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EXPERIMENTAL CLOUDY SWELLING OF THE KIDNEY IN RABBITS

A thesis submitted to the Faculty of the Graduate School

of the University of Minnesota

By W. Ray Shannon

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of Master of Science

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The University of Minnesota
The Medical School
Minneapolis

DEPARTMENT OF PATHOLOGY,
BACTERIOLOGY, AND PUBLIC HEALTH

May 26, 1915.

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Dear Sir:

I am enclosing the report of the committee on the thesis of Mr. W. R. Shannon.

Sincerely yours,

E. T. Bell

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REPORT

of

COMMITTEE ON THESIS

THE undersigned, acting as a committee of the Graduate School, have read the accompanying thesis submitted by William Raymond Shannon for the degree of Master of Science. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science.

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Cloudy swelling, as generally described, is a condition found at times in the parenchymatous organs, in which the organ is swollen and turbid. This turbidity is often described as a "cooked appearance." Microscopically, in the fresh specimen, the cells are seen to be opaque, due to the accumulation of albuminous granules within their cytoplasm.

Cloudy swelling is regarded by many as the most common of pathologic conditions. It is often recorded at routine autopsies. Frequently, however, when the gross diagnosis is checked by microscopic examination, it will be found that there is no increase of albuminous granules within the cells. Turbidity and swelling of an organ are not always associated with increase of albuminous granules within its cells. On the other hand, it has been found that there may be a marked increase in albuminous granules within the cells of an organ without the presence of turbidity and swelling. It is, therefore, evident that cloudy swelling as commonly described includes more than one type of pathologic process. No important advance can be made until the several phenomena have been studied separately. With this in mind I have un-

dertaken the study of experimental cloudy swelling of the kidney, paying particular attention to the study of the albuminous granules.

Virchow[1] introduced the term "cloudy swelling" in 1858 to describe a condition often found in the parenchymatous organs, such as the liver and kidney, in which the organ is swollen and light colored. It frequently presents a cooked appearance. When examined under the microscope in the fresh state, the cells are seen to be opaque, due to the presence of small albuminous granules. These granules may almost entirely hide the nucleus. The gross picture is due to the presence of these albuminous granules within the cells.

This classical description has been adopted with minor modifications by the majority of observers since Virchow's time. It has been copied into practically all of the modern text books of pathology.

Cohnheim[2] adds to Virchow's description that the condition is more easily recognized grossly than microscopically in organs such as the liver and kidney, in which the cells normally contain some granules. He states that

cloudy swelling occurs also in muscle (heart muscle, especially) and in the mammary glands.

Klebs[3] and Ribbert[4] agree with Cohnheim that cloudy swelling is more readily recognized grossly than microscopically.

Rindfleisch[5], Birsh-Hirschfeld[6], Thoma[7], Ziegler [8], Albrecht[9], Landsteiner[10], Adami[11], and Von Gierke [12] all adhere closely to Virchow's description.

Benario[13] states that fatty granules were always to be found together with the albuminous granules in cloudy swelling.

Volhard and Fahr[14], working on the human kidney, find that the gross picture can not be relied upon. Swelling is sometimes present and sometimes not, and the degree of cloudiness is very variable. The microscopic picture is more dependable. The epithelium of the convoluted tubules is swollen. The lumina of these tubules are decreased in size if not entirely obliterated by the swollen cells. Albuminous material is to be found in precipitated stringy masses in the lumina of some of the tubules and Bowman's capsules. The Altman granules are enlarged and very irreg-

ular in arrangement. The rods are present in places.

Bell[15] noted that organs will sometimes show this gross appearance of cloudy swelling when there is no increase of albuminous granules; and, conversely, that sometimes, especially in the kidney, there may be a marked increase of albuminous granules in the absence of any gross indication. He recommends that the term "cloudy swelling" be used for gross description only, and that a modifying phrase be added to indicate the microscopic picture accompanying it.

A number of observers have studied experimental cloudy swelling in animals. Favre[16] in 1892 produced the condition in rabbit kidneys by removing the opposite kidney or by tying off its vein or ureter. He described an intense clouding of some of the convoluted tubules of the functionating kidney, due to the accumulation of albuminous granules within the cells.

Schilling[17] produced cloudy swelling in rabbit kidneys by tying the opposite renal vein for 48 hours. At the end of this time the unoperated kidney showed a swollen grayish-yellow cortex which was easily distinguishable from

the blood-red medulla. Crushed preparations showed, microscopically, opaque tubules which were filled with albuminous granules. These granules hid the nucleus almost completely. He found no fat present.

Albrecht[9] also used rabbits for the study of experimental cloudy swelling of the kidney. He produced the condition by the following procedure. The renal artery was clamped off for two hours, after which time the clamp was removed. Within two or three hours more the clamp was again replaced and left for 24 hours. He obtained some fatty granules in the tubules at the same time.

Bell[15] found that there was considerable discrepancy between the gross and microscopic appearances of experimental as well as human cloudy swelling.

The term "cloudy swelling" will be used in this paper to designate a turbid swollen organ without regard to the microscopic picture that may be present.

MATERIAL AND METHODS

Since the number and character of the granules in the renal tubules of different animals vary considerably, it was decided to use but one species. Rabbits were used ex-

clusively. All kidney operations were made thru lumbar incisions. The left kidney was operated on most frequently because it is more accessible than the right.

Compensatory changes in the kidney were studied by removing the opposite kidney or by ligature of its ureter. One form of cloudy swelling was produced by subcutaneous injections of tartaric acid. Cloudy swelling was also produced by placing sterile macerated liver into the peritoneal cavity. It was found that large subcutaneous abscesses will produce a marked increase in albuminous granules in the kidney in the course of a week or two. Rabbits were therefore given pasteurella and proteus infections to produce abscesses. They were killed at various stages of the infectious process. These several procedures will be explained in more detail under the separate headings.

Thin pieces of fresh kidney were fixed in Zenker-formol and 10% formalin. Both these reagents preserve the granules well, but Zenker-formol gives a better cytoplasmic fixation than the formalin alone. Zenker or Bouin's solutions could not be used because the acetic acid in them destroys the granules rapidly.

Zenker-formol material was found most useful for histological study. Paraffin sections were cut at three micra and stained with iron-hematoxylin and other stains. Frozen sections were prepared from the formalin-fixed material and stained for fat. In every case crushed preparations of the fresh kidney were examined to control the fixed material and to study the effect of various reagents upon the albuminous granules.

THE NORMAL KIDNEY

The normal rabbit kidney is dark red in color. The external surface is smooth and the capsule strips readily. The cut surface is moist. The cortex is quite distinctly marked off from the medulla and is slightly paler in color. The medulla shows two zones, an outer area just under the cortex which is usually slightly darker than the inner area which includes the papilla. The line of demarcation between the two zones is usually quite sharp and regular, and extends parallel to the inner border of the cortex, thus making the outer zone of the medulla uniform in thickness.

Crushed preparations of the fresh cortex usually show a few dark tubules microscopically. Upon high magnification

these are seen to be filled with rather large weakly refractive granules or droplets. Upon the addition of 5% NaOH or KOH these granules can be seen to disappear suddenly, like the bursting of a bubble, as the reagent comes into contact with them. This leaves the tubules light and the nuclei more clearly visible. These granules are not entirely confined to the dark tubules, for a few scattered ones are noticeable in the light tubules as well. The rods of Heidenhain can also be made out in the fresh preparations in some cases. One occasionally finds a kidney which shows no distinctly dark tubules but high magnification will always reveal occasional granules within the tubules.

The granules cannot be demonstrated in tissues which have been fixed with Zenker's or Bouin's fixing fluids. Apparently the acetic acid in these reagents destroys them. 10% formalin or Zenker-formol preserves the granules very satisfactorily, however.

In tissues fixed with Zenker-formol or 10% formalin and stained with iron-hematoxylin, the granules are well shown (Fig. 1). They appear as darkly staining spherical bodies, mainly in the basal portion of the cells. They are

often arranged in rows between the rods. Sometimes, however, they are found in the inner clear portion of the cells. The tubules containing these granules tend to be grouped so that one sees, under low power, small groups of darkly staining tubules scattered thru the cortex (Fig. 2).

The rods of Heidenhain can be seen in the basal portion of the cells. They are apparently independent of the granules under consideration. The inner portion of the cells is clear and has a convex inner border projecting into the lumen. It is not uncommon to find vacuoles within the inner light area of the cells. The lumina of the tubules are generally narrow and stellate shaped, due to the rounded inner borders of the cells. In some of the tubules there may be no visible lumen, the inner border of the cells meeting and entirely obliterating it.

There is a relatively fewer number of convoluted tubules of a distinctly different type. These contain no granules but the cells are thickly set with definite rods which extend from the basal membrane to the inner border. The cells lining these tubules are lower than those lining the tubules of the former type. The lumina are generally

wide and distinctly outlined. These are probably the second convoluted tubules.

Albrecht[9] described the granules under consideration in the renal epithelium of rabbits and stated that he could find no previous mention of them in the literature. He thought that they were of some functional significance. Disse[18], however, in 1892 described granules in the cortical epithelium of the rabbit kidney which correspond closely to these. He did not examine them in the fresh tissue, nor did he attribute any functional importance to the granules.

Rothstein[19] described these granules in the kidneys of mammals in 1890. In the fresh crushed preparations they appeared as definite refractive granules with darkly limited periphery, sometimes isolated and sometimes in groups within the cells. In fixed and stained preparations they were seen to be sometimes spherical, sometimes oval, and even sometimes spindle-shaped. He evidently considered them of functional importance.

Modragowski[20] mentions these granules in normal rabbit kidneys and gives them some functional significance.

Hirsch[21] gives a detailed description of them in

preparations stained with iron-hematoxylin. Under low power the first thing noticed is the varying intensity with which the different tubules stain. Some are dark; others are light. This variation in staining capacity is seen, upon high power examination, to be due to the variation in number of darkly staining granules within the tubules. In the dark tubules there are numerous granules and in the light tubules the granules are few or absent. The number of granules depends upon the functional condition of the tubules. Many of the cells are crowded full of the granules, whereas others contain more granules in the basal part and fewer in the inner light portion of the cells. In some cells the granules are packed closely around the nucleus. The rods of Heidenhain show plainly in the basal parts of the cells. Some of them have knotty thickenings within them, but the granules do not come from the rods.

Bell[15] also described these granules in the renal epithelium of the normal rabbit. He studied them in fresh preparations only.

No one has proven definitely that these granules are functional in character but it seems almost certain that

they are related in some way to the activity of the cells. A t any rate, since they are present in the normal, we must consider them physiological at least and accept as the most reasonable explanation that they are in some way related to excretion.

COMPENSATORY CHANGES IN THE KIDNEY

Favre, Schilling, and Albrecht have all recorded the production of compensatory cloudy swelling in rabbit kidneys by the removal of the opposite kidney or by tying its vein or ureter. Favre did not describe the gross changes. He says that he obtained a clouding in some of the tubules, apparently not knowing that this is present in the normal. Schilling states that grossly the cortex was of a grayish-yellow color, easily distinguishable from the blood-red medulla. Microscopically, the tubules were opaque, due to the accumulation of albuminous granules within the cells. This author apparently overlooked the fact that some of the tubules are dark in the normal kidney. Albrecht does not give a description of his findings.

Hirsch described an increase in the albuminous granules one week after the removal of the opposite kidney, but

did not consider the gross changes worth mentioning.

Bell was unable to produce a definite gross cloudy swelling by removing the opposite kidney. From microscopic examination of fresh tissues he was not certain that there was an increase in the number of dark tubules over the normal.

EXPERIMENTS

Experiment 1. Rabbit; male; Sept. 23, 1914. Left kidney removed. 24 hours later the animal was killed and the right kidney examined.

Gross examination. The left kidney is normal in appearance. The right kidney is swollen and congested but no cloudiness can be seen.

Microscopic examination. No certain differences can be made out in the fresh specimens. The fixed and stained material shows a few more dark tubules in the right than in the left kidney.

Experiment 2. Rabbit; male; weight 1080 grams; Jan. 7, 1915. Left kidney removed. 48 hours later the animal was killed and the right kidney examined.

Gross examination. Left kidney normal. The right

kidney is somewhat swollen and the cut surface is moist, but there is no distinct cloudiness present.

Microscopic examination. The right kidney shows definitely more dark tubules than the left. There is also an increase in albuminous granules thruout the lighter tubules in the right kidney.

Experiment 3. Rabbit; male; weight 2910 grams; Jan. 13, 1915. Removed left kidney. 48 hours later the animal was killed.

Gross examination. Left kidney normal. The right kidney is swollen and its cut surface is slightly pale.

Microscopic examination. The right kidney contains at least two or three times as many dark tubules as the left. The granules in the right kidney are larger than those in the left.

Experiment 4. Rabbit; female; weight 2000 grams; Jan. 8, 1915. The right ureter was ligatured. One week later the animal was killed and the left kidney examined.

Gross examination. Possibly swollen. No cloudiness was detectable.

Microscopic examination. The fresh shows no certain increase in the number of dark tubules. Fixed and stained material shows no increase over the normal number of dark tubules.

These experiments have shown that a moderate increase in the number of granules occurs, temporarily at least, after the removal of the opposite kidney. This is so slight as to be indistinguishable with certainty in the fresh specimens. It is only after a comparison of fixed and stained preparations that it can be determined. The gross changes are so slight that they cannot be recognized with certainty.

CLOUDY SWELLING PRODUCED BY TARTRATES

Rabbits were given intravenous injections of racemic tartaric acid neutralized with sodium carbonate, in varying doses from .05 gm. per kilo to .15 gm. per kilo. At different times after the injection the rabbits were killed and their kidneys examined. The earlier stages were studied especially, since the later stages are of a frankly degenerative character and since many authors hold that parenchymatous nephritis passes thru a preliminary stage of

cloudy swelling.

Experiment 5. Rabbit; male; weight 1500 grams. Injected subcutaneously with 0.1 gm. racemic tartaric acid. The right kidney was removed one hour later. Two hours after the injection the animal was killed.

Right kidney: gross examination. Kidney appears normal.

Microscopic examination. Dark tubules are present in the fresh preparation. Paraffin sections show a few hydropin cells. Otherwise the appearances are normal.

Left kidney: gross examination. Cut surface is slightly pale.

Microscopic examination. Dark tubules are seen in the fresh preparations. Paraffin sections show nothing abnormal except a few hydropic cells.

Experiment 6. Rabbit; male; weight 2050 grams. Injected subcutaneously with 0.1 gm. racemic tartaric acid. Killed three hours later.

Gross examination. No definite changes.

Microscopic examination. Crushed preparations of fresh tissue show no dark tubules. In paraffin sections

stained with iron-hematoxylin most of the convoluted tubules show a few granules. There are no dark tubules. There are a few hydropic tubules in the peripheral part of the cortex.

Experiment 7. Rabbit; male; weight 1800 grams. Injected subcutaneously with 0.2 gm. racemic tartaric acid. The left kidney was removed two hours later. Twenty-four hours after the injection the animal was killed.

Left kidney: gross examination. The kidney is swollen. The cut surface is succulent and a little pale.

Microscopic examination. The fresh crushed preparations show a few slightly dark tubules. These are not so prominent as in the normal. Paraffin sections show some of the dark tubules containing granules. The lighter tubules also contain a few granules. Hydropic tubules are noted especially in the peripheral part of the cortex.

Experiment 8. Rabbit; female; weight 1570 grams. Injected subcutaneously with 0.2 gm. racemic tartaric acid. The right kidney was removed 3 hours later. 24 hours after the injection the animal was killed.

Right kidney: gross examination. The organ is slightly

swollen. The cut surface is slightly paler than normal.

Microscopic examination. In the fresh preparations most of the tubules show a few granules. There are no distinctly dark tubules to be seen. Paraffin sections show extreme hydropic degeneration of the convoluted tubules. There are a few tubules which do not show this change but none of the dark tubules are present. The normal tubules show a few scattered granules.

Left kidney: gross examination. The organ is swollen and the cut surface is distinctly cloudy.

Microscopic examination. The fresh specimen shows no dark tubules. Paraffin sections show some dilated tubules at the periphery of the cortex. These contain casts and cellular debris. There are some necrotic tubules at the periphery of the cortex. No dark tubules are present. There are no hydropic cells. The rods are very prominent in a large number of the tubules near the medulla.

Experiment 9. Rabbit; male; weight 1330 grams. Injected subcutaneously with 0.2 gm. racemic tartaric acid. Killed 24 hours later.

Gross examination. Kidneys are swollen. The cut sur-

faces are succulent and a little paler than normal.

Microscopic examination. The fresh preparation shows a few dark tubules. These contain some fatty granules besides the albuminous granules. Paraffin sections show some dilated tubules which contain casts and cellular debris. There are a number of dark tubules present. The rods are prominent in most of the tubules.

Experiment 10. Rabbit; male; weight 2050 grams. Injected subcutaneously with 0.3 gm. racemic tartaric acid. The right kidney was removed 24 hours later. 48 hours after the injection the animal was killed.

Right kidney: gross examination. The organ is swollen and cut surface is succulent and moderately cloudy.

Microscopic examination. The fresh specimen shows a large number of tubules filled with fat droplets. Paraffin sections show a large number of dilated tubules containing casts and cellular debris (Fig. 3). There are a few of the dark tubules present. There are some necrotic tubules at the periphery of the cortex. A few convoluted tubules contain large deeply-staining granules, apparently different from those in the dark tubules. Fat stain shows a large

amount of fat in both the collecting and the convoluted tubules.

Left kidney: gross examination. The organ is swollen. The cut surface is only slightly pale.

Microscopic examination. There are a few fatty tubules present. Paraffin preparations show fewer dilated tubules and less fat than in the right. There are some of the dark tubules present.

Experiment 11. Rabbit; male; weight 1970 grams. Injected subcutaneously with .3 gm. racemic tartaric acid. The left kidney was removed in 24 hours. 48 hours after the injection the animal was killed.

Left kidney: gross examination. The organ is swollen. The cut surface is succulent and moderately cloudy.

Microscopic examination. The fresh preparation shows a large amount of fat thruout the collecting and convoluted tubules.

Right kidney: gross examination. The organ is swollen. The cut surface is slightly pale.

Microscopic examination. The fresh preparation shows a few fatty tubules. Paraffin sections show only a few

dilated tubules. There are some dark tubules present. Most of the convoluted tubules contain a small amount of fat.

Experiment 12. Rabbit; male; weight 2050 grams. Injected subcutaneously with .3 gm. racemic tartaric acid. The left kidney was removed 7 hours later. 48 hours after the injection the right kidney was removed.

Left kidney: gross examination. The organ is possibly swollen. The cut surface is succulent and pale.

Microscopic examination. The fresh preparation shows a few dark tubules. Some of the tubules contain fatty granules. Paraffin preparations show a large number of hydropic tubules. There are some dark tubules. There are dilated tubules containing casts and cellular debris.

Right kidney: gross examination. The organ is swollen. The cut surface is moist and slightly pale.

Microscopic examination. There are a few dark tubules in the fresh preparation. Paraffin sections show no hydropic tubules. The larger number of tubules appear normal and the dark tubules are present. There are a few extremely dilated tubules which contain casts and cellular debris.

From the above experiments it will be seen that very small doses produce no noticeable changes in the kidney. The minimum effective dose causes, in the first few hours, an hydropic degeneration of some of the convoluted tubules. There is no increase in albuminous granules and sometimes they seem to be actually decreased in number. 24 hours after the minimum effective dose is given the hydropic condition has disappeared. Most of the tubules have regained their normal appearance but a few have become necrotic.

After larger doses there is a marked hydropic degeneration of almost every tubule within a few hours. There is no increase in albuminous granules. After 24 hours the hydropic condition has disappeared and a severe parenchymatous nephritis has taken its place (Fig. 3). Many tubules show necrosis and marked disintegration of the epithelium. Some contain considerable fat. There are but few normal appearing tubules and there is no increase in albuminous granules.

Sometimes in the more severe cases a few tubules may contain large irregularly arranged intensely staining granules. These, however, seem to be the result of, rather than

preliminary to, parenchymatous nephritis. In these tubules there is no suggestion of the rods of Heidenhain. Such granules are undoubtedly due to a granular degeneration of the cytoplasm.

The minimum effective dose produces no gross changes in the kidneys. Larger doses, however, give a definite cloudy swelling at the end of 24 hours. The organ cannot be said to have a "cooked appearance" but it nevertheless is swollen and turbid. This cloudiness and swelling are in no way due to the presence of albuminous granules. The albuminous granules are never increased in number above the normal and even, at times, seem to be decreased. The opacity of the kidneys is apparently due, for the most part, to anemia, fatty droplets, and necrosis and disintegration of the cells.

CLOUDY SWELLING BY THE INTRODUCTION OF AUTOLYZED LIVER INTO THE PERITONEAL CAVITY

Severe renal injury may be produced by introducing a large quantity of autolyzed proteins into the body.

A rabbit's liver was removed sterilely and cut up into fine pieces. Sterile physiological saline was added to this and the tissue was allowed to autolyze in the incubator.

This fluid was injected into the peritoneal cavity.

Experiment 13. Rabbit; female; weight 1665 grams. The urine was normal. 20 c.c. of fluid obtained by macerating a sterile rabbit liver over night with 50 c.c. of sterile physiological saline at 37°C. was injected intraperitoneally. 4 hours later the urine showed numerous hyaline casts and considerable albumin. The left kidney was removed. The animal died two days later. The urine remained about the same.

Left kidney: gross examination. The organ is swollen. The cut surface is succulent and moderately cloudy.

Microscopic examination. The fresh preparation shows no distinctly dark tubules. Some of the tubules contain a few albuminous granules, however. Paraffin preparations show a few dilated convoluted tubules. These contain sloughed off portions of cells within their lumina. The greater number of tubules appear normal. No dark tubules are present but some tubules contain a few darkly staining granules.

Right kidney: gross examination. The organ is darkened by postmortem change.

Microscopic examination. The fresh specimen shows no dark tubules altho some of the tubules contain a few albuminous granules. Paraffin preparations show a large number of the tubules containing albuminous material within their lumina. There are no dark tubules but some contain a few granules.

Experiment 14. Rabbit; male, weight 1600 grams. Examination of the urine showed no albumin. 74 gm. of sterile rabbit liver which had been macerated for 5 hours with 25 c.c. of sterile physiological saline was placed into the peritoneal cavity. 18 hours later the left kidney was removed. The urine was cloudy with granular casts and contained a large amount of albumin. 8 days later the animal died. During this time the urine remained about the same.

Left kidney: gross examination. The organ is swollen. The cut surface is extremely cloudy and succulent.

Microscopic examination. The fresh preparation shows no dark tubules. Paraffin sections show a pronounced parenchymatous nephritis but no dark tubules.

Right kidney: gross examination. The organ is swollen. The cut surface is succulent and moderately pale.

Microscopic examination. The fresh specimen shows no dark tubules. There are a large number of fatty granules present. Paraffin sections show considerable interstitial edema. There are a few tubules which contain a few granules. Some of the tubules are dilated and contain casts and cellular debris.

No increase in the number of albuminous granules occurred in these experiments. Instead the granules entirely disappeared and a very pronounced parenchymatous nephritis resulted. In spite of the disappearance of the granules an extreme degree of cloudy swelling occurred. This must be taken as further proof that the swelling and clouding of the kidney and the accumulation of albuminous granules within the cells may be the results of distinctly different pathological processes.

(Whether the changes in the kidney were due to autolyzed proteins or to the bile salts present was not determined.)

CLOUDY SWELLING PRODUCED BY INFECTIONS.

In this group of experiments the conditions simulate some of the human diseases in which a cloudy swelling may

occur.

Bell mentioned the occurrence of an albuminous degeneration (cloudy swelling) in rabbit kidneys in a case of infection. He examined the kidneys of a rabbit which had a large abscess, and found the tubules filled with albuminous granules. Acting upon his suggestion a rabbit with a large abscess was found. Cultures were made from this abscess and other rabbits were infected from these cultures. The animals were weighed each day and the progress of the infection was measured by the loss in weight. By killing the animals at different stages in the infectious process different degrees of cloudy swelling were obtained.

Most of the cases were pasteurella infections, since these are very common in rabbits. Some animals with proteus abscesses and one with a streptococcus infection were studied. The renal changes were similar in all three types of infections.

Experiment 15. Rabbit; male; weight 1040 grams. Inoculated subcutaneously with pasteurella. An abscess developed. 13 days later the animal was killed. Weight 890 gm.

Kidneys: gross examination. There are no marked

changes from the normal.

Microscopic examination. The fresh specimen shows a large number of dark tubules. There are no fatty granules. Paraffin sections show considerably less than half the tubules dark (Fig. 4). These are crowded with granules which tend, in some tubules, to be arranged in rows in the basal part. The rods are present between the granules and are very prominent in the clear tubules. The cells of the tubules are swollen so that no lumen is visible. Frozen sections stained with sudan III. show that no fat is present.

Experiment 16. Rabbit; male; weight 1900 grams. The animal was inoculated subcutaneously with pasteurella. A large abscess developed. Fourteen days after the animal died. Weight 1300 gm.

Kidneys: gross examination. The organ is discolored. It is not swollen.

Microscopic examination. The fresh specimen shows numerous dark tubules filled with albuminous granules. No fatty granules are present. Paraffin sections show numerous dark tubules filled with deeply staining granules. These are confined to the basal part of the cells in only a few

tubules. The rods are not present. (No fat could be demonstrated in frozen sections.)

Experiment 17. Rabbit; male; weight 2010 grams. A phenolsulphonephthalein test gave 75 per cent for the first two hours. The urine was normal. The animal was inoculated subcutaneously with pasteurella . An abscess developed. Ten days later a phenolsulphonephthalein test was about the same. Two days later an examination of the urine showed a faint trace of albumin and a few hyaline casts. Thirteen days after inoculation the animal died. Weight 1360 gm.

Kidneys: gross examination. The organ is discolored. It is not swollen.

Microscopic examination. The fresh specimen shows numerous dark tubules containing albuminous granules. Paraffin sections show the cells of slightly less than half the tubules filled with albuminous granules. A few of the tubules have wide lumina and fragmented cells. There is often albuminous material within the lumina of the tubules. The rods are not present. (These kidneys were not obtained until some hours after death.)

Experiment 18. Rabbit; male, weight 1470 grams. The rabbit had had a spontaneous abscess on the jaw which had been noticed for about a month. Nine days after I received the rabbit it was killed. Weight 1170 gm.

Kidneys: gross examination. The organs are not swollen. The cut surface is moderately cloudy.

Microscopic examination. The fresh preparation shows a large number of dark tubules which are filled with albuminous granules. Paraffin preparations show the cells of slightly more than half the tubules filled with deeply-stained granules. The rods of Heidenhain are prominent in places between the granules. No fat is present.

Experiment 19. Rabbit; male; weight 2000 grams. The left kidney was removed. One week later the rabbit was inoculated with proteus. A diffuse infection resulted. 8 days after the inoculation the animal died.

Right kidney: gross examination. The organ is markedly swollen. The cut surface is succulent and slightly pale.

Microscopic examination. The fresh preparation shows numerous dark tubules filled with albuminous granules. Some of these granules are immense. Paraffin sections show the

cells of slightly more than one-half of the tubules filled with deeply staining granules. The rods are not present. (The rabbit had been dead for some time when it was found.) The lumina of most of the tubules are obliterated by the swollen cells. No fat could be demonstrated.

Experiment 20. Rabbit; female; weight 1830 grams. The animal was inoculated subcutaneously with pasteurella. An extremely large abscess developed. Nine days later the left kidney was removed. Weight 1330 gm. The next day the animal was killed.

Left kidney: gross examination. The organ is swollen. There is no noticeable cloudiness.

Microscopic examination. The fresh specimen shows numerous dark tubules which are filled with albuminous granules. These granules are very irregular in size. Paraffin preparations show a little less than one-half the tubules dark. These are crowded with darkly staining granules. The granules are very large in certain tubules. The rods of Heidenhain are present between the granules in the basal portion of the cells. Sections stained for fat show a little present in a few of the convoluted and collecting tubules.

Right kidney: gross examination. The organ is swollen. The cut surface is slightly cloudy.

Microscopic examination. The microscopic examination shows a few more dark tubules than the left kidney. Otherwise they are the same.

Experiment 21. Rabbit; male; weight 1520 grams. Phenolsulphonephthalein test before inoculation with B. proteus 80 per cent. Six days later the test measured 75 per cent. Nine days after inoculation the test measured 50 per cent and the animal was killed. Weight 1200 gm.

Kidneys: gross examination. The organ is swollen. The cut surface is succulent and cloudy.

Microscopic examination. Fresh preparations show a large number of dark tubules present which contain albuminous granules. Paraffin preparations show over one-half of the tubules filled with darkly staining granules. The rods are well preserved. Fat stains show only a very few fatty granules in some of the tubules.

Experiment 22. Rabbit; male; weight 1610 grams. Phenolsulphonephthalein test, 70 per cent. The rabbit was inoc-

ulated subcutaneously with B. proteus. A diffuse infection resulted. Three days later the phthalein test was the same. Five days after the inoculation the animal died. Weight 1090 gm.

Kidneys: gross examination. No swelling is present. The cut surfaces are succulent but not cloudy.

Microscopic examination. The fresh preparation shows a large number of moderately dark tubules. Paraffin preparations show that about half of the tubules are dark. The number of granules is less than in pronounced cases. Considerable fat was demonstrated in some of the convoluted tubules and in the collecting tubules.

Experiment 23. Rabbit; male; weight 1910 grams. Urine examination showed nothing abnormal. Phenolsulphonephthalein test, 80 per cent. The animal was inoculated subcutaneously with B. proteus. A large abscess developed. Nine days later the phthalein test measured 70 per cent. The urine showed a faint trace of albumin but no casts. Eleven days after inoculation the left kidney was removed. Weight, 1660 gm. The next day the animal died.

Left kidney: gross examination. The organ is swollen.

The cut surface is succulent and markedly cloudy.

Microscopic examination. The fresh specimen shows an extremely large number of dark tubules filled with albuminous granules. Paraffin preparations show more than half of the tubules dark, due to the presence of deeply stained granules within the cytoplasm of the cells. The rods of Heidenhain are present in the basal part of the cells between the granules. The cytoplasm of the cells in all the tubules is intact. No fat is present.

Experiment 24. Rabbit; male; weight 1555 grams. The left kidney was removed. An abscess developed at the site of the operation. Weight 1425 gm.

The organ is swollen. The cut surface is succulent and extremely cloudy.

Microscopic examination. Fresh preparations show extremely numerous dark tubules. Paraffin sections show most of the tubules dark, due to the presence of deeply-stained granules. Sections stained for fat show none present.

Experiment 25. Rabbit; female; weight 2210 grams. The animal was inoculated with B. proteus. A large abscess

to the basal portion of the cells. The rods are prominent between the granules. The cells of most of the tubules are swollen so that no lumen is visible. There are a few tubules, however, which have distinct lumina and these often contain albuminous material. No fat could be demonstrated in frozen sections.

Experiment 27. Rabbit; male; weight, 1850 grams. The animal was recovering from a pasteurella abscess. It was inoculated with pasteurella. Fourteen days later it was killed. Weight, 1565 gms.

Kidneys: gross examination. The organ is moderately swollen. The cut surface is slightly cloudy and succulent.

Microscopic examination. The fresh preparation shows numerous dark tubules which are filled with albuminous granules. Paraffin sections show most of the tubules dark, due to the presence of darkly staining granules within the cells. In a few tubules they are arranged in rows between the rods of Heidenhain. The rods of Heidenhain are present in places between the granules and are very prominent in the less granular tubules. There are some dilated tubules which con-

tain casts and albuminous material. These are found particularly in fibrotic areas within the cortex. No fat could be demonstrated.

Experiment 28. Rabbit; male; weight, 1945 grams. The urine was normal. Phenolsulphonephthalein, 81 per cent. Inoculated subcutaneously with B. proteus. An abscess developed. Nine days later the urine was normal and the phenolsulphonephthalein test was about the same. Eleven days after inoculation the animal was killed.

Kidneys: gross examination. The organs are markedly swollen. The cut surfaces are definitely cloudy and succulent.

Microscopic examination. The fresh preparation shows a large number of dark tubules. Paraffin sections show that almost all the tubules are dark. The granules vary considerably in size. The rods are well preserved and prominent.

Experiment 29. Rabbit; male. Inoculated with pasteurellæ. A large subcutaneous abscess developed. Three weeks after inoculation the animal was killed.

Kidneys: gross examination. No swelling is present.

The cut surface is distinctly cloudy.

Microscopic examination. The fresh preparation shows numerous dark tubules filled with albuminous granules. Paraffin preparations show almost all the convoluted tubules dark, due to the presence of numerous darkly staining granules within the cells. These granules vary in size. Some are half the size of the nucleus. The rods show in the basal part of the tubules between the granules. The cytoplasm of the cells of all the tubules is intact. No fat is present.

Experiment 30. Rabbit; male; weight, 1560 grams. Phenolsulphonephthalein test, 75 per cent. Inoculated subcutaneously with B. proteus. An abscess developed. Thirteen days later phthalein test was 85 per cent. The urine showed a trace of albumin but no casts. The animal died shortly after the test was made.

Kidneys: gross examination. The organs are not swollen. The cut surfaces are slightly pale. The inner part of the medulla is extremely light colored.

Microscopic examination. The fresh specimen shows numerous dark tubules. Paraffin sections show that almost

every convoluted tubule is dark. The rods are distinctly visible in most of the tubules. The cytoplasm of the cells is intact in all of the tubules. No fat is present.

Experiment 31. Rabbit; male; weight, 2140 grams. The animal was inoculated subcutaneously with pasteurella. A large abscess resulted. Twelve days later the animal died. Weight, 1365 grams.

Kidneys: gross examination. There is no swelling present. The cut surface is moist and definitely cloudy.

Microscopic examination. The fresh specimen shows numerous dark tubules filled with albuminous granules. Paraffin sections show almost all the tubules dark, due to the presence of darkly staining granules. In but few tubules are they confined to the basal part of the cells. The rods are present in the basal parts of the cells between the granules. The cells of the tubules are swollen so as to obliterate the lumina.

Zenker fixation. Paraffin preparations show no dark tubules. The granules are absent with the exception of a few scattered ones in some of the tubules. These do not stain intensely with iron-hematoxylin.

Experiment 32. Rabbit; male; weight 2260 grams. The animal was inoculated subcutaneously with pasteurella. A large abscess resulted. Twelve days later the left kidney was removed. Weight, 1690 grams. Three weeks after the inoculation the animal was killed. Weight, 1325 grams.

Left kidney: gross examination. The organ is swollen. The cut surface is moist and slightly cloudy.

Microscopic examination. The fresh preparation shows numerous dark tubules filled with albuminous granules. In some of the tubules the granules are as large as the nucleus. There are a few of the granules which do not burst upon the addition of alkali but gradually dissolve. These are less refractive than the other granules. Paraffin preparations show the greater number of tubules to be extremely dark, due to the accumulation of darkly staining granules within the cells (Fig. 5). In some tubules these granules are immense, being as large as the nucleus (Figs. 6 and 7). Most of the granules are spherical but some are oval and others spindle-shaped. The rods are distinctly visible in places between the granules. The cells of the tubules are swollen so that the lumina are almost all obliterated. No

fat is present.

Right kidney: gross examination. The organ is swollen. The cut surface is extremely cloudy and succulent.

Microscopic examination. There are more dark tubules than in the left kidney and the granules are larger. Otherwise the kidneys are the same. There is no fat present.

Zenker fixation (right kidney). Paraffin sections. The granules are absent except in relatively few tubules. There are numerous light spaces in the cytoplasm of the cells. These are probably the spaces from which the granules have been dissolved out.

Experiments 33-50. In a large number of experiments on infection the rabbits have died very soon after the inoculation, within one to four days. The pictures presented by the kidneys in these cases have been almost absolutely uniform and may all be described together. Grossly, the kidney is swollen. The cut surface is succulent but not cloudy. The inner part of the medulla is often extremely light colored. Microscopically the fresh tissue shows no dark tubules. There is often fat present in the form of small droplets. Paraffin preparations show no dark tubules.

There are usually a few granules in some of the tubules. There are usually some tubules in which the cells are disintegrated. The lumina of these tubules are wide and contain albuminous material or casts. The rods are absent or if present at all may be made out in only a part of the tubules. There are usually a number of small fat droplets in the collecting tubules and in many of the convoluted tubules near the medulla.

Experiment 51. Rabbit; male; weight, 2395 grams. The animal was inoculated with proteus. Four days later the left kidney was removed. Weight 2175 grams. The animal was then reinoculated with a large dose of proteus intended to be rapidly fatal. Death the next day. Weight, 2080 grams.

Left kidney: gross examination. The organ is swollen. There is no cloudiness present.

Microscopic examination. Dark tubules are present in the fresh preparation. Paraffin sections show about half of the tubules moderately dark. These tubules contain fewer dark granules than the dark tubules of more severe infections. The rods are well preserved. The cytoplasm of the cells is intact in all of the tubules.

Right kidney: gross examination. The organ is swollen. The cut surface is succulent but not cloudy. The inner part of the medulla, however, is extremely pale.

Microscopic examination. The fresh preparation shows no dark tubules altho there are a few albuminous granules in some of the tubules. Paraffin preparations show no dark tubules. The cytoplasm of the cells of many of the tubules is fragmented. The lumina of these tubules are wide and often contain albuminous material. The rods are well preserved in only a few tubules.

Experiment 52. Rabbit; male; weight 1890 grams. Phenolsulphonephthalein test, 68 per cent. The animal was inoculated subcutaneously with proteus. Thirteen days later the phthalein test was 70 per cent. The animal was then given a very large dose of B. proteus. Death the next day. Weight, 1150 gms.

Kidneys: gross examination. The kidneys are swollen. The cut surfaces are succulent and moderately cloudy.

Microscopic examination. There are no dark tubules in the fresh preparation. Paraffin sections show no dark tubules. There are a few scattered darkly staining granules

in some of the tubules, however. The rods of Heidenhain are present in most of the tubules. A few of the tubules are dilated and contain casts and albuminous material within their lumina. The cells of a few tubules are fragmented on their inner borders. Sections stained for fat show a considerable quantity present in the convoluted and collecting tubules in the form of fine granules.

It will be seen from the foregoing that the experiments on infection may be divided into two groups: (1) a chronic or subacute type in which the rabbits lived more than a week; (2) an acute type in which the animals died within the first few days.

The characteristic picture found in kidneys of the first group of animals is as follows.

Gross examination. The gross picture is variable. In some cases the cortex is distinctly cloudy and swollen but in other cases these features are not so noticeable. The medulla rarely shows any change. It may be lighter than normal and have a sort of homogeneous appearance. The cut surface is moist and glistening.

Microscopic examination (fresh). The fresh crushed

specimen shows, under low power, a large number of dark tubules. These are seen upon high magnification to be filled with weakly refractive, definitely circumscribed granules. They almost hide the nuclei of the cells. Upon addition of alkali these granules disappear like the bursting of a bubble, leaving the tubules light and the nuclei clearly visible. These granules are also present in the light tubules but they are fewer and scattered. In the more pronounced cases almost every convoluted tubule may be dark. In these instances some tubules contain immense granules, almost as large as the nucleus. These also burst upon the addition of alkali. No fatty granules are present.

In severe cases there appears another type of granule. this is less refractive than the former type and dissolves gradually in alkali.

Fixed and stained preparations. Hematoxylin and eosin. The cells of the convoluted tubules appear swollen, their inner borders projecting into and often obliterating the lumina. The cytoplasm stains well and, upon low power, seems to be perfectly homogeneous. Upon examination with oil immersion, however, the granules can be seen as bright

red-staining bodies. Where the granules are large they give rather a fragmented appearance to the cells.

Iron-hematoxylin. The cells of the greater number of convoluted tubules are seen to be filled with intensely staining granules. These are, as a rule, more numerous in the basal portion where they often show a tendency to be arranged in rows. In the upper portion of the cells they are irregularly scattered thru the cytoplasm. In some tubules the granules are distributed uniformly thru the whole cell. As described in the fresh specimen, the size of the granules varies. In the more pronounced cases they are very irregular in size, some being as large as the nucleus. Most of the granules appear spherical but there are also oval and spindle-shaped ones in some of the tubules. The rods of Heidenhain may be seen in places between the masses of granules and are very prominent in the less granular tubules. There is no fat present.

The characteristic picture of kidneys of the second group of animals is as follows.

Gross examination. The gross, as a rule, shows no change, but sometimes the organ is succulent and swollen.

In some cases the inner part of the medulla is extremely pale.

Microscopic examination. In fresh preparations there are no dark tubules. There are generally a few albuminous granules, however, scattered thru the tubules. There are often scattered granules which do not dissolve upon the addition of acid or alkali and might therefore be taken for fat. These are often particularly numerous in the glomeruli.

Fixed and stained preparations. Hematoxylin and eosin. There is always a varying number of tubules with wide lumina containing albuminous material and sloughed off portions of cells. The inner border of the cells in many of the tubules contain vacuoles. These often give a ragged appearance to the cells.

In fixed material stained with iron-hematoxylin, the large granules are found to be almost entirely absent. A varying number of tubules contain small sparsely scattered granules which do not often show any tendency to be arranged in rows. The basal portion of a great many of the tubules has an indefinite granular appearance, however. The rods are absent as a rule. In some of the kidneys they

are present in a few of the tubules, but in the greater number of tubules they are absent. In these acute cases there are often darkly staining bodies in the glomeruli. There is considerable fat in the form of fine granules in the collecting tubules and in the convoluted tubules near the medulla.

The most striking difference between the kidneys of acute and those of chronic infections is the almost complete absence of albuminous granules in the former and their presence in enormous numbers in the latter.

In the acute cases the renal tubules always show much more marked signs of injury than they do in the chronic cases. In the chronic group the phthalein test remains usually about normal and the cell structure is well preserved. These facts suggest that the marked increase of albuminous granules is not a degenerative change, but rather the expression of increased function.

The number of dark tubules is greatest in those cases where there has been an extreme but very gradual loss of weight(Exps. 29-32). The albuminous granules in the dark tubules in the chronic cases are larger and more numerous than those in the dark tubules of a normal kidney. In some

cases they attain an enormous size, sometimes being as large as the nucleus. The large granules are probably formed by fusion of smaller granules, since the granules are fewer in cells containing the large types.

Nearly all the albuminous granules in the chronic cases closely resemble the granules of the dark tubules of the normal kidney. They burst when sodium hydroxid is applied, and they disappear in acetic acid solutions. They are fixed and stained by the same procedures. They are entirely different from the hyaline granules often seen in human nephritic kidneys. They are evidently thin-walled vesicles filled with fluid and not solid bodies.

In very severe infections one often sees granules that are less refractive than those described above. These granules disappear gradually in sodium hydroxid. They do not burst in this solution.

There is no fat present in any of the chronic cases. There is no evidence that this increase of albuminous granules is in any way related to the formation of fat.

Fat droplets appear in the acute cases. It seems that toxic substances which cause the formation of fat droplets

at the same time destroy the albuminous granules.

The gross changes in the kidneys of the chronic cases usually vary in degree, depending upon the number of albuminous granules present. Sometimes, however, there are many more granules present than is suggested by the gross picture. The kidneys are sometimes very opaque, but a typical "cooked appearance" was never obtained.

ETIOLOGY AND ULTIMATE SIGNIFICANCE OF CLOUDY SWELLING

Various interpretations of cloudy swelling are to be found in the literature. The ideas may be grouped as follows:

1. Excessive functional activity. This was the belief of Virchow. He regarded the granules as nutritive material taken into the cells but not assimilated. Birch-Hirschfeld recognizes one kind of cloudy swelling of this type, and another in which the granules represent surplus waste material. Albrecht and Landsteiner interpret some cases of cloudy swelling (compensatory) as due to increased physiological activity. Adami believes that the granules are due to excessive and prolonged stimulation of the cells.

2. Coagulation or precipitation theory. Cohnheim,

Rindfleisch, and Klebs believed that the granules are formed from the coagulation of fluid albumins in the cell. Klebs and Fischer explained the coagulation as due to acid formation in the cytoplasm.

3. Degeneration theory. Many authors regard cloudy swelling as essentially a degenerative process. It is explained as due to decreased oxidation (Benario), to poisonous substances (Ribbert, Schilling), and to decreased nutrition (Thoma). Others who subscribe to this view are Birch-Hirschfeld, Albrecht (one type of cloudy swelling), Volhard and Fahr. Some observers emphasize the intimate relation between cloudy swelling and fatty metamorphosis (Benario, Von Recklinghausen, Ziegler, Birch-Hirschfeld, Ribbert, Rindfleisch, Wells[24], Thoma, and Adami). Many believe that cloudy swelling is a process that may readily pass into definite cell degeneration and necrosis (Virchow, Cohnheim, Ziegler, Ribbert, Rindfleisch, Thoma, Adami, Volhard and Fahr).

4. Emulsification theory. Albrecht believes that one form of cloudy swelling represents an emulsification of the cytoplasm, due to imbibition of fluid and separation of

lipoidal substances. Von Gierke and Anitschkow[25] accept this interpretation in a modified form.

Albrecht recognized three fundamental types of cloudy swelling: emulsification, excessive function, and disintegration. Some other observers also believe that there is more than one fundamental process concerned.

Nearly all the authors mentioned above have worked exclusively with human cloudy swelling. It is easily possible that some of the processes involved here are different from those concerned in the rabbit kidney.

My observations indicate that the cloudy swelling occurring in tartrate nephritis is due to edema, anemia, fat, tissue disintegration, etc., and is not associated at all with albuminous granules.

But the cloudy swelling of the kidney following chronic infections is evidently due in part to a marked increase of albuminous granules in the cells. This type of cloudy swelling is best interpreted as due to excessive functional activity.

DISCUSSION

Much of the confusion in the diagnosis of cloudy swel-

ling is due to lack of agreement among pathologists as to what constitutes the gross picture. If we make the diagnosis only when the organ looks "cooked" and the cells have a glassy appearance, then we shall almost invariably find this gross picture associated with a marked increase of albuminous granules in the cells. If we take the position that this classical picture and this alone constitutes cloudy swelling, then the condition becomes very rare. All the milder degrees of this same process would be excluded, since the typical "cooked" and glassy appearances occur only when the cells are crowded with albuminous granules. This definition of cloudy swelling would also exclude all the experimental lesions described in this paper, since none of them had the typical cooked appearance.

The average pathologist often makes a diagnosis of cloudy swelling in an organ that is merely turbid and swollen, in the absence of the typical "cooked" appearance, and without a microscopic examination of the fresh tissue. If the term is used in this sense then cloudy swelling becomes one of the most frequent of autopsy findings. Cloudiness and swelling in an organ may be due to edema, anemia, fat, album-

inous granules, tissue disintegration, etc. This use of the term obviously makes it include several distinct pathologic phenomena.

In my experiments the kidneys of animals injected with tartrates and autolized liver tissue were often swollen and cloudy. These changes in the gross appearances were apparently due to edema, anemia, tissue disintegration, etc.

The kidneys from the cases of chronic infections were also often cloudy and swollen, but here the gross changes were due mainly to an enormous increase of albuminous granules.

In my opinion the term cloudy swelling should be dropped out of pathologic literature. The classical cloudy swelling is merely an intense accumulation of albuminous granules in the cells and is more clearly described as such. If the term is to be used to describe a turbid swollen organ, it becomes worse than useless, since it groups together several unrelated pathologic phenomena.

There would be less confusion if the term cloudy swelling were discarded entirely and the several phenomena which produce this appearance were considered separately. Thus,

instead of studying cloudy swelling, we should study the increase of albuminous granules, edema, fatty metamorphosis, emulsification of the cytoplasm, etc.

SUMMARY

The normal rabbit kidney always contains, in the convoluted tubules, coarse albuminous granules. Usually these granules are so numerous in a few tubules that these appear dark in the fresh tissue. The granules are apparently thin-walled vesicles filled with fluid. They are best fixed by solutions containing formalin. They are not fixed in solutions containing acetic acid.

When one kidney is removed the dark tubules are increased in the opposite kidney during the first 24 or 48 hours, but the increase of albuminous granules is not sufficient to cause any definite change in the gross appearance of the kidney.

Subcutaneous injections of tartrates produce a swollen, cloudy kidney, but there is no increase of albuminous granules. The cloudiness and swelling are apparently due to edema, anemia, tissue disintegration, etc.

Intraperitoneal injections of autolized liver tissue

produce a markedly cloudy and swollen kidney. The albuminous granules disappear entirely. The gross changes are apparently due to the same factors concerned in the tartrate experiments.

Chronic suppurative processes attended with marked emaciation cause an enormous increase of albuminous granules in the kidneys. These granules are often larger than the normal and irregular in shape, but they seem to have the same chemical composition.

Acute suppurative processes cause a rapid disappearance of the normal albuminous granules.

An acute toxemia superimposed upon a chronic suppurative process causes a disappearance of the albuminous granules.

Kidneys which show an enormous increase of albuminous granules usually give a normal phthalein output, and the cells are usually intact. This form of cloudy swelling is therefore probably due to excessive function, and is not a degenerative change.

There is no relation between the formation of albuminous granules and fatty metamorphosis.

It is suggested that the term cloudy swelling be discarded and that the several processes producing this appearance be considered separately.

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EXPLANATION OF FIGURES

Fig. 1. Normal kidney. Drawing showing dark tubule. X1000.

Fig. 2. Normal kidney. Photomicrograph showing groups of dark tubules. X 80.

Fig. 3. Tartrate cloudy swelling kidney. Photomicrograph showing extreme dilatation of some tubules. X 80.

Fig. 4. Kidney in infection. Photomicrograph showing moderate increase in dark tubules over normal. X 80.

Fig. 5. Kidney in infection. Photomicrograph showing extreme increase in dark tubules over normal. This kidney showed a pronounced cloudy swelling. X 80.

Fig. 6. Kidney in infection. Photomicrograph of a dark tubule in a pronounced case of cloudy swelling. Same kidney as Fig. 5. X 500.

Fig. 7. Kidney in infection. Drawing of a dark tubule in a pronounced case of cloudy swelling. From same kidney shown in Figs. 5 and 6. X 1000.