alters the course of the illness by prolonging the period of disability. Early diagnosis and treatment will decrease the prolonged debility which often results in unrecognized and untreated cases.

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MORE GLOMERULAR CHANGES IN DIABETICS*

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DURING A REVIEW of 290 necropsies on diabetics, a renal glomerular lesion was encountered which differed fundamentally from that described by Kimmelstiel and Wilson.[1] In a search of the literature, only one previous description of such a lesion[2] was found. Elsewhere, even if it appeared in photographs of diabetic glomeruli, *e.g.*, Fahr[3] (Fig. 3), Allen[4] (plate 239C), McManus[5] (Figs. 88, 89), it has not been differentiated from an associated intercapillary sclerosis. The changes we are referring to affect the glomerular tuft, the capsule, and possibly the basement membrane of the tubules.

CHARACTERISTICS OF THE LESION

Glomerular changes: the fibrin cap.—In sections stained with hæmatoxylin and eosin (Figs. 1 and 2), the convex outer borders of the capillary loops are capped by a crescentic, glossy, bright pink homogeneous deposit. If intercapillary sclerosis is also present, the latter lesion contrasts clearly because of its lighter, more matt pink colour and its position on the other side of the capillary loop.

To study the early stages of this change and the exact relationship of the deposit to the components of the glomerular tuft, one must use Mallory's phosphotungstic acid hæmatoxylin stain, for when it first appears, the material stains evenly dark blue like fibrin and this colour contrasts well with the yellow glassy membrane of the reflected layer of the capsule. The material first appears in the convexity of the capillary loop between the endothelial cell and the glassy membrane, Fig. 3, and then acquires a pointed crescentic shape by spreading down between the same two layers into the sulcus between the loops. At first there is no visible change in the glassy membrane and the material looks just like an exudate of fibrin separating the basement membrane from the endothelial cell. The evolution of the lesion shows few changes other than increase in size and slight modification in staining reaction. Some of the material may lose the staining qualities of fibrin as seen with the P.T.A.H. stain. Frequently the cap develops small vacuoles and becomes irregularly sudanophilic but it never becomes invaded by cells or becomes organized into fibrous tissue. Even when the whole glomerulus has become sclerotic, the crescentic cap is still obvious inside the pale shrunken tuft owing to its more intense pink colour. In the Masson stain the cap is red and is at first sharply defined from the rest of the structures of the glomerulus but if the glomerulus becomes fibrosed the line of demarcation of the cap from the surrounding tissue becomes blurred. With the periodic acid stain the material is dark pink and with Laidlaw's silver stain it is not argentophilic. These staining reactions are exactly those of the bright pink material found in diabetic arteriolosclerosis and the fibrin cap was never present without associated severe arteriolar disease.

Capsular changes: the capsular drop.—Somewhat similar lesions develop in relation to the basement membrane of the capsule. At first they are localized drop-like swellings which stain slightly paler with H. and E. than do the glomerular hyaline caps (Fig. 4). They stain red with Masson connective tissue stain, dark blue in part at any rate with P.T.A.H. (Fig. 5), and, like the glomerular lesion, are variably sudanophilic. With the P.A.S. stain it is difficult to be sure of the exact staining reaction of the lesion under

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discussion because the kidneys in which they appear usually show complex capsular lesions of various ages and possibly of differing causes. Most commonly, the basement membrane is sharply defined and the material which stains a very pale pink lies between it and the capsular epithelium. Sometimes the swelling appears to be part of the basement membrane and stains as darkly as the latter does and sometimes the material is enclosed by frayed fibres of the basement membrane.

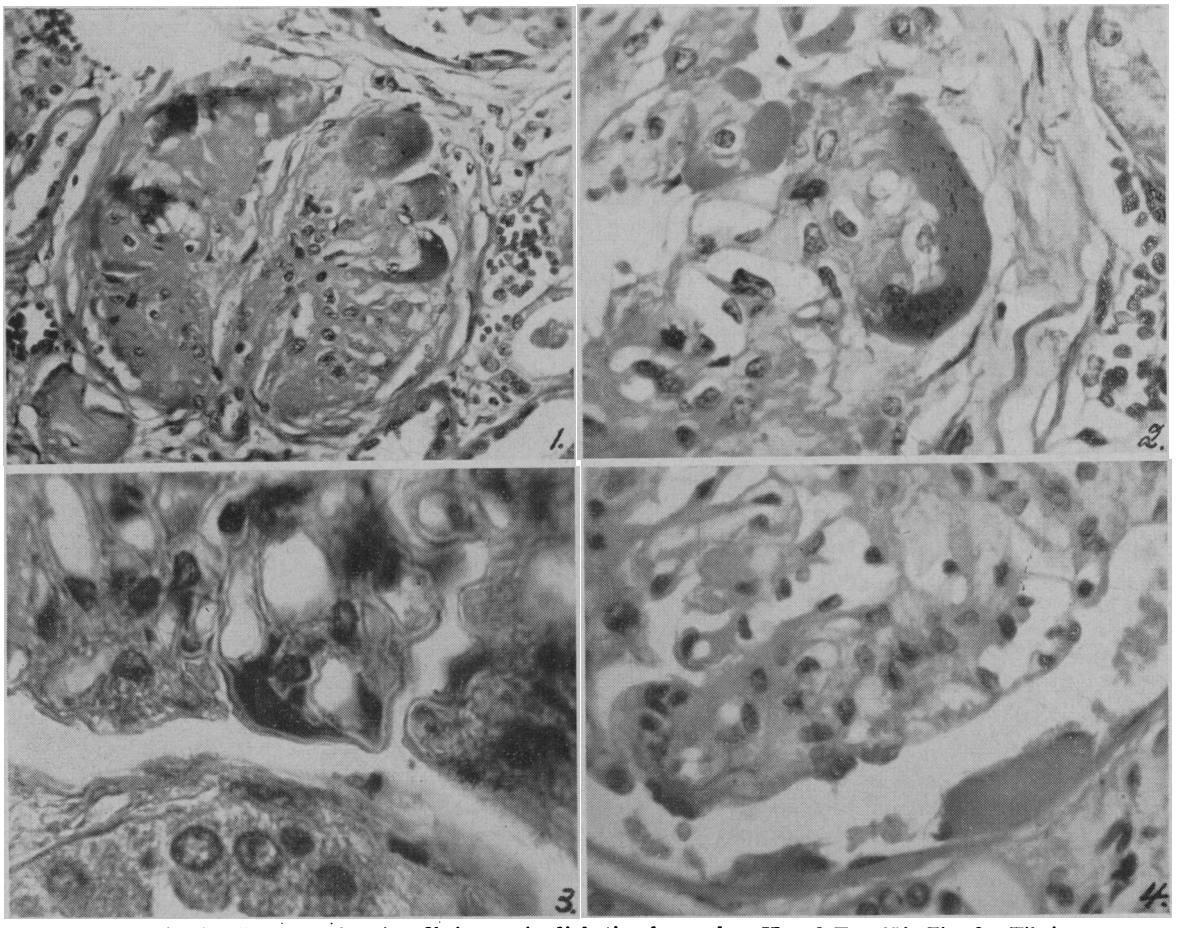

Fig. 1.—Crescents forming fibrin cap in diabetic glomerulus. H and E x 256. Fig. 2.—Fibrin cap showing its position outside endothelial cells of glomerular tuft. H and E x 538. Fig. 3.—Early formation of fibrin cap between basement membrane and endothelial cell of glomerular tuft. Phosphotungstic acid hæmatoxylin x 900. Fig. 4.—Capsular drop in diabetic glomerulus. H and E x 538.

Secondary changes occur rapidly and the frayed fibres seen may possibly be proliferative. The site of appearance of these swellings is nearly always on that part of the capsule opposed to the place of entry of the glomerular arteriole and sometimes can be seen to be closely related to the origin of the efferent tubules. Indeed pink material may extend down between the epithelium of the tubule and the basement membrane for a short distance. The evolution of the lesion differs from that in the glomeruli. As the material increases it becomes crescentic and cells appear in it which, in part, may be derived from the capsular epithelium but which, more usually, are derived from fibroblasts which as Ohmori[6] described, can be seen streaming in through breaks in the basement membrane (Fig. 6). This cell invasion is followed by a transformation of the pink material into fibrous tissue which stains green with the Masson stain. Adhesions often form between it and the glomerular tuft. This difference in behaviour of the material in

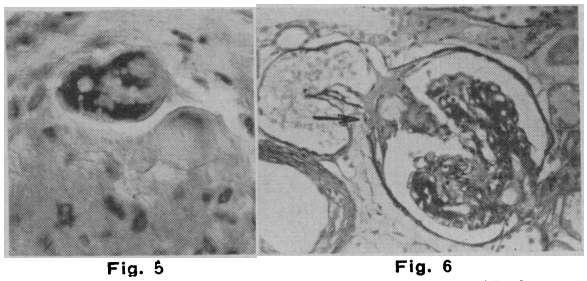

Fig. 5 Fig. 6

Fig. 5.—Capsular drop phosphotungstic acid hæmatoxylin x 538. Fig. 6.—Break in basement membrane of capsule near origin of tubule (arrow). H and E 192.

the two sites may lie in their different relationship to the basement membrane. In the glomerulus the exudate, if exudate it is, is separated from the connective tissue of the mesangium by the capillary. In the capsule, it is separated from the connective tissue surrounding the glomerulus only by the basement membrane which seems to be crossed easily by connective tissue.

Tubular changes.—We have already mentioned that the capsular exudate may extend down between the epithelium and the basement membrane of the first convoluted tubule. Minor degrees of exudate are seen in other places in the convoluted tubules and seem to be replaced by fibrous tissue at a later stage. This is associated with considerable thickening of the basement membrane which however occurs in many forms of tubular atrophy.

TABLE I.

INTERRELATIONSHIP OF GLOMERULAR LESIONS

	Capsular drops	*Fibrin caps*	*Intercapillary sclerosis*
Capsular drops....	3	2	10
Fibrin caps.....	2	4	5
Intercapillary sclerosis.....	10	5	16
All 3 lesions together.....	5	5	5
Totals...	20	16	36

(This table is arranged to show the incidence of each lesion alone (underlined numbers) and in combination with the others).

Incidence of lesions.—Table I shows the incidence of the glomerular and capsular lesions compared with the incidence of the classical Kimmelstiel-Wilson lesion in the same series of 290 diabetic kidneys. As can be seen, fibrin caps and capsular drops such as we have described can be found together or separately and either combined or not with the Kimmelstiel-Wilson lesion. Fibrin caps occur half as commonly as intercapillary sclerosis. The average age of patients showing fibrin caps was 62.4 years and the average age of those showing intercapillary glomerular sclerosis was 63.5 years. The blood pressure was markedly elevated in all cases except two and these two patients were desperately ill with heart failure and septicæmia respectively when the only blood pressure recordings were made.

Specificity.—The changes we have described are not individually specific for diabetes and it would be surprising if they were. Thus the fibrin cap was found in 11 out of 15 cases of glomerulonephritis and the four cases in which they were absent were early ones. Capsular drops were, however, absent in this series and so were fibrin-staining hyaline changes in the extra-glomerular part of the arterioles. None of the changes were seen in a careful study of 15 cases each of benign hypertension, malignant hypertension, atherosclerotic nephrosclerosis and pyelonephritis. The fibrin caps found in diabetes were larger than those in glomerulonephritis and the combination of fibrin caps, capsular drops and hyaline changes in the extra-glomerular part of the arterioles is probably at least as specific for diabetes as is the Kimmelstiel-Wilson lesion.

DISCUSSION

The first problem is the nature of the material in the glomerular tufts. Zollinger[2] suggested it to be fibrinoid degeneration of the basement membrane. In the early lesions, however, the basement membrane is intact and the material appears between it and the endothelium. The earliest deposition of amyloid occurs at the same site (Ohmori[6]) and only later the glassy membrane is obscured by the growing lesion. This suggests that the material, like amyloid, may be a deposit rather than a degeneration of existing tissue and since it behaves tinctorially like fibrin, probably is a fibrinous exudate.

The next problem is the mechanism of its deposition. In diabetic nephrosclerosis, especially in the Kimmelstiel-Wilson syndrome, albuminuria occurs, sometimes in large amounts, indicating an abnormal permeability of the glomeruli to protein. If the capillary and the basement membrane should develop a different permeability to a large molecule like fibrinogen or if abnormal molecules should be present in the plasma a pool might accumulate between the two layers. The presence of sudanophilic substance in the lesions could likewise be explained by the high lipoid content of diabetic blood. It is of interest that the material accumulates at the convexity of the loop, where the static pressures are maximal. This suggests that mechanical factors may play a part, probably the same which cause urine to filter only into the capsular space and not into the mesangium. Since the deposit only occurs at the convexity it does not come into direct contact with the fibroblasts of the mesangium and thus it fails to become organ-

ized. By the time the lesion has become extensive and fuses with the remainder of the glomerulus, the tuft usually has become hyalinized and no fibroblasts remain to organize the fibrin.

The third problem is the relation between the fibrin cap and intercapillary sclerosis. Histologically they are quite distinct as regards position and staining reaction, for the latter lesion always stains green with Masson's stain. It is difficult however to deny the possibility that the two conditions might have a similar pathogenesis, for any exudate occurring into the mesangium would become organized very rapidly. In favour of some close association is the remarkable correlation in age and sex incidence. Against it is the fact that intercapillary sclerosis seems to develop from radial fibrosis of the mesangium while the fibrin cap, as Zollinger pointed out, is closely associated with arteriolar lesions and resembles them in staining properties.

The changes in the capsule are less easy to discuss. As can be seen from Table I, capsular drops were more often associated with intercapillary sclerosis than with fibrin caps and they are described in Kimmelstiel and Wilsons' original paper. It is tempting to explain their development as being due to degenerative changes in the basement membrane, for to suggest that the accumulation of pink material is due to a hold-up in the passage of certain components of fluid is to assume that there is normally traffic of fluid across the capsule. However, the latter supposition is not intrinsically unlikely, for as Kaiserling[7] has shown, the glomerular capsule is partly enclosed by a crescentic lymphatic channel. If such a traffic of fluid exists, our explanation of the genesis of the fibrin cap would also fit that of the capsular drop. The presence, in the drop, of fat and protein other than fibrin, would merely reflect the composition of the fluid crossing the capsular space and the hold up of these components would be due to a decrease in permeability of the basement membrane. In the present state of our knowledge we do not regard the question as being anything else but an open one, but feel that it would not necessarily be clarified by falling back on the fashionable term of fibrinoid degeneration, and denying the possibility of an exudate. However, even if the material proves to be an exudate, it is either composed of abnormal molecules or there are changes in the basement membrane, for the common albuminous and fibrinous exudates which occur in Bowman's capsule as the result of inflammation do not produce fibrin caps or capsular drops. We think that the exact analysis of this lesion may throw some light on the metabolic disturbances in diabetes.

SUMMARY

1. In 16 out of 290 necropsies on diabetics a crescent of material staining like fibrin was found between the basement membrane and the endothelium of the renal glomerular tufts. We call this *"the fibrin cap"*.

2. The fibrin cap occurs half as commonly as intercapillary sclerosis but has exactly the same age incidence and relation to high blood pressure.

3. It occurs with or independently of intercapillary sclerosis but is always associated with severe arteriolosclerosis.

4. Similar material is found between the epithelium and basement membrane of the capsule forming a *"capsular drop"*. This lesion differs from the *fibrin cap* in that it rapidly becomes organized into fibrous tissue.

5. The combination of fibrin caps, capsular drops and fibrin-staining hyaline changes in the extra-glomerular part of the arterioles is probably specific for diabetes.

6. The pathogenesis of these lesions is discussed.

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The gene theory has become one of the great unifying principles of modern biology. Far from being merely pawns with which the geneticist plays games to amuse himself, genes are the units that were aggregated, mutated, and recombined to give rise to the countless forms of subcellular, unicellular, and multicellular forms of life that exist now or have existed in the last 2 billion years. They are the sets of pattern molecules or templates with which each of us started development as a fertilized egg and they represent the essential self-duplicating units that we pass on to our children through the nuclei of our eggs and sperm.—Geo. W. Beadle.