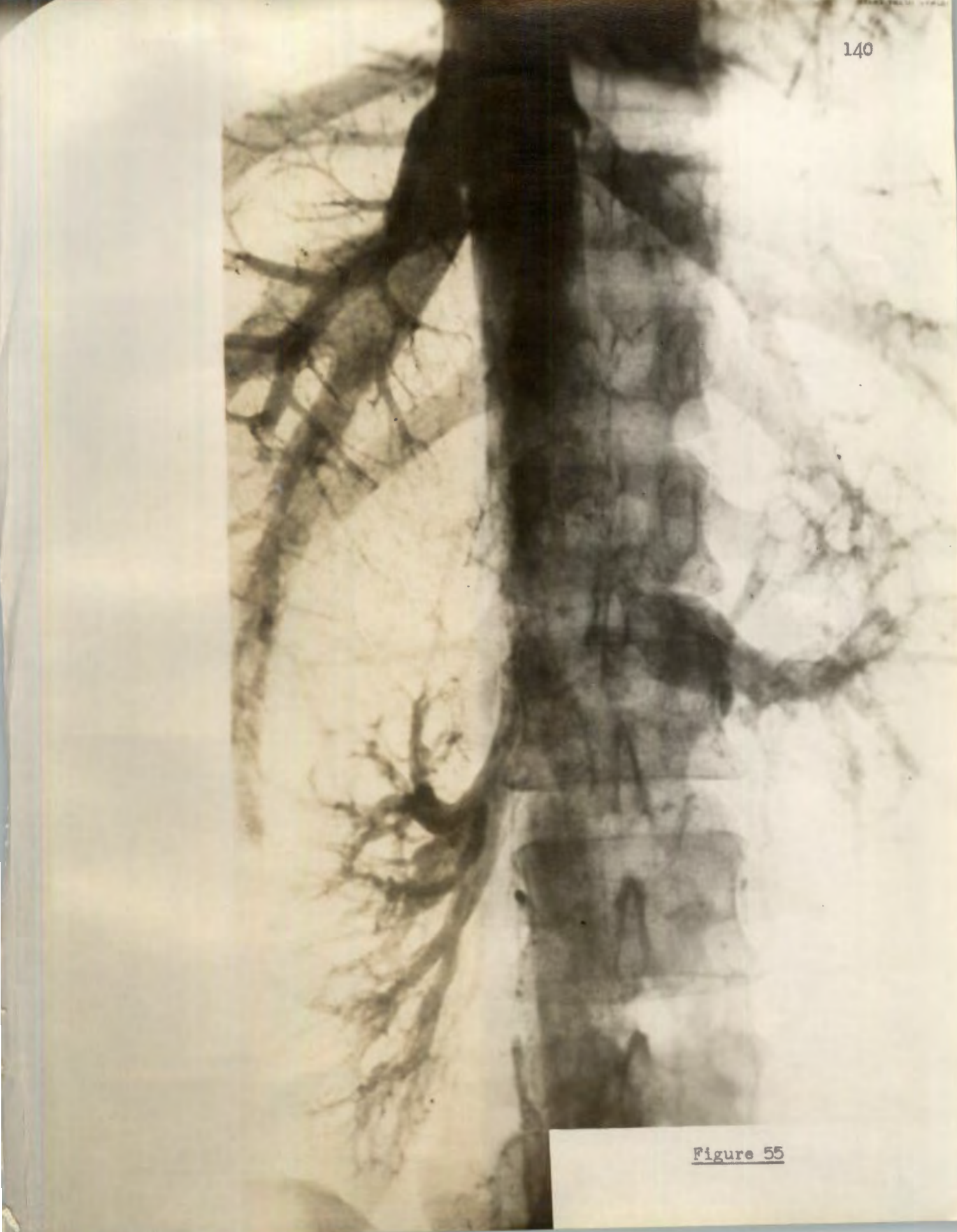


Figure 55

Figure 56

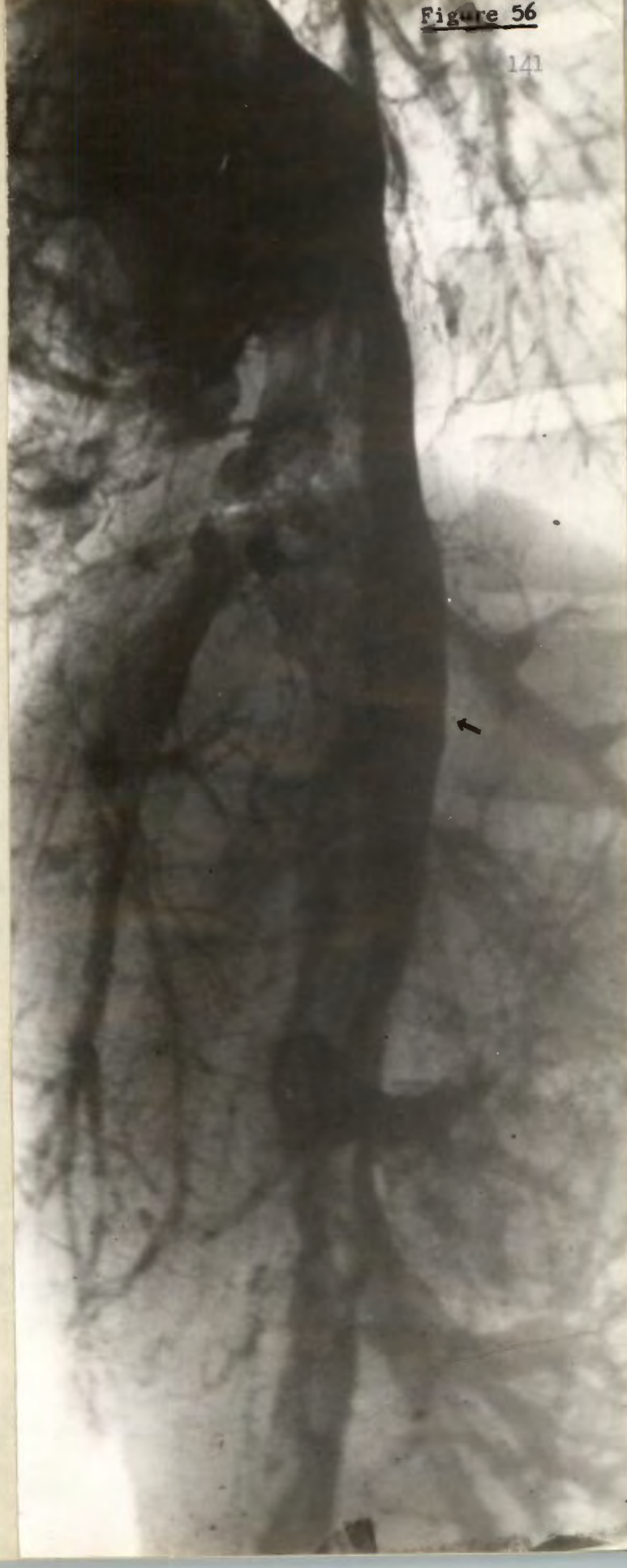


Figure 57

Certain Features of Postural Proteinuria Explained on the Liver and Inferior Vena Cava Theory

1. Fainting reactions

Dukes (33) was the first to describe fainting as occurring unduly frequently in postural proteinuries. Postural fainting reactions have occurred frequently in the present series. It usually happens that the subject, while standing in a posture of extreme lordosis, becomes pale, yawns, develops a tachycardia and soft pulse and complains of a faint feeling. If he is not immediately placed in a recumbent posture, he faints. These reactions sometimes occur extremely rapidly.

The subject of these fainting reactions will be discussed more fully in a separate paper and is still being investigated. A tentative explanation of their occurrence is as follows:-

In the erect lordotic posture, the inferior vena cava is compressed by the liver and stagnation of blood below the obstruction occurs. This leads to the proteinuria and at the same time, there is a diminution of venous return to the heart. This diminished venous return brings certain compensatory mechanisms into play. Eventually these fail to maintain adequate cerebral circulation and the subject faints.

2. The incidence of benign proteinuria

It is extremely difficult to obtain a clear picture of the incidence of benign proteinuria from a study of the literature because such variable results are obtained by different workers. (For reviews covering the subject of incidence see 1,2,5 and 6) Figures for the incidence as widely divergent as 2.6 % (58) and 88.7 % (59) are quoted. With the exception of a very few studies which will be quoted later, all the work on the incidence has been undertaken with insufficient regard to the posture of the subjects during the period of urine secretion. The present studies on the incidence reveal how variable the percentage of proteinurics may be when the posture is uncontrolled (Experiment 1). A true incidence can only be obtained if the urine secreted in forced, erect lordosis is examined. Examination of the urine during a period of uncontrolled posture merely provides an index of the activities and posture of the subjects during the test. In the light of this, even such large series of cases as those of Mc Lean (60) and Diehl and Mc Kinlay (41,61) are seen to be of little value.

The so-called epidemics and seasonal variations in incidence of proteinuria described by Ashburn (62) and Murphy (58) are best explained by the varying activities and postures of the successive groups of subjects examined.

The high figure of 88.7 % found by Hamill and Blackfan (59) for the incidence was arrived at by repeated testing of the urine. If one adopts this measure, one must at some time obtain a specimen secreted in lordosis. The same end result is obtained more quickly and certainly by testing the urine secreted in forced, erect lordosis. All postural proteinurics are thereby detected and in children about the age of 15 constitute approximately 3/4 of the population.

Jeanarret (63) found that the erect lordotic posture plus immobility caused 49 % of girls to pass protein in the urine. Nassau (64) induced proteinuria in 22.6 % of healthy soldiers under the same conditions and Theobald (45) induced proteinuria 16 out of 18 times in subjects placed in Walcher's position.

Age incidence

It is generally agreed that postural proteinuria occurs less frequently with increasing age. The present study confirms this (Experiment 1). It is a matter of common observation that children have more lax joints and ligaments than older people. Their spines are more mobile and in them a greater degree of lordosis is possible because of this. In the 50 years and over age group in the present study, the lack of spinal mobility was striking and in these subjects, only minimal degrees of lordosis were possible. Progressive diminution of spinal mobility therefore explains the falling incidence with increasing age.

Sex incidence

The incidence in the sexes appears to be about the same (See Post and Thomas (2) for a review of this aspect). The point however requires investigation under properly controlled conditions of posture.

The relative frequency of postural proteinuria and other benign proteinurias

A consideration of the incidence of postural proteinuria would be incomplete without reference to its relative frequency in the whole group of the benign proteinurias. The present study, in which post-exercise proteinuria was excluded by the conditions of the experiments revealed that a postural mechanism could be demonstrated in the vast majority of cases. Only two cases of continuous, non-postural proteinuria were seen in otherwise normal subjects. There is some doubt as to whether they can properly be classified as benign.

The results of this study, showing that postural proteinuria is the commonest of the benign proteinurias is difficult to reconcile with the findings of Calvin, Isaacs and Meyer (6), Hamill and Blackfan (33), Saundby (65) and Lauener (66). Jehle (32), however believes that a postural mechanism can be demonstrated in every case of benign proteinuria.

Calvin, Isaacs and Meyer's work is open to criticism because they failed to control the posture and activities of their subjects in their original tests to detect proteinurics. They therefore almost certainly

missed a large number of postural cases. In the small group of 25 cases which they believed not to be due to a postural mechanism, they failed to consider the possibility of contamination of the urine secreted in recumbency at night by urine secreted while the subjects were up and about the night before. Their subjects were children in a boarding institution and it is the usual practice at such places to make the children kneel in prayer before retiring. This posture is especially apt to induce proteinuria and would account for the suspected contamination. Finally, they do not show that these children slept in a kyphotic posture. Recumbent lordosis may induce proteinuria in some subjects.

Hamill and Blackfan state that they did not find posture to play any part in the production of proteinuria but provide no details of their postural tests. From their paper, one must assume that they were unaware of the necessity of inducing lordosis in the erect posture if proteinuria is to occur.

Saundby does not state his reasons for believing that the postural type of benign proteinuria is less common than others so that his conclusions cannot be analysed. Leuener's paper (66) is not available here and therefore cannot be commented on.

The Albumin/globulin Ratio in Postural Proteinuria

A striking feature of the benign proteinurias is the frequent finding that a large proportion of the protein in the urine is globulin (59,71,88). This aspect will be discussed below.

The origin of the protein

There appears to be little if any doubt that where proteinuria occurs, almost all if not all of the protein is derived from the blood and enters the urine via the glomerulus. Furthermore, proteins and other colloidal matter pass through the glomerular filter more or less readily according to whether their molecules are small or large. The evidence for these statements is well reviewed by Ekehorn (87), Fishberg (1) and Dock (68) and does not require repetition.

The factors determining the albumin/globulin ratio

The nature of the proteins in bladder urine must be determined by the nature of the plasma proteins, the conditions at the glomerulus and possible alterations in the filtrate in its passage down the renal tubules.

The plasma proteins

The characters of the plasma proteins that are of greatest importance in this connection are their size and shape. Recent work suggests that plasma proteins are elliptical in shape. Table 40 shows some of the characters of fibrinogen, gamma globulin and albumin. The data are derived from an article by Cohn, Oncley, Strong, Hughes and Armstrong (69).

Table 40

The Physical Characters of Certain Plasma Proteins

	Mol. Wt.	Mol. Length	Equatorial Diameter
Fibrinogen	500,000	900 Å	33 Å
Gamma globulin	156,000	320 Å	36 Å
Albumin	69,000	150 Å	36 Å

The nature of the glomerular filter and its relation to the passage of protein

As the glomerulus passes proteins which are substances of definite physical dimensions, its membrane must be in the form of a filter with definite pores.

If we consider the state of affairs at the glomerular membrane and assume that the pores are slightly

larger than the narrowest diameter of the albumin molecule, both albumin and globulin could pass through provided they were orientated with their long axes pointing at the pores. Other orientations would cause the molecules to straddle the pore and they could not pass through. The orientation, however, would be less critical for albumin than for globulin because of the former's rounder molecule. Random orientation would be favoured by the Brownian movement of the molecules and some molecules of both albumin and globulin should pass through. The passage of albumin would, however, be greater than that of globulin because of the fact that the angle of approach of the albumin molecule to the pore would be less critical.

However, the molecules of protein must be flowing in a stream along the membrane and when long molecules are in such a current, they tend to orientate themselves with their long axes in the axis of the flow (70). The force opposing the Brownian movement and orientating them im this way is greatest when the ratio of the long to the short axis of the molecule is high and when the velocity gradient between the centre and edge of the stream is high (70). The globulin molecule with an axial ratio of 8.9/1 will have a greater tendency to orientate in the axis of the flow of the blood than the albumin molecule

which has an axial ratio of 4 / 1. The result of this will be a further favouring of the passage of albumin relative to globulin and a high ratio of albumin to globulin in the capsular urine. Actually at pore sizes near the narrowest diameters of the molecules, no globulin should pass through at all while the blood is flowing.

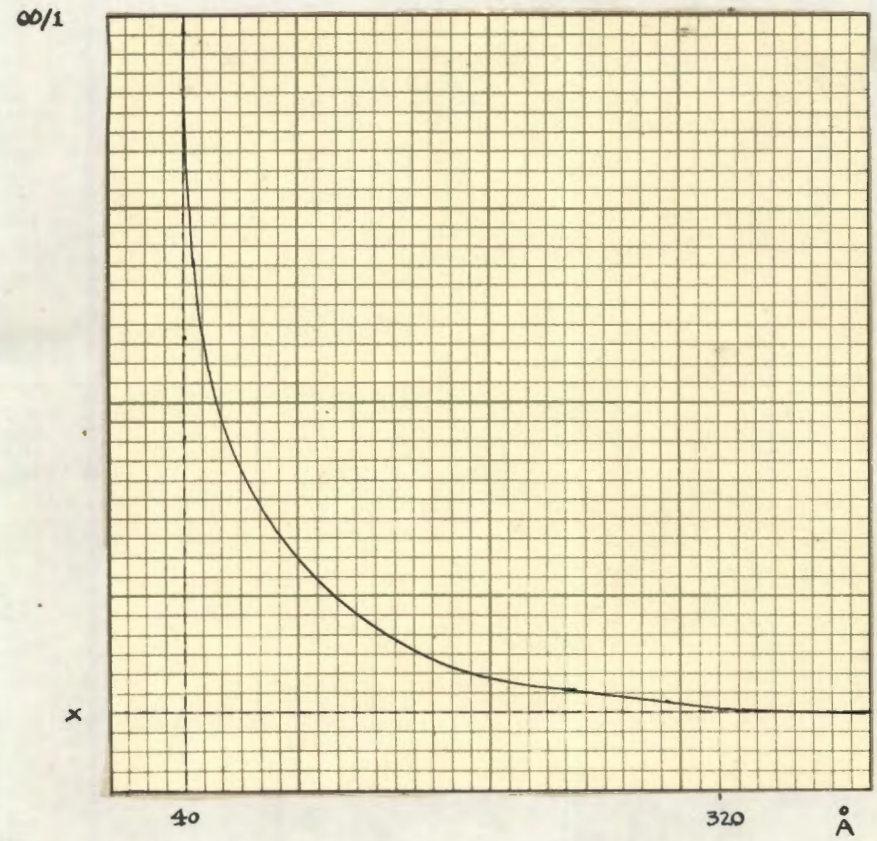
With increasing pore size, the orientation of the molecules will become less and less critical and even long molecules of globulin will be passed. The ratio of albumin / globulin in the capsule should therefore, fall progressively with increasing pore size until at pore sizes of over 320 Å, the ratio should equal that in the blood.

When the pore size lies between about 38 Å and 320 Å the rate of blood flow should also affect the albumin / globulin ratio. Slow rates of flow would favour lower ratios than high rates of flow at equal pore size.

The theoretical effect of pore size on the albumin / globulin ratio in capsular urine is illustrated in Figure 58.

Figure 58

The Theoretical Effect of Glomerular Pore Size on the Albumin/Globulin Ratio in Capsular Urine



Where "x" is the ratio of albumin to globulin in the blood.

Another consideration which must affect the passage of protein and the albumin/globulin ratio in the capsule, is the electrical charge on the glomerular membrane and on the molecules of protein. This factor may well be as important as that already discussed, but in the absence of knowledge of the location of the charge on the molecules, its effect cannot be predicted.

However, the conclusion reached above, that albumin should be more readily filtered at small pore diameters probably still holds. There is in fact experimental evidence favouring it. Experiment 13 shows that at low rates of protein secretion, most or all of the protein passed, is albumin and globulin only appears at moderately high rates of protein loss. This fact has been noted before (99). Only one of the cases in the present series (Case 182) on one occasion passed urine containing fibrinogen which clotted spontaneously. The total protein content of this specimen of urine was 3.5 gm. / 100 cc. This suggested that the pore size had become extremely large. If molecular diameter alone, governed the passage of protein, fibrinogen should be the commonest protein in the urine because of its small equatorial diameter.

The fate of the protein in the tubules

In benign proteinuria, ratios of albumin to globulin in the urine of less than that in the blood were observed in cases 172, 174, 179, 180, 190 and 200. In cases 190 and 200 the ratio was actually less than 1/1. This phenomenon has been noted before (59,71). Only three possibilities could account for this:-

1. Preferential filtering of the globulin molecule by the glomerulus

This has already been shown to be unlikely from considerations of the physical conditions at the glomerular membrane.

2. Alteration of proteins of low molecular weight (the albumins) into those of higher molecular weight (the globulins)

This appears to be unlikely. Incubation of protein containing urine at 56° C for 6 hours caused no detectable alteration in the albumin/globulin ratio.

3. Albumin reabsorption by the tubules

This appears to be the most likely explanation of the phenomenon.

There is considerable evidence to show that the tubules can reabsorb protein and other colloidal

matter. Ekehorn (67) goes into the question in some detail. From consideration of the concentration of protein in frogs' glomeruli as obtained by glomerular puncture and the concentration of protein in the bladder, he calculated that about 90 % of the protein passed through the glomerulus is reabsorbed by the tubules. In man he considers that the tubules have a similar high capacity for protein reabsorption. This conclusion was reached from a study of microscopical sections of kidneys from patients dying with nephrosis. He noted that the concentration of protein in the glomeruli and tubules was about the same as judged by the density of protein precipitate in the two parts. As considerable water reabsorption occurs in the tubules, this indicated that protein too must be reabsorbed.

Pol Gerard (72) in an excellent comparative review of the physiology of the vertebrate nephron, summarieses the work on the capacity of the tubular cells to take up a number of colloids, including protein, from the urine. In the tubular cells these colloids are either stored (athrocytosis) or metabolised and returned to the blood. The proximal convoluted tubule is apparently responsible. It appears that this portion of the tubule

acted as an organ of recovery of material from coelomic fluid which passed through it at a primitive stage of evolution when certain nephrons opened into the coelomic cavity. Gerard believes that the tubular changes seen in the kidneys in nephrosis are the result of athrocytosis. The same conclusion had previously been reached by Ekehorn. Dock (68) reviews the evidence in favour of this suggestion and agrees that it is the most likely explanation of these tubular changes.

The extent of protein reabsorption

1. Evidence from microscopical sections

Ekehorn (67) from examination of sections of kidney from patients dying of nephrosis estimated that about 90 % of the protein passed by the glomerulus was reabsorbed by the tubules. There are two main objections to this method of estimation:-

a. Only a very rough estimate of the protein concentration in the glomerulus can be obtained. This concentration must be inferred from the staining characters of protein films of known protein content.

b. It is difficult to be certain that the protein in

the capsules is evenly distributed. Strands and films of protein are so apt to form on fixing that retraction of the precipitate from the capsule walls almost invariably occurs.

2. Indirect evidence from the reabsorption of other proteins

Myohaemoglobin. Yuile and Clark (73) working on dogs, estimated the clearance of myohaemoglobin at various levels of plasma concentration of the substance. They found that a definite threshold level of plasma myohaemoglobin concentration existed, below which all the myohaemoglobin was reabsorbed. One of their dogs weighing 10.5 Kilos could reabsorb 6 mg. per minute. This is equivalent to:-

820 mg. / Kilo body weight / 24 hours.

(The molecular weight of myohaemoglobin is given as 17,500)

Haemoglobin Yuile, Steinman, Hahn and Clark (74) again working on dogs, estimated the clearance of dog haemoglobin at various levels of plasma haemoglobin concentration. They found that the haemoglobin clearance in dogs which had had repeated injections of haemoglobin was lower than in animals which had not had haemoglobin before. In a dog weighing 17 Kilos which had not received previous haemoglobin injections they found the tubular reabsorptive capacity for haemoglobin to be 3.36 mg. / min. This is

equivalent to:-

285 mg. / Kilo body weight / 24 hours.

(The molecular weight of haemoglobin is 65,000 - 68,000)

It will be seen that the molecular weight of haemoglobin is roughly four times that of myohaemoglobin while its reabsorption under the same conditions is roughly a third of that of myohaemoglobin. This suggests that molecular weight is a determining factor in the amount of reabsorption that can occur. If this is the case, serum albumin with a molecular weight of the same order as that of haemoglobin should be reabsorbed to about the same extent. Furthermore, globulin with a molecular weight twice that of albumin should be reabsorbed more slowly. That some globulin is reabsorbed is, however, likely despite the large size of the molecule for Gerard found that the tubule could even take up particulate matter.

3. Evidence from the study of subjects with postural proteinuria

In a number of subjects with postural proteinuria the urinary albumin/globulin ratio was less than that in the blood at high levels of protein secretion. This is best explained on the basis of the suggestion made in the preceding section, that globulin is more slowly reabsorbed than albumin. Given the following data and assuming that no globulin is reabsorbed, one can estimate the minimal quantity of albumin reabsorbed. If globulin is reabsorbed as it probably is, the figure obtained by this means will be too low.

Ratio A/G in the blood - R

Urine flow in cc. / minute - V

Urine albumin concentration in mg./ cc. - A

Urine globulin concentration in mg./ cc. - G

VA will be the amount of albumin passed in mg. / min.
VG will be the amount of globulin passed in mg./ min.

As the ratio A/G in the glomerular capsule is likely to be higher than that in the blood as shown above, we can assume that at a minimum A/G in capsular urine equals R.

If R is the ratio of albumin to globulin in capsular urine and no reabsorption of globulin occurs, one can calculate the amount of albumin filtered at the glomerulus to be - RVG

The difference between this calculated figure and the observed figure for albumin passed in bladder urine must indicate reabsorbed albumin.

Therefore RVG - VA = albumin reabsorbed in mg. / min.

This formula may now be applied to those specimens of urine from subjects with postural proteinuria which have a ratio of albumin/globulin of less than that in the blood:-

Case 179 Coloured male. Weight 57 Kilos.
(Data from period (2) 11.1.46)

R . 1.54
V . 0.44
A . 3.55
G . 2.48

(1.54 x 0.44 x 2.48) - (0.44 x 3.55) . 0.12
Minimum albumin reabsorption . 0.12 mg./min.
or 3.04 mg. / Kilo body weight / 24 hours.

Case 190 European male. Weight 62 Kilos.

(Data from period L)

R . 3.94
V . 0.28
A . 3.0
G . 5.4

(3.94 x 0.28 x 5.4) - (0.28 x 3.0) . 5.2
Minimum albumin reabsorption . 5.2 mg./min.
or 121 mg. / Kilo body weight / 24 hours

Case 200 Coloured female. Weight 52 Kilos.

(Data from period 6)

R . 1.44
V . 0.41
A . 1.21
G . 1.21

(1.44 x 0.41 x 1.21) - (0.41 x 1.21) . 0.12
Minimum albumin reabsorption . 0.12 mg./min.
or 3.3 mg. / Kilo body weight / 24 hours

(Data from period 8)

R . 1.44
V . 0.38
A . 1.25
G . 1.45

(1.44 x 0.38 x 1.45) - (0.38 x 1.25) . 0.305
Minimum albumin reabsorption . 0.305 mg./min.
or 8.5 mg. / Kilo body weight / 24 hours

The figures obtained from the experiments on subjects with postural proteinuria are extremely variable but it is evident that they should be so, because we have no means of knowing the true albumin/globulin ratios in

the capsular urine under varying conditions. Nor do we know whether either the albumin or the globulin reabsorptive mechanisms are working at capacity or whether the one interferes with the absorption of the other in the same way as for example, various substances compete with dietrast for a common excretory mechanism.

However, we can say that man can probably reabsorb :-

<u>121 mg. or more of albumin / Kilo body weight / 24 hrs.</u>

It will be noted that this figure is not far removed from that derived by inference from the haemoglobin experiments of Yuile et al (74).

Postural proteinuria as a failure of protein reabsorption

Having established that the tubule can reabsorb protein and obtained a rough estimate of its reabsorptive capacity, it could be postulated that the normal glomerulus filters protein which is ordinarly reabsorbed and that an increase in venous pressure in some way prevents this reabsorption.

Does the normal glomerulus filter protein ?

Glomerular puncture experiments have shown the glomerular urine to be protein-free within the limits of accuracy of the methods of detection. However, Ekehorn (67) calculates that the protein concentration has to be ± 40 mg. per 100 cc before it can be detected regularly. A concentration of as little as 10 mg. per 100 cc. in capsular urine would give a concentration of as much as 1000 mg. per 100 cc. in bladder urine due to water reabsorption in the tubules. Therefore, the absence of detectable protein in capsular urine by glomerular puncture experiments does not exclude the possibility of protein's passing into the capsule in sufficient quantities to give rise to marked proteinuria.

However, if protein were passing through

the glomerular filter in sufficient amounts to cause protein concentrations in bladder urine of as much as 2 grammes per 100 cc. as sometimes occurs in postural proteinuria, athrocytosis should be demonstrable in normal tubules. This has never been found in mammals with the exception of certain hibernating species (72). Therefore, on these grounds it is very unlikely that the normal glomerulus passes protein.

If phloridzin interferes with protein reabsorption as it does with other proximal convoluted tubule functions, phloridzinised man and animals should pass measurable quantities of protein in the urine. There is one report by Kossa (103) of the finding of proteinuria in phloridzinised rabbits but proteinuria has not been reported in other phloridzinised animals or in phloridzinised man (75,76,77). Rabbits are subject to proteinuria from slight trauma so this single observation can probably be neglected.

All the evidence therefore, is against there being any protein in normal capsular urine and the theory of defective protein reabsorption being responsible for postural proteinuria is unlikely.

The mechanism by which increased venous pressure causes proteinuria

Winton (43) showed that an increase in venous pressure of a sufficient degree to cause proteinuria, did not do so by producing glomerular anoxia. The venous blood issuing from the renal veins was "invariably scarlet". In support of this he quoted Cruickshank and Takeuchi (78) who showed that the renal blood flow can be reduced by 40 % before the oxygen consumption of the kidney is reduced. This reduction is greater than has been found in certain postural proteinurics (Experiment 11). Furthermore, even considerably greater reductions in blood flow would not be likely to cause glomerular anoxia because all blood entering it is oxygenated and its oxygen requirements must be very small.

It is therefore almost certain that the mechanism of production of the proteinuria is not one of glomerular anoxia and is much more likely to be entirely mechanical. It is suggested that distension of the capillaries in the glomerulus occurs because of the raised pressure at its efferent side. This distension in turn stretches the glomerular membrane, enlarging its pores and also slows the rate of flow of the blood in the

lumen. The effect of this is to allow protein to pass out into the capsule. With small degrees of distension, the proteinuria will be slight and most of the protein will be albumin for the reasons given earlier. As the distension increases, because of the increasing pore size and slowing of the blood stream, more protein will pass and the albumin/globulin ratio in the capsule will fall towards the same value as in the blood.

In the tubule, some of the protein will be reabsorbed and the reabsorption of albumin will exceed that of globulin so that at times, the albumin/globulin ratio of the bladder urine may be below that in the blood.

The low albumin/globulin ratios found in postural proteinuria are very characteristic of the condition and probably depend on intact tubular function. In nephritis and most other forms of renal disease, the ratios are higher. There are two probable reasons for this:-

1. The functioning tubular tissue is usually diminished in these conditions (104,105).
2. Most other proteinurias are continuous. It is probable that albumin reabsorption is diminished in the same way as haemoglobin reabsorption by continuous functioning.

For example, the same dog in the haemoglobin experiment of Yuile et al. quoted earlier could only reabsorb haemoglobin at the rate of 0.141 gramme / kilo body weight / 24 hours after repeated haemoglobin administration, whereas previously it could reabsorb 0.285 gramme / kilo body weight / 24 hours.

Theories based on presumed congenital or acquired lesions of the kidney and particularly of the glomeruli

One cannot picture any alteration in the renal parenchyma which could occur with posture unless it be due to mechanical or reflex alterations in the blood supply to the organ as a whole. These have been considered already. However, there remains the possibility that congenital or acquired lesions of the glomeruli do occur in postural proteinuria and cause them to be more permeable to protein. These lesions would allow them to pass protein under conditions such as very slight increase in venous pressure which would not affect normal glomeruli.

Congenital lesions

Among the earliest theories for the pathogenesis of postural proteinuria were some that postulated congenital abnormalities of the glomeruli and associated abnormalities of vasomotor tone, build and habits. In conjunction with these theories a "proteinuric diathesis" was described (33,84,85,86). Hooker (5) reviews these old theories very fully.

As postural proteinuria occurs in approximately 3/4 of children at the age of 15, one can hardly speak of an abnormality, congenital or otherwise. Furthermore, congenital abnormalities do not tend to revert to normal with advancing age as would have to occur to explain the diminishing incidence in older age groups.

The present investigation also reveals no special proteinuric diathesis. Postural proteinuria occurred in subjects of all types. It is, however, just possible that postural proteinuria is slightly commoner in asthenic persons than in sthenics for Diehl and Mc Kinlay (41) investigating a large group of 16,748 students found a slight positive correlation between the height/weight ratio and proteinuria. This association may have been missed in the present smaller series of 50 subjects in whom the point was investigated. Long spines such as asthenics have would favour a wider range of spinal movement so that a possible association with proteinuria would not be surprising. However, against Diehl and Mc Kinlay's finding is that of Bashford (79) and Palmer (80). These workers found no special type of individual to be liable to postural proteinuria.

Acquired glomerular lesions

Some schools of thought hold that postural proteinuria is a manifestation of nephritis or other renal disease and that it may be the only evidence of such a lesion. Prominent among the upholders of this view are Russell (81,82) and Thorp and Wakefield (83). Their reasons for concluding that nephritis and postural proteinuria are related to one another are, however, open to criticism.

Russell bases his opinion on three main points.

1. He found a greater percentage of children who had recently had scarlet fever to have postural proteinuria than a control series. His control series consisted of 35 non-consecutive children in whom he found a 3.1% incidence of proteinuria. In his post scarlet fever cases, the incidence was 26.5%

   It appears from his paper that neither of these two groups was examined under uniform and controlled conditions of posture and exercise during the period of urine secretion. As has been shown earlier, this is essential in any work on incidence. Furthermore, neither the post scarlet fever nor the control group showed as high an incidence of proteinuria

as might occur in random collections (see Expt.1).

2. He believed that symptoms such as headache, fatiguability, lassitude and occasionally some swelling of the face were commoner in the postural proteinuria group than in normal subjects. All his cases had been patients referred to him for specific complaints or because proteinuria was discovered by their private doctors. Such cases must have had symptoms or else they would not have been discovered, so that his arguments based on a highly selected series of cannot be accepted.

3. He found a number of cases with what appears to have been undeniable signs of nephritis plus postural increase in the proteinuria. He believed that these were merely a severer grade of postural proteinuria. One has seen such cases but they probably represent nephritics who have at the same time postural proteinuria. Any condition which can affect 3/4 of the population can occur in a high percentage of people with other conditions including nephritis.

Thorp and Eskefield (83) analysed the findings in 185 subjects admitted to the Mayo Clinic over a 10 year period in whom postural proteinuria had occurred either

alone or combined with other signs of nephritis or with a continuous proteinuria. They showed that, at times, cases of nephritis could present with all the features of postural proteinuria either in the stage of recovery from nephritis or very rarely during its development. They argue that there is a gradation from an apparently benign and purely postural proteinuria to a full picture of nephritis and that there is a common etiology.

The same argument can be raised here as was against Russell, namely that it is much more likely that postural proteinuria and nephritis are occurring together. Thorp and Wakefield themselves admit that when a recovering nephritic shows only orthostatic proteinuria, the prognosis is excellent. The fact that some cases of nephritis in the stage of recovery or development have all the features of postural proteinuria is only to be expected in the light of the high incidence of the latter in the general population.

Russell's and Thorp and Wakefield's conclusions are therefore, not acceptable. Furthermore, on the evidence of the present investigation, any causal relationship between postural proteinuria and nephritis is unlikely for the following reasons:-

1. It is difficult to picture a type of nephritis that can cause such a characteristic and selectively postural proteinuria in about 3/4 of youths.

2. If such a lesion exists, one would expect to find other evidence of it than the proteinuria. This is not the case.

   a. No detectable oedema was found in any of the cases.

   b. The serum protein concentrations in the proteinuric and non-proteinuric groups of cadets did not differ in any way. This agrees with the findings of Schlutz and Swanson (89) and Linder, Lunsgaard and van Slyke (90). If the proteinuric subjects had had nephritis, one might have expected some lowering of their serum protein concentrations even although all readings were in the normal range.

   c. None of the cadets showed evidence of arteriosclerosis on examination. Only one of them (Number 31) had a raised blood pressure at any time. In this case, the blood pressure in the erect posture was 165/95 mm.Hg and when recumbent 125/70 mm.Hg. The high reading was probably due to nervousness. Examined statistically there was no significant difference in the systolic or diastolic blood pressures between the proteinuric

and non-proteinuric groups. Diehl and Mc Kinlay (41) and Nicholson (87) came to the same conclusion. Had nephritis been responsible for the proteinuria, some difference in the blood pressures in the two groups might have been expected.

d. No case in the 1944 series of cadets gave a history suggestive of nephritis, oedema or any renal disturbances in the past.

e. The histories of the 1944 series of cadets showed that there is no special incidence of diseases such as scarlet fever or tonsillitis which are liable to be complicated by nephritis. Furthermore, there was no disproportionate frequency of occurrence of the exanthemata in either the proteinuric or non-proteinuric groups.

f. There was a lack of subsequent development of patent nephritis on follow up. Had the proteinuria been due to nephritis, some cadets should have shown signs of it later. The 1943 and 1944 classes were followed for two years each and the 1946 class for 6 months.

g. There is almost universal agreement that the prognosis for future life and health of postural proteinurics is excellent. This would not be the case if nephritis was responsible. Wolman (3) reviews this aspect very fully so that repetition is unnecessary.

h. The nucleated cells in the urinary sediment are not of the same type as are found in nephritis or nephrosis (Experiment 11).

Therefore, it can be concluded that nephritis plays no part in the pathogenesis of postural proteinuria.

Outline of the Methods used in Differentiating Postural Proteinuria from other Conditions

For practical purposes, postural proteinuria does not occur in patients who are confined to bed because extreme lordosis is necessary to induce it in the recumbent posture. Furthermore, not all postural proteinurics pass protein in the erect posture unless it is combined with forced lordosis. These facts considerably simplify the problem of differentiation of postural proteinuria from other conditions. This is so because a number of subjects will be automatically excluded from the necessity of further investigation on account of their urines containing no protein at the time of the original examination. Nevertheless, where considerable numbers of subjects are being examined such as occurs during school medical or army entry examinations, a large number of cases is to be expected.

Young, Haines and Prince (37) lay down the following criteria for diagnosis:-

1. No history of renal disease in the past.
2. Normal blood chemistry.
3. Normal kidney functions
4. No nucleated cells, erythrocytes or casts in the urine

except intermittently and in small numbers.

5. Normal blood pressure.
6. Negative plain X-rays of the kidney and pyelograms.
7. Absence of proteinuria in the recumbent posture.

As Nolsen (93) has already pointed out, this detailed diagnostic programme is not practical. Furthermore, it is not necessary and in the author's opinion a past history of renal disease and the finding of slightly raised urinary sediment counts does not exclude postural proteinuria.

The following programme is usually sufficient to establish the diagnosis:-

In addition to complete physical examination, the urine is re-examined under controlled conditions.

1. The patient is instructed to empty his bladder and then immediately placed in a recumbent kyphotic posture for about 10 to 15 minutes. At the end of this period he passes more urine. If this specimen contains protein a further period of recumbency follows immediately, so as to exclude the possibility of protein contamination

from urine secreted previously. This specimen is also tested for protein.

2. A centrifuged deposit of urine is examined for formed elements and doubly refractile fat. The latter is a very simple and rapid procedure and has been much neglected in the study of renal disease.

In the event of there being no protein in the urine secreted in recumbency and no evidence of oedema, arteriosclerosis or hypertension, no doubly refractile fat or undue excess of formed elements in the urinary sediment, the case may be presumed to be one of uncomplicated postural proteinuria. Any case not fulfilling these criteria warrants further study to exclude nephritis or other renal disease. The use of the Addis count and differential nucleated cell count, combined with other investigations is often helpful in this connection.

Only a very few of the cases of postural proteinuria will require further investigation and they are likely to be subjects in whom the postural proteinuria

is combined with other conditions. The only exception to this is the case in which the only doubtful factor is the finding of doubly refractile fat in the urine. If all other tests are negative, this fat probably comes from the prostate (94).

Summary and Conclusions

Summary and Conclusions

A survey of the literature on postural proteinuria reveals considerable difference of opinion regarding the incidence and pathogenesis of the condition. The theories advanced to explain the proteinuria have been divided into four groups; those relating it to disturbances of arterial circulation to the kidney; those relating it to disturbances of venous return from the kidney and those relating it to congenital or acquired lesions of the kidney, particularly nephritis. Experiments designed to investigate these theories and the incidence of the condition have been presented and the findings discussed in conjunction with the available literature.

It is concluded that postural proteinuria is an extremely common condition, occurring in approximately 3/4 of youths, 1/3 of young men and 1/10 of old men.

The proteinuria is strictly related to a posture of lordosis and is associated with certain very characteristic disturbances of renal function and a slowing of the circulation in the inferior vena cava.

The current theories to explain the condition have been shown to be inadequate and disturbances of

arterial circulation and congenital or acquired lesions of the glomeruli play no part in the pathogenesis.

A new theory has been presented, relating postural proteinuria to obstruction of the inferior vena cava by the liver, and evidence supporting this theory has been derived from experiments on postural proteinuric subjects and on others with a variety of liver diseases. Certain of the inconsistencies in the literature on the subject have been analysed and explained on the basis of this new theory.

The effect on the kidney of the increased venous pressure produced by the inferior vena cava obstruction has been discussed and the circulatory dynamics in the kidney analysed.

Evidence from the study of postural proteinuric subjects has been presented to show that the renal tubules can reabsorb considerable quantities of protein.

Criteria for the diagnosis of postural proteinuria have been presented.

During the course of the investigation it became necessary to develop a method of determining the origin of the nucleated cells found in urine. Standards by which they may be recognised have been submitted.

Protocols

Protocol 1

Protein in the Urine of the 1945 Class Cadets in 3 Postures

Case No.	Posture Uncontrolled	Erect Lordotic	Recumbent Kyphotic
51	5	1200	0
52	0	1000	
53	20	1000	0
54	5	900	0
55	5	800	0
56	20	800	0
57	0	800	
58	5	600	0
59	0	500	
60	0	400	
61	0	300	
62	50	200	0
63	0	200	
64	10	150	0
65	0	150	
66	5	150	0
67	0	150	
68	0	100	
69	10	100	0
70	0	100	
71	0	30	
72	0	20	
73	5	10	0
74	5	10	0
75	0	5	
76	0	5	
77	5	5	0
78	0	5	
79	0	5	
80	0	5	
81	0	0	
82	0	0	
83	0	0	
84	0	0	
85	0	0	
86	0	0	
87	0	0	

A Case number.

B Age in months.

C Protein concentration in urine in mg./100cc. Posture uncontrolled.

D Protein concentration in urine in mg./100cc. Erect lordosis.

E Protein concentration in urine in mg./100cc. Recumbent kyphosis.

F Weight in pounds.

G Height in inches.

H Degree of lumber lordosis. N is normal and + more than normal degree of lumbar lordosis.

I Ratio of circumference of chest at nipple line to circumference of abdomen.

J Serum protein concentration in Gm./100 cc.

K Systolic blood pressure in recumbency in mm.Hg.

L Diastolic blood pressure in recumbency in mm.Hg.

M Systolic blood pressure in the erect posture in mm.Hg.

N Diastolic blood pressure in the erect posture in mm.Hg.

O Maximum rise in systolic pressure on application of the cold pressor stimulus in mm. Hg.

P Maximum rise in diastolic pressure on application of the cold pressor stimulus in mm. Hg.

Protocol 2
1944 Class Cadets

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	192	20	20	0	125	66.5	+	1.25		115	75	105	65		
2	180	3	20	0	105	67	N	1.15	8.0	115	70	115	70	- 5	+ 5
3	192	3	80	0	128	67.5	+	1.10	8.0	115	60	135	85	+ 5	+10
4	177	0	40		103	63	N	1.17		115	70	100	65	+15	+25
5	196	0	200		160	67.5	N	1.17	7.9	105	60	125	80	+15	+20
6	192	0	60		125	66.5	+	1.25		105	65	120	65	+20	+25
7	187	60	60	0	122	64	N	1.11	6.6	100	65	115	70	0	+ 5
8	187	0	140		110	65	N	1.15	8.2	110	60	125	70	+20	+30
9	192	5	40	0	126	67.5	N	1.19	7.5	120	60	130	90	0	+10
10	189	40	120	0	130	64	N	1.22	7.8	110	60	120	85	+ 5	+ 5
11	194	3	40	0	127	68	N	1.11	8.1	100	70	110	55	- 5	0
12	194	0	20		121	66	N	1.15	7.6	110	70	110	70	+ 5	+10
13	174	40	25	0	108	66	N	1.18		120	60	125	85	+10	+10
14	195	10	20	0	100	64	+	1.10	6.7	120	75	150	65	0	+ 5
15	192	40	280	0	130	69.5	+	1.25	7.6	120	50	130	70	+20	+25
16	180	5	300	0	129	68	+	1.20	7.4	110	70	115	65	+ 5	0
17	189	50	60	0	113	65.5	+	1.16	8.1	120	70	105	70		
18	193	0	100		117	67	N	1.19	6.5	115	75	115	65		
19	191	0	30		112	69	N	1.27	8.0	105	75	125	80	0	0
20	180	5	120	0	132	66.5	N	1.15	7.1	120	65	115	60	- 5	+ 5
21	172	10	180	0			N		7.7	115	50	100	50	+15	+10
22	185	0	10		140	70	N								
23	182	0	10		90	61	+	0.89	7.6	125	65	105	75		
24	185	0	10		138	71	N	1.22	8.7	115	70	125	70	+ 5	0
25	190	5	20	0	120	65	N	1.11	7.5	120	80	130	85	+10	+10
26	192	0	15		132	66		1.26	8.7	125	60	115	80	+ 5	+ 5
27	171	0	5		86	60		1.10		110	55	105	55	+ 5	+ 5
28	173	5	5	0	110	63	N	1.11		115	70	110	60	+ 5	+15
29	184	5	5	0	91	64	N	1.18	7.9	110	60	115	50	- 5	+ 5
30	189	3	5	0	128	69.5	+	1.11	7.7	140	70	125	70	+10	+20
31	177	5	15	0	111	66	N	1.18	9.3	125	70	165	95	0	+ 5
32	185	0	5		105	66	+	1.13	7.4	120	70	140	90	- 5	+15
33	177	0	5		110	65	N	1.20		115	55	80	50	+ 5	+20
34	190	0	0		137	67.5	N	1.18	7.9	115	60	115	75	+30	+35
35	195	0	5		165	71	N	1.20	7.1	120	75	130	85	+10	+10
36	171	0	0		114	63	+	1.20	8.6	115	80	120	80	+15	+10
37	187	0	0		124	71	N	1.15	8.0	90	60	100	75	+10	+15
38	189	0	0		120	66	+	1.11	8.6	110	65	130	65	+10	+15
39	194	0	0		105	64.5	N	1.15	7.1	100	70	115	55	+ 5	+10
40	189	0	0		118	67.5	N	1.07	7.5	100	60	100	80	+ 5	
41	195	0	0		130	71	+	1.17	6.5	110	70	115	75	+10	0
42	194	0	0		134	67.5	N	1.19	7.9	115	70	130	75	+ 5	+ 5
43	181	0	0		97	59.5	N	1.16	8.1	105	65	105		+10	+10
44	192	0	0		130	67	N	1.17		110	80	120	80	+10	+ 5
45	179	0	0		100	64.5	N	1.16	7.5	120	60	105	70	0	+ 5
46	189	0	0		122	66	N	1.18	7.0	115	70	110	70	+15	+15
47	184	0	0		125	68	N	1.17	8.2	130	65	135	75		
48	180	0	0		95	63	N	1.13	7.5	110	60	95	55		
49	186	0	0		110	63	N	1.22				115	60		
50		0	0		124	66	N	1.21				130	90		

	A	Case Number
	B	Time to secrete spec. 1 in mins.
Urine Specimen 1	C	Volume per 12 hrs. in cc.
Posture	D	Protein concentration in mg./100cc.
uncontrolled	E	Erythrocytes in millions per 12/hrs.
	F	Nucleated cells in millions per 12 hrs.
	G	Casts in millions per 12 hrs.
	H	Time to secrete specimen 2 in mins.
	I	Volume urine per 12 hrs. in cc.
	J	Protein concentration in mg./100cc.
	K	Erythrocytes in millions per 12 hrs.
Urine Specimen 2	L	Nucleated cells in millions per 12 hrs.
Erect lordotic	M	Casts in millions per 12 hrs.
posture.	N	Number polymorphs seen in smear.
	O	Number lymphocytes seen in smear.
	P	Number renal tract cells seen in smear.
	Q	Number renal parenchymal cells seen in smear.
	R	Number small cells seen in smear.
	S	Number unclassifiable cells seen in smear.
	T	Doubly refractile fat.

All casts were hyaline or granular.

Protocol 5

The Urinary Protein and Sediment of the 1946 Class Cadets

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
88	60	336	0	0	0.05	0	17	53	20	0	0.1	0							
89	60	348	0	0	0	0	28	180	60	0	0.34	0	1	1	5	0	3	0	-
90	60	468	200	0.7	1.9	0.2	45	225	500	0	2.25	0.23	0	0	50	0	0	0	-
91	60	600	100	0	0.91	0	28	65	500										
92	60	696	200	1.6	3.1	0	39	200	500	0	3.2	1.8							
93	60	768	100	0	0.1	0	50	350	400	0	0.7	0	7	0	11	0	0	2	-
94	60						14	310	10	0	0	0	0	0	0	0	0	0	-
95	60	498	10	0.1	0.1	0	55	265	40	0	0.53	0	1	0	16	0	2	1	-
96	60	300	0	0	0.1	0.02	13	194	5	0	0.68	0	12	2	5	0	0	1	-
97	60	1512	0	0	0	0	20	1150	0	0	0	0	0	0	0	0	0	0	-
98	60	684	50	0.2	0.4	0.1	20	270	50	0	0.27	0	3	6	4	0	2	5	-
99	60	1488	20	0	0	0	31	1310	0	0	0	0	1	0	0	0	0	0	-
100	60	1668	200	0	0.74	0	39	535	500	0	1.07	0.54	7	3	6	0	1	8	-
101	60	372	5	0	0	0	56	260	20	0	0	0	2	0	18	0	0	5	-
102	60	1176	10	0	0.15	0	27	1090	0	0	0	0	1	1	5	0	3	0	-
103	60	1332	0	0	0	0	34	200	0	0	0.5	0	1	1	19	0	0	0	-
104	60	684	0	0	0	0	25	187	5	0	0.19	0	1	1	17	0	0	1	-
105	60	732	10	0	0.7	0	19	309	80	0.51	2.04	0	0	6	9	0	0	5	-
106	60	2152	50	0	0	0	14	205	500	0	0	0	1	0	1	0	0	1	-
107	60	744	5	0	0.65	0	24	105	5	0	0.32	0	3	10	4	1	0	2	-
108	60	912	0	0	0.7	0	25	260	15	0	1.56	0	8	5	3	0	31	3	+
109	60	564	130	0	0.2	0	17	225	200	0.68	0.45	0	2	4	11	0	2	2	-
110	60	1260	5	0	0	0	29	210	500	0	0.63	0	1	6	1	0	38	2	-
111	60	288	5	0	0.41	0.1	31	500	10	0	0.6	0.3							-
112	60	936	0	0	0	0	42	163	500	0	0.33	0	2	6	24	0	0	1	-
113	60	288	50	0	0.1	0	21	171	10	0	0.17	0	0	0	9	0	1	0	-
114	60	588	5	0	0	0	34	220	50	0	0	0	0	2	46	0	0	2	-
115	60	264	0	0	0	0	33	215	0	0	0.22	0	0	0	0	1	0	0	-
116	60	384	40	0	0.3	0	20	250	500	0	1.75	0	3	0	46	0	0	1	-
117	60	2460	0	0	0	0	20	630	0	0	0	0	0	0	3	0	2	4	-
118	60	4404	0	0	0.85	0	22	345	500	2.4	4.72	0.7	1	39	3	1	0	0	-
119	60	1152	10	0.1	0.9	0.1	28	380	500	1.6	10.9	1.87	1	3	8	4	4	0	-
120	60	2260	0	0	0.5	0	30	360	1000	1.1	0.3	0.72	1	0	22	2	0	0	-
121	60	552	100	0	0	0	31	196	200	0	0.2	0.2	0	0	0	0	3	0	-
122	60	744	5	0	0.1	0	19	300	500	0	0.3	0	14	5	3	0	3	3	-
123	60	2628	5	0.1	0.7	0	20	1310	500	2.6	5.2	2.6	17	21	3	0	1	2	-
124	60	312	5	0	0	0	22	260	0	0	0.26	0	0	0	3	0	0	2	-
125	60	768	0	0	0.13	00	23	310	50	0	0.31	0	0	0	3	0	0	1	-
126	60	220	400	1.1	4.1	0.3	73	73	2000										
127	60	262	5	0.2	0	0	20	180	400	0	0.72	0	3	0	11	1	1	0	-
128	60	1044	5	0	0.1	0	17	255	10	0	0.5	0	0	3	3	0	1	11	-
129	60	1188	10	0	0	0	17	210	40	0	0.21	0	0	0	0	0	0	0	-

1. Chicken Pox

2. Whooping Cough.

3. Measles.

4. Mumps.

5. "Tonsillitis".

6. German Measles.

7. Scarlet Fever.

Protocol 4

Past Illnesses of the 1944 Class Cadets

Case	1	2	3	4	5	6	7	Other Illnesses
2			x		x			
3			x					Osteitis of femur at 6 years.
4	x		x					Intussusception. Broncho-pneumonia.
6	x		x	x	x		x	Malta fever at 13 years.
7	x	x	x	x				
8	x	x	x	x				
9			x		x	x		Influenza frequently.
10	x		x					Jaundice.
11	x		x					
12	x		x	x				Migraine.
13	x	x	x				x	
14			x					
15		x	x		x			
16	x		x					Appendicitis.
17		x	x	x	x			
18	x	x			x			
19	x						x	Asthma.
20		x	x	x	x			Appendicitis.
21	x	x	x		x			
22	x	x	x	x	x			
23	x	x	x		x			
24	x							
25	x	x	x	x				Diphtheria at 9 years.
26	x	x	x		x			
27	x	x	x					
28		x			x			
29	x		x		x	x		
30			x	x		x		Enteric fever. Appendicitis.
31		x	x					
32	x	x	x					
33		x		x				
34			x	x	x	x		Jaundice.
35	x							
36	x		x	x	x			
37	x	x	x					Malaria.
38			x	x				
39	x	x	x	x				
40		x	x					
41	x	x	x		x		x	
42	x	x	x	x	x		x	Malaria.
43				x				
44	x			x	x			
45	x	x	x					
46	x	x	x					
47	x		x		x			
48	x		x		x			

Protocol 5

Protein Content of Urine of Subjects Between 20 and 30 Years in Two Postures

Case No.	Age Yrs.	Age Mths.	1	2
253	23	4	0	0
254	21	3	0	0
255	21	2	0	0
256	23	1	0	0
257	25	1	0	0
258	22	0	0	0
259	21	7	0	40
260	29	1	0	5
261	21	6	0	0
262	22	0	0	0
†263	20	0	0	10
264	23	3	0	15
265	23	9	0	0
▼266	20	11	0	0
267	21	8	0	500
268	20	7	0	15
269	25	6	0	0
270	24	5	5	320
271	25	7	0	5
272	23	0	0	0
273	30	0	0	100
274	24	1	0	0
275	22	2	0	200
276	28	4	0	0
277	21	6	0	0
278	29	11	0	0
†279	21	0	0	200
280	21	8	0	0
†281	20	1	0	200
282	20	4	0	10
†283	24	11	0	0
†284	26	6	0	0
285	22	10	0	0
286	21	5	0	10
287	20	7	0	0
288	22	0	0	0
289	23	0	0	0
290	21	7	0	0
291	21	4	0	15
292	22	9	0	0
293	26	1	0	0
294	25	0	0	60
295	22	10	0	5
296	21	8	0	0
297	24	1	0	0
298	25	0	0	0
299	21	8	0	5
†300	21	9	0	0
301	22	2	0	0
302	22	4	0	0

† These subjects had scarlet fever in childhood.
▲ This subject had an attack of acute nephritis at 15 years.

1. Urinary proteins in mg. per 100 cc. posture uncontrolled.
2. Urinary proteins in mg. per 100 cc. posture erect lordotic.

Protocol 6

The Urinary Proteins in Subjects over 50 years of Age in Two Postures

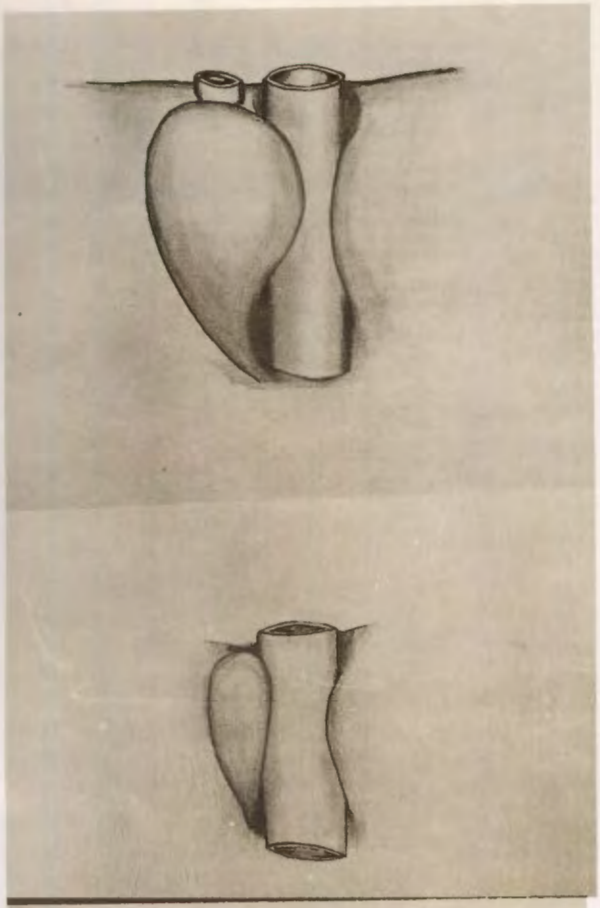
Case No.	Age Years	Spec.1	Spec.2
202	65	0	0
203	59	10	50
204	48	0	0
205	58	0	0
206	60	0	0
207	56	0	0
208	54	0	0
209	64	0	0
210	51	0	5
211	54	0	0
212	56	0	0
213	52	0	0
214	53	0	0
215	64	0	0
216	71	0	0
217	57	0	0
218	65	0	5
219	55	0	0
220	76	0	0
221	65	0	0
222	76	0	0
223	75	0	0
224	80	0	0
225	51	5	20
226	78	0	0

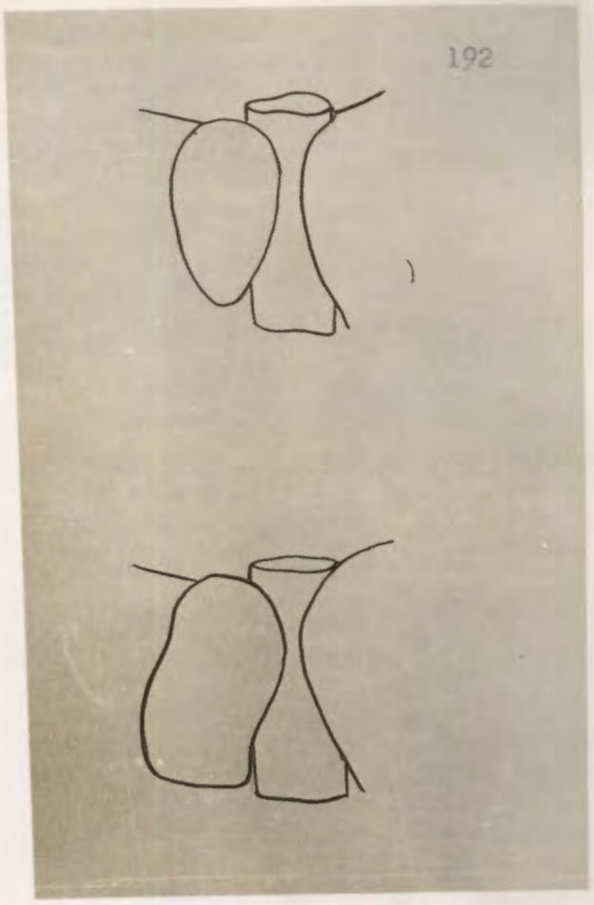
Case No.	Age Years	Spec.1	Spec.2
227	74	0	5
228	58	0	0
229	66	0	0
230	75	0	0
231	51	0	0
232	56	0	0
233	62	0	0
234	62	0	0
235	65	0	0
236	64	0	0
237	78	0	0
238	66	0	5
239	84	0	0
240	82	0	0
241	71	0	0
242	85	0	0
243	66	0	0
244	79	0	0
245	54	0	0
246	76	0	0
247	69	0	0
248	79	0	0
249	60	0	0
250	57	0	0
251	72	0	0

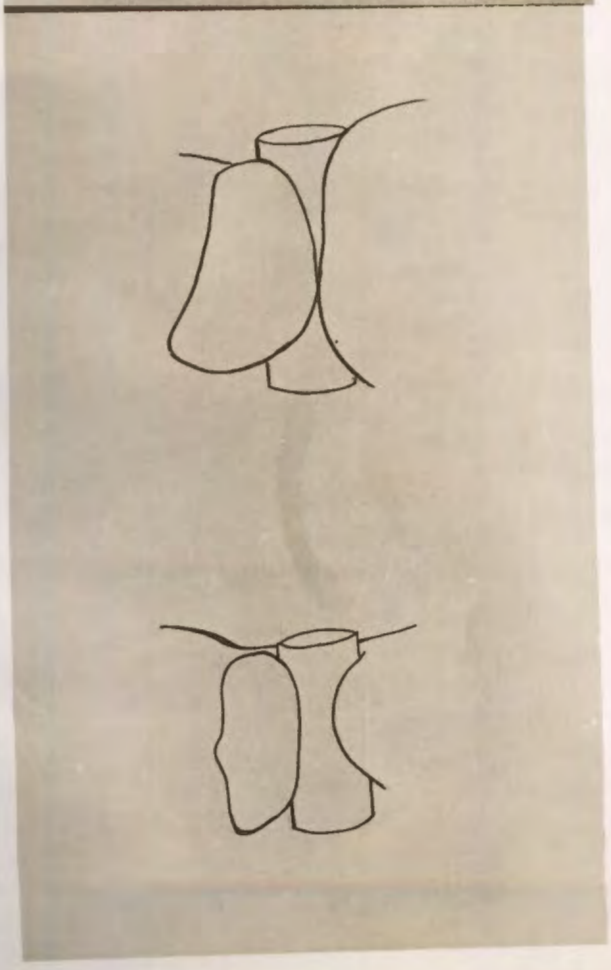
Specimen 1 Posture uncontrolled.
Specimen 2 Erect lordotic.

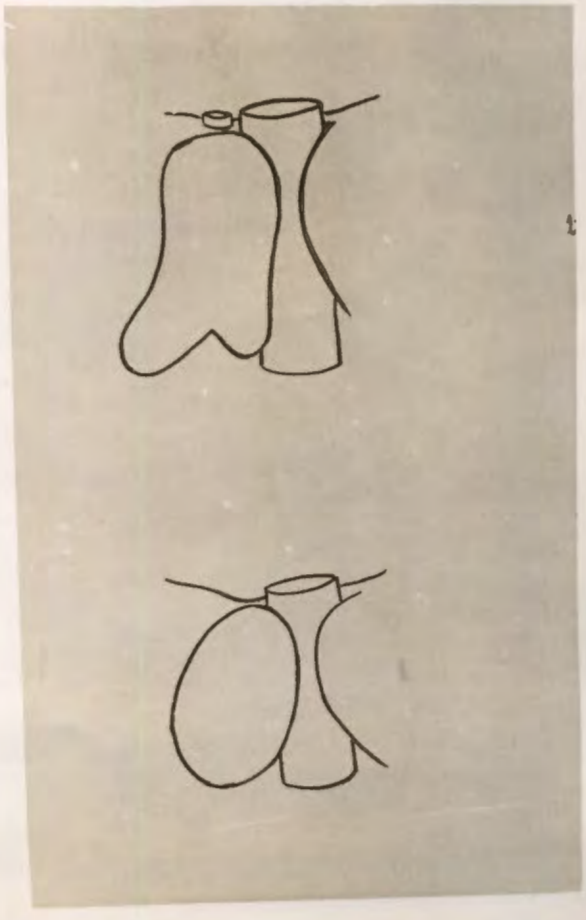
Protocol 7

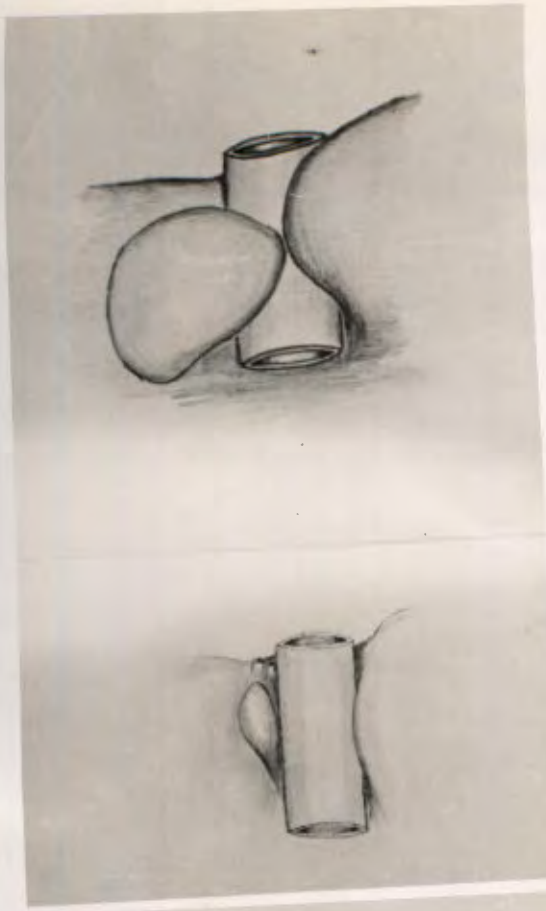
Drawings of the posterior aspect of the liver to illustrate its relationship to the inferior vena cava

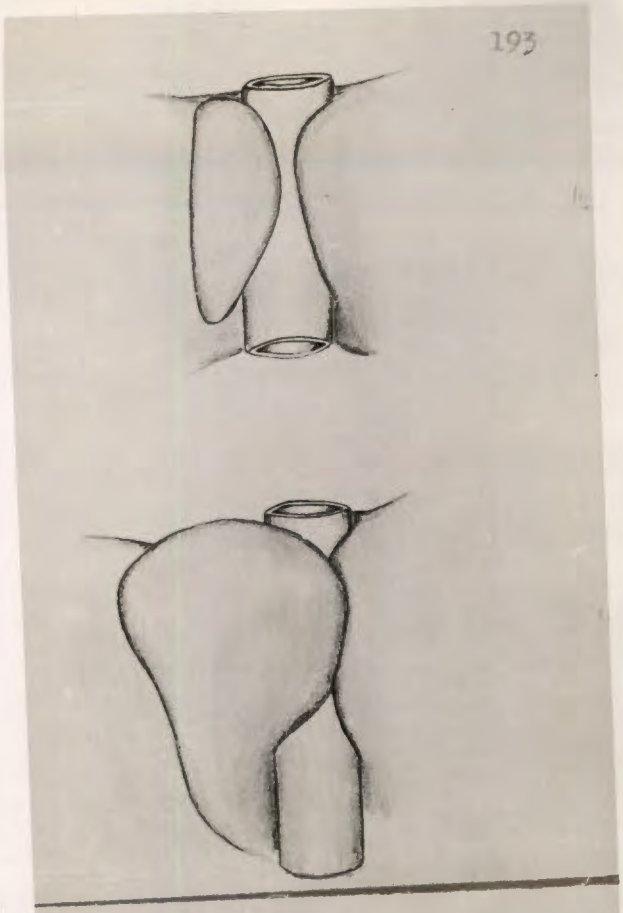


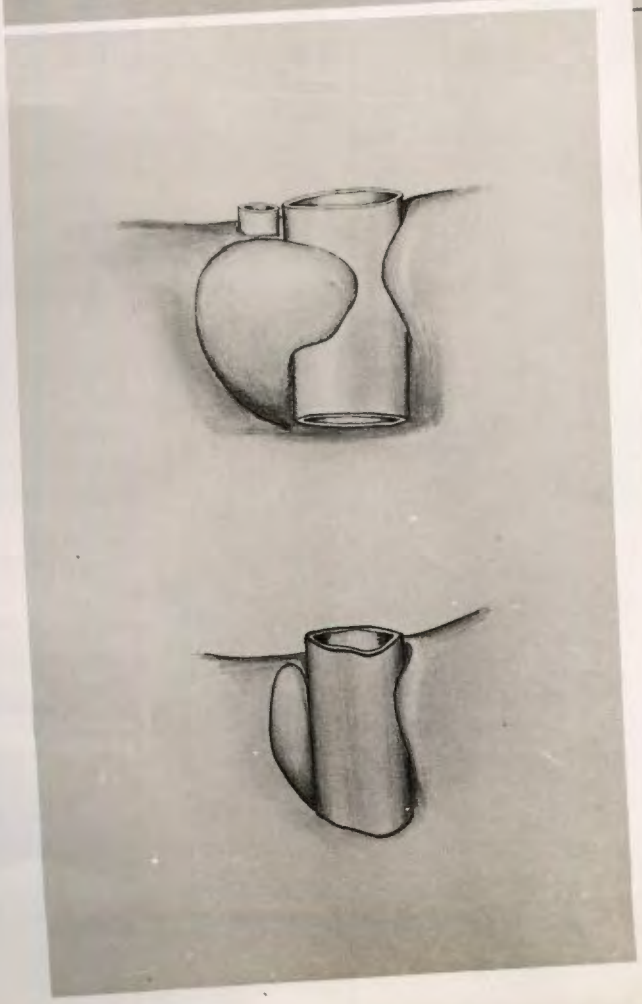


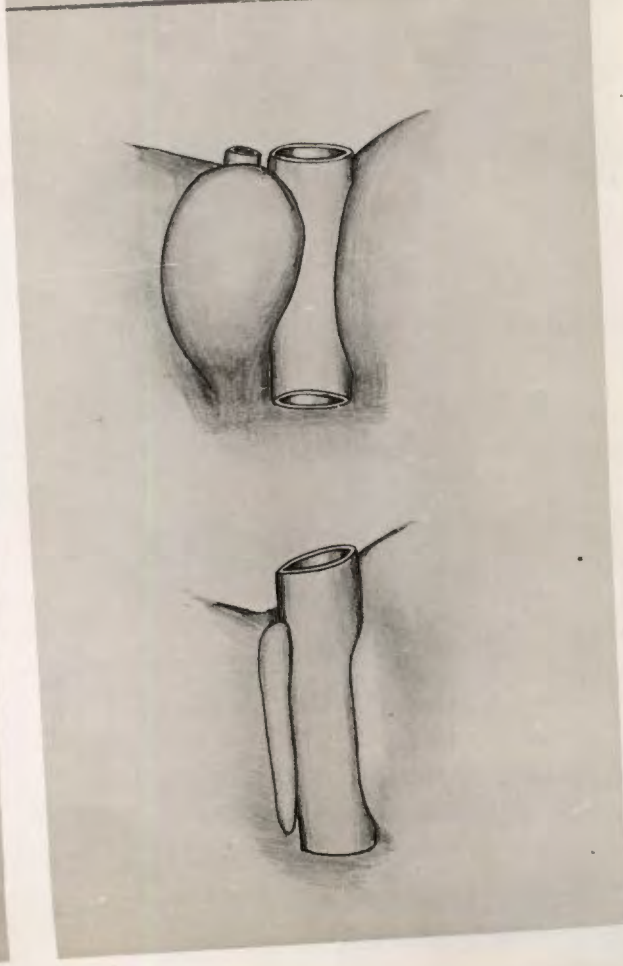


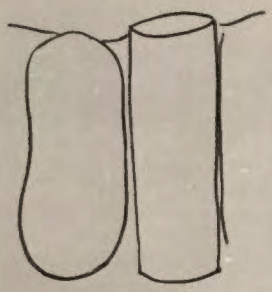


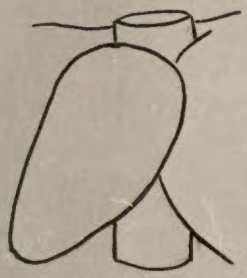


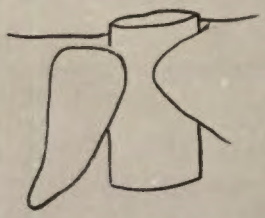


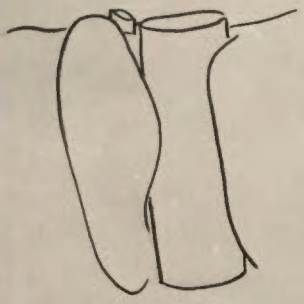


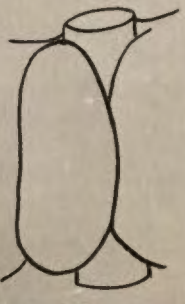


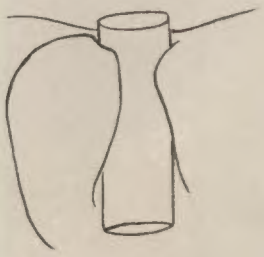


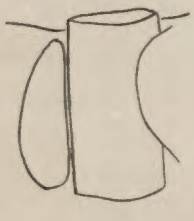












Suggestions for Further Study

Certain lines of investigation have suggested themselves during the course of this study. Certain of them bear directly on the problems of postural proteinuria itself and have been mentioned in the discussion. Others, however, have a less direct connection and some are considered below:-

1. The differential nucleated cell count

It is proposed to continue to apply the technique of differential counting of the nucleated cells in the urine to a wider range of diseases. Preliminary work to date suggests that changes in the total numbers and proportions of the nucleated cells in the urine are less liable to be affected by such factors as the urine concentration and pH than the accompanying changes in the erythrocytes and casts. Therefore, it may be that a study of the nucleated cells in the urine may provide a better index of activity and type of renal disease than the erythrocytes or casts.

A particular application of the method is to the investigation of those cases of glomerulo-nephritis which are difficult to distinguish from other diseases.

To date 32 cases of glomerulo-nephritis of various types have been examined and all have shown evidence of inflammatory change in the kidney in that the urine has contained an abnormal number of polymorphs. Case No.146 with the clinical picture of nephrosis had a urine with a greatly increased cell count but no polymorphs were seen. In contrast to this, three cases of glomerulo-nephritis of predominantly hydraemic type had polymorphs in the urine. The counts of one of these (No.144) are shown in Table 5. Does this finding represent a true difference between nephritis and nephrosis ?

There is often difficulty in deciding whether a subject with cardiac failure and urinary changes is suffering from nephritis. It is proposed to investigate a group of such cases for evidence of inflammatory change in the urinary sediment. Preliminary investigation suggests that they do not show this change.

From what has been said above, it will be seen that many more cases of nephritis, particularly of the more chronic varieties will have to be examined to establish whether inflammatory change is <u>always</u> present.

2. The renal lesion in cardiac failure

Disturbance of renal function is known to occur in cardiac failure (107-110). The picture, as shown by modern methods (108,109,25) is consistent with its being produced by an increase in venous pressure and "it is quite possible that altered circulatory dynamics in the kidney could lead to retention of salt" (107). In fact, Futcher and Schroeder (108) suggest that the sodium and chloride retention that occurs might be due to increased tubular reabsorption of the substances. The similarity of the dynamics in the kidney to those in postural proteinuria are striking. However, Warren and Stead (107) found that the renal disturbance could occur at a stage of failure "before there is a rise in venous pressure". They do not state, however, how the venous pressure was measured and it is almost certain that only pressures in the neck veins or arms were taken. It is possible that a rise in venous pressure in the renal veins may occur before becoming manifest at the sites they examined. Local differences in venous pressure are known to occur. Duomarco, Rimini and Recrate found that the pressure in the inferior vena cava of normal dogs was higher than in the auricle. Fishberg (106)

found that in some subjects with extreme right sided cardiac failure, the pressure in the neck veins might be as much as 20 mm. Higher than in the antecubital veins. He attributed this to vasoconstriction in the peripheries. A similar difference in pressure between the neck veins and auricle or inferior vena cava might well be present. Mechanical distortion of the inferior vena cava by the rotation or displacement of the large heart or by the engorged liver, might determine a higher pressure in the inferior vena cava than in the auricle.

It is proposed to investigate a number of cases of cardiac failure along similar lines to that used in the localisation of the cause of the increased venous pressure in postural proteinuria. Subjects will have the pressures in the inferior vena cava and auricle measured simultaneously by the catheter technique, both in failure and in remission. The effect of posture and position of the heart and liver on the foot-to-tongue circulation time will be determined. Rotation and displacement of the heart accompanies postural change and its position can be checked by screen examination and correlated with the circulation times. In this way it should be possible to prove any possible obstruction to venous return in the inferior vena cava which might cause the renal change.

3. Tubular reabsorption of protein

There are many aspects of the problem of protein reabsorption that require elucidation. The suggestions made to account for the variable albumin/globulin ratio in the urine of postural proteinurics requires proof. The factors controlling this ratio should be capable of discovery by a combination of full clearance techniques with the examination of the urinary proteins by more exact methods than have been used or are available here. The effects of urine pH and Cation content should be studied especially as they have been suggested to affect proteinuria.

Postural proteinuric subjects are ideal for the study of many of these problems of protein reabsorption because the proteinuria can be induced and stopped at will.

If the factors controlling protein reabsorption can be discovered, means might be found for increasing this reabsorption in subjects with nephrotic diseases, so saving valuable protein.

4. Hepato-renal syndrome and continuous proteinuria

In Experiment 17, Cases 152 and 201, both with hepatic disease, spontaneously passed protein in the urine and this proteinuria could be abolished by upward rotation of the liver. This findings suggests that it might be possible to separate off an easily recognised variety from the rather vague complex of the hepato-renal syndrome.

There is also the possibility that a similar venous obstructive mechanism might be responsible for some cases of continuous proteinuria.

Bibliography

Bibliography

1. Fishberg A.M. Hypertension and Nephritis. 4th Ed. Lea and Febiger 1939.

2. Post W. and Thomas W.A. J. Amer. med. Ass. 80,295,1923.

3. Wolman I.J. Amer. J. med. Sci. 210,86,1945.

4. Fox R.H. Lancet 1921,i,116.

5. Hooker D.R. Arch. intern. Med. 5,491,1910.

6. Calvin J.K., Isaacs B.L. and Meyer J. J. Amer. med. Ass. 86,1821,1926.

7. Mason E.H. and Erickson R.J. Amer. J. med. Sci. 156,643,1918.

8. Kagan B.M. J. clin. Invest. 17,369,1938.

9. Fine J. Bio-chem. J. 29,799,1935.

10. Daley R.M. Urol. cutan. Rev. 46,13,1942.

11. Conway E.J. Bio-chem. J. 27,430,1933.

12. Alpert L.K. Johns Hopk. Hosp. Bull. 68,522,1941.

13. Steinitz K. and Turkand H. J. clin. Invest. 19,285,1940.

14. Reeve E.B. J. Path. Bact. 56,95,1944.

15. Foa P., Woods W.W., Peet M.M. and Foa N.L. Arch. intern. Med. 69,822,1942.

16. Miller B.F. and Winkler W.W. J. clin. Invest. 17,31,1938.

17. Smith W.W., Finkelstein N. and Smith H.W. J. biol. Chem. 135,231,1940.

18. Fisher R.A. Statistical Methods for Research Workers. 8th Ed. Oliver and Boyd. 1941.

19. Hines E.A. and Brown G.E. Amer. Heart J. 11,1,1936.

20. Addis T. J. clin. Invest. 2,409,1926.

21. Naeraa A. Acta med. scand. 95, Fasc. 2, 341 & 351,1938.

22. Mac Kay E.M. Proc. Soc. exp. Biol. 34,119,1936.

23. Goldring W. Amer. J. med. Sci. 182,105,1931.

24. Stewart H.J. and Moore N.S. J. clin. Invest. 9,409,1931.

25. Berkson J. Medical Physics. 1st Ed. p.110.
Edited by Otto Glasser. The Year Book Publishers. 1944.

26. Barach J.H. Arch. intern. Med. 5,382,1910.

27. Barach J.H. Amer. J. med. Sci. 159,398,1920.

28. Collier W. Proc. Roy. Soc. Med. 1911, Sect. Med. 127.

29. Hellebrandt F.A. Amer. J. Physiol. 101,557,1932.

30. Hellebrandt F.A., Brogdon E. and Kelso L.E.A.
Amer. J. Physiol. 101,565,1932.

31. Porges O and Fribram E. Deutsch. Arch. f. Klin. Med.
90,367,1907. (Quoted from Starr I. J. exp. Med.
45,31,1926.

32. Stirling A.W. Lancet 1887,ii,1157.

33. Dukes C. Brit. med. J. 1905,ii,848.

34. Erlanger J. and Hooker D.R. Johns Hopk. Hosp. Rep.
12,145,1904.

35. Hooker D.R., Hegeman R.F. and Zartman L.V.
Amer. J. Physiol. 23, Sect. Proceedings p XI, 1908.

36. Hooker D.R. Amer. J. Physiol. 27,24,1910.

37. Young H.H., Haines J.S. and Prince C.L. Milit. Surg.
92,353,1943.

38. Prince C.L. J. Urol. 50,608,1943.

39. Lee R.I. Med. Clin. N. Amer. 3,1059,1920.

40. Bass M.H. and Wessler H. Arch. intern. Med. 11,403,1913.

41.

41. Diehl H.S. and Mc Kinlay C.A. The kidney in health and disease; edited by Berglund et al. p 454. Lea and Febiger. 1955.

42. Posnor Virchows Arch. 79,511,1880. (Quoted from 2.)

43. Winton F.R. J. Physiol. 72,49,1931.

44. Ludwig C. Lehrbuch d. Physiol. 2nd Ed. 2,573,1861 (Quoted from 43).

45. Theobald G.W. Lancet 1951,ii,948.

46. Theobald G.W. Lancet 1930,i,904.

47. Warren J.V. and Stead E.A. Arch. intern. Med. 73,138,1944.

48. Loeb A. Deutsch. Arch. f. Klin. Med. 83,452,1905.

49. Rytand D. Arch. intern. Med. 59,848 & 837,1937.

50. Medes G. and Neemes M.R. The kidney in health and disease; edited by Berglund et al. Lea and Febiger. 1955.

51. Kelling Zbl. inn. Med. 40,313,1919. (Quoted from 1).

52. Jehle L. Wien. med. Wschr. 82,1245,1932.

53. Rieser W and Rieser S.L. J. Amer. med. Ass. 78,644,1922.

54. Sonne C. Z. klin. Med. 90,1,1921.

55. Beer E. J. Mt. Sinai Hosp. 3,193,1937.

56. Theobald G.W. Lancet 1930,i,1115.

57. Jehle L. Ergebn. inn. Med. Kinderheilk 1913,bd. 12. (Quoted from 54).

58. Murphy W. Nav. med. Bull., Wash. 43,321,1944.

59. Hamill S.M. and Blackfan K.D. Amer. J. Dis. Child. 1,139,1911.

60. Mc Lean H. Med. Research Comm. Special Reports 1919-1920, No. 45.

61. Diehl H.S. and Mc Kinlay C.A. Arch. intern. Med. 49,45,1932.

62. Ashburn P.M. J. Amer. med. Ass. 90,535,1928.

63. Jeanarret Arch. Med. Enf. 18,461,1915. (Quoted from 2).

64. Nassau E. Z. Klin. Med. 84,1917. (Quoted from 81).

65. Saundby Proc. Roy. Soc. Med. 1911 Med. Sect. 120.

66. Lauener P. Schweiz. med. Wschr. 52,1170,1922. (Quoted from 6).

67. Ekehorn G. On the principles of renal function. Norstedt. 1951.

68. Dock W. N. Engl. J. Med. 227,655,1942.

69. Cohn E.J., Oncley J.L., Strong L.E., Hughes W.L. and Armstrong S.H. J. clin. Invest. 23,417,1944.

70. Sinha R. J. Physic. Chem. 44,25,1940.

71. Wallis M.R.L. Proc. Roy. Soc. Med. 1919-1920. Med. Sect. 96.

72. Gerard P. J. Anat., Lond. 70,554,1935-1936.

73. Yuile C.L. and Clark W.F. J. exp. Med. 74,167,1941.

74. Yuile C.L., Steinman J.F., Hahn P.F. and Clark W.F. J. exp. Med. 74,197,1941.

75. Cushny A.R. The secretion of urine. p. 190. Longmans Green and Co. 1917.

76. Chasis H., Joliffe N. and Smith H.W. J. clin. Invest. 12,1063,1935.

77. Goldring W. J. clin. Invest. 13,749,1934.

78. Cruikshank E.W.H. and Takeuchi H. J. Physiol. 60,120,1925.

79. Bashford H.H. Practitioner 135,272,1935.

80. Palmer R.S. J. Amer. med. Ass. 96,1559,1931.

81. Russell J.A. Quart. J. Med. 16,75,1923.

82. Russell J.A. Lancet 209,683,1925.

83. Thorp E.G. and Wakefield E.G. Ann. intern. Med. 8,1565,1935.

84. Armstrong H.G. Proc. Roy. Soc. Med. 1911. Med. Sect. 123.

85. Bass M.H. Med. Clin. N. Amer. March 1921,1595.

86. Moor F. Brit. med. J. 1921,i,671.

87. Nicholson F.D. Practitioner 93,113,1914.

88. Saito H. Amer. J. Dis. Child. 22,388,1921.

89. Schlutz F.W. and Swanson W.W. J. Amer. med. Ass. 87,1193,1926.

90. Linder G.C., Lunsgaard C. and van Slyke D.D. J. exp. Med. 39,887,1924.

91. Monke J.V. and Yuile C.L. J. exp. Med. 72,149,1940.

92. Mann D. Physiology and pathology of the urine. Charles Griffin and Co. 1913.

93. Wolman I.J. Amer. J. med. Sci. 208,767,1944.

94. Huggins C. Physiol. Revs. 25,281,1945.

95. Schmaus H. Virchows Arch. Sup. 138,1,1895.

96. Lyttle J.D. J. clin. Invest. 12,87,1933.

97. Becquerel Semiotoque des urines. Paris 1841,p.394. (Quoted from 1).

98. Stone W.J. Bright's disease and arterial hypertension. Saunders. 1936.

99. Jehle L. Die Albuminurie, klinische und experimentelle Beitrage zur Frage der orthostatisch-lordotischen und der nephritischen Albuminurie. Julius Springer. 1914.

100. Wright A.E. and Ross G.W. Lancet 1905,ii,1164.

101. Harrison G.A. Lancet 1921,ii,991.

102. Fox R.H. Lancet 1908,ii,497.

103. Kossa Z. f. Biol. 40,324,1900. (Quoted from 75).

104. Earle D.P., Tagard J.V. and Shannon J.A. J. clin. Invest. 23,119,1944.

105. Smith H.W. J. clin. Invest. 20,651,1941.

106. Fishberg A.M. J. clin. Invest. 17,519,1938.

107. Warren J.V. and Stead E.A. Arch. intern. Med. 73,138,1944.

108. Futcher P.H. and Schroeder H.A. Amer. J. med. Sci. 204,52,1942.

109. Seymour W.B., Pritchard W.H., Longley L.P. and Hayman J.M. J. clin. Invest. 21,229,1942.

110. Page H. and Corcoran A.C. Hypertension. The Year Book Publishers. 1945.

111. Ducmarco J., Rimini R. and Recarte P. Rev. Argent. de Cardiol. 11,275,1945. (Quoted from abstract in Amer. Heart J. 30,421,1945.

(Abbreviations of titles of journals according to "World list of Scientific Periodicals. 2nd. Ed. Oxford University Press. 1934.)

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