

plete recovery and no further treatment is given. But a few months later the patient returns with marked nervous or mental symptoms. As is well known, such symptoms, in the ordinary course of syphilis, usually occur in the tertiary stage. These early nervous manifestations after salvarsan were at first thought to be due to the toxic action of arsenic. It was soon pointed out by Bernario,¹² however, that such symptoms occasionally occur in the secondary stage after treatment with mercury. Furthermore they do not occur after the use of salvarsan in other diseases, such as yaws. They occur only in the secondary stage of syphilis, and only several months after treatment has been stopped. The Wassermann reaction becomes positive and examination of the spinal fluid gives all the indications of an active inflammation. Further treatment with salvarsan or with mercury improves the condition. All these considerations have led to the conviction that nervous symptoms after salvarsan constitute a true syphilitic relapse. Up to the present time, however, the presence of *Spirochaeta pallida* in the nervous system in this condition has never been demonstrated. We have now furnished this demonstration and we believe that the proof of the syphilitic nature of nervous relapses is now complete.

The question still remains why these relapses are more frequent under treatment with salvarsan than with mercury. Some authors hold that salvarsan damages the nervous system and thus predisposes to a localization of the spirochetes in this region. It seems to us, however, that these relapses can be satisfactorily explained according to Ehrlich's ideas. In a considerable number of cases, in the secondary stage, the nervous system is infected with or without symptoms. Our patient undoubtedly would have shown pleocytosis in the spinal fluid at the time of his first treatment.

When such a case is treated with salvarsan the great bulk of spirochetes are suddenly destroyed. They are not simply repressed as is the case under mercury, and the resistance of the body is not gradually stimulated against them. There remain, however, small foci of spirochetes, especially in areas which are less accessible to the circulation, such as are found in the central nervous system. After a time these spirochetes begin to multiply and they meet no resistance such as is afforded by the continuous administration of mercury or by the natural defenses of the body, because these defenses have not been continuously stimulated by a large number of organisms all over the body. As a result, the spirochetes which have remained grow with increased vigor and presently produce symptoms where they are located—in the nervous system. Ehrlich¹³ compares the extent of their growth to the relative size of a few colonies of bacteria on an agar plate as contrasted with the size of the same colonies when several hundred are present. And we may also compare their rate of reproduction to that of rats and rabbits when a large number have been killed off in a given area. The remaining animals reproduce at a greatly increased rate and soon they are as numerous as ever.

The clinical lesson is that in the early secondary stage our treatment must be vigorous and prolonged. In attempting a radical cure during this stage we must give a minimum of three or four intravenous injections of salvarsan combined with an intensive treatment with mercury covering at least two months. If an examination of the spinal fluid can be made, it is of great advan-

tage, because an increased cell count and protein content indicate the cases which are potentially those of nervous relapse.

As one of us¹⁴ has previously pointed out, the rabbit is now the animal of choice for certain lines of work in syphilis and the result of the present experiment shows that the rabbit is also suitable for inoculation experiments when the spirochetes are present in small numbers. In this case the organism was undoubtedly present in small numbers in its spiral form. In view of the possibility of a complex life-cycle of the spirochetes and of other forms than the spiral one and in view of the possibility that such forms might be present in tabes and paresis in which diseases spirochetes, as such, have never been found, we have made several inoculations in rabbits of the spinal fluid and of the cortex of paretics during the past year and a half. So far we have obtained no positive results, but further work must be done before these possibilities are excluded. Uhlenhuth and Mulzer¹⁵ also report negative results from the inoculation of rabbits with the spinal fluid from patients with early paresis and tabes.

THE HUMAN PROSTATE GLAND AT BIRTH

WITH A BRIEF REFERENCE TO ITS FETAL DEVELOPMENT *

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This discussion is based on the study of serial cross-sections of the prostate of a human baby which were cut and mounted in the usual manner, being stained on the slides in hematoxylin and eosin. The sections were cut 30 micromillimeters in thickness. A part of the work done includes the reconstruction in wax of the various groups of tubules composing the gland, the prostatic urethra, the ejaculatory ducts, and the utriculus prostaticus, enlarged twenty times. This model is so constructed that normal relations are exactly maintained, the different parts being held together by pins and wire buried in the wax. In order to gain a clearer idea of the entire structure of the organ its different parts were separated and supplied with fixtures so that it can be fitted together or taken apart at will.

In this specimen the five lobes of the prostate¹ were clearly identified, and the two groups of tubules, which might appropriately be called accessory glands from their intimate relationship to the prostate anatomically and in diseases of this part of the genito-urinary tract, were found present.

The duct openings of the nine tubules which make up the middle lobe are quite widely separated from those of other lobes, and occur on the floor of the urethra rather close to the openings of the ejaculatory ducts, but between those structures and the bladder, as shown in Figure 1. It is noticed that the mouths of these tubules do not open in the middle of the floor of the urethra as in the younger fetuses, but are pushed laterally to a slight extent, owing, no doubt to the great increase in the size of the verumontanum. Careful identification of the tubules of the middle lobe and their branches discloses the fact that although in many cases the tubules of this lobe lie side by side with those

14. Nichols: Jour. Exp. Med., 1911, p. 196.

15. Uhlenhuth and Mulzer: Zentralbl. f. Bakteriologie, 1912, Orig. lxxiv, p. 165.

* Read in the Section on Genito-Urinary Diseases of the American Medical Association, at the Sixty-Third Annual Session, held at Atlantic City, June, 1912.

1. Lowsley: Am. Jour. Anat., No. 3, July, 1912.

12. Bernario: Ueber Neurorecidiv, 1911.

13. Ehrlich. Ztschr. f. Chemotherapie, 1912, Orig. 1, 6.

of the lateral lobes there is at no point an intermingling. Therefore the middle lobe is at birth an independent structure." On the other hand, no evidence is found of a definite fibrous layer separating the middle from the lateral lobes, and the fact that the middle lobe is independent in its location and development is of slight practical importance. In this specimen the middle-lobe tubules have extended up behind the sphincter to its uppermost border. The end of the tubule which has extended the highest is situated in the middle line just above the ampulla of the vas, and its branches are surrounded by rather dense muscular tissue. The whole mass lies imbedded in the loose connective tissue beneath the bladder musculature. Lower down in the direction of the mouths of the tubules these branches are reinforced by others of a like nature, and a very short distance below become connected with the musculature surrounding the urethra. The musculature surrounding the tubules of the middle lobe are quite thick and firm, being in some instances as large as the walls of the ejaculatory ducts.

The lateral lobes are made up of seventeen tubules on each side, which form the main mass of the gland. These tubules empty into the right and left prostatic furrows, and a few on the lateral walls of the urethra. By their great development they cause the base of the prostate to bulge laterally and posteriorly. The right lateral

lobe tubules are found to have extended back only to a point above the opening of the seminal vesicles into the ejaculatory ducts, while the uppermost ends of the left lateral lobe tubules have extended back under the bladder and are found contained in their thick muscular envelope, adherent to the sides of the seminal vesicles. Where the prostate reaches its broadest dimension the branches of the tubules are exceedingly numerous, a surprisingly large number joining together to empty into the urethra through a duct which is no larger in size than one of its smallest branches. The two lateral lobes are separated posteriorly by the posterior lobe, the mid-

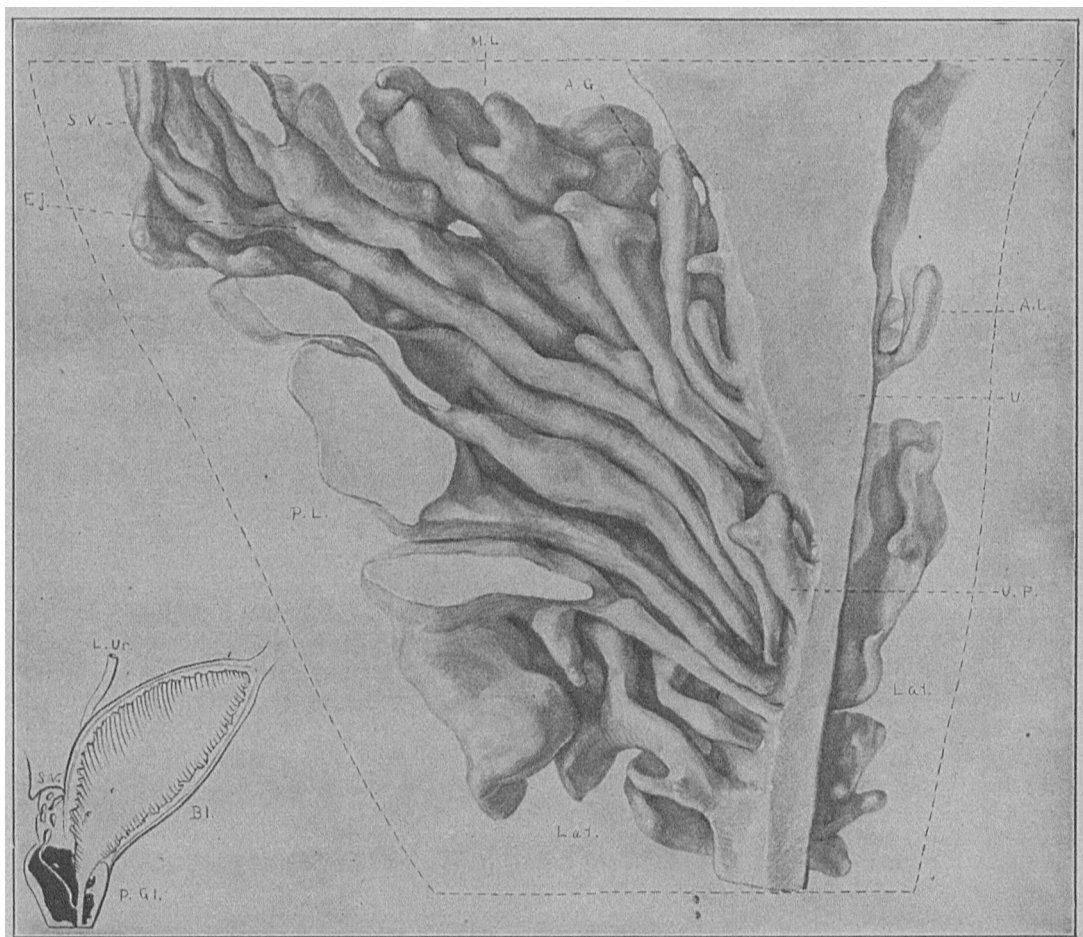


Fig. 1.—Sagittal view of a wax model of the prostate of a new-born infant. Lat., anterior branches of lateral lobes; P. L., posterior lobe; E.J., ejaculatory duct; S. V., seminal vesicle; A. L., anterior-lobe tubule; U., urethra; U. P., utricle; A. G., subcervical glands of Albarran; M. L., middle-lobe tubules; L. Ur., left ureter; Bl., bladder; P. Gl., prostate gland.

2. Griffiths (*Jour. Anat. and Physiol.*, 1889, xxiii, 374) expressed the opinion that the middle lobe was independent, "having glands of its own, which open on parts of the hinder wall of the prostatic urethra." Tandler and Zuckerkandl (*Folia Urolog.*, 1911, v, 587) have utilized this fact in their consideration of prostatic hypertrophy. Gustaf Pallin (*Arch. f. Anat. u. Physiol.*, 1901), Evatt (*Jour. Anat. and Physiol.*, 1908, xliii, 314), and Jores (*Virchows Arch. f. path. Anat.*, 1894, cxxxv, 224), all maintain that the so-called middle lobe is always formed by ingrowths from the lateral lobes. In my studies on the embryology of the prostate I observed in one specimen an entire absence of middle-lobe tubules. There were two large tubules noted in this case to be extending into the region usually occupied by the middle lobe. All of the other series showed independent middle lobes. A full description of the above-mentioned specimen is given in the *American Journal of Anatomy*, xlii, No. 3, p. 318. One hundred and three prostates obtained at autopsy, from dissecting-room cadavers and from fetuses, were studied with the result that in only one specimen, the fetus already mentioned, was there observed an absence of middle-lobe tubules. In five other instances the presence of a middle lobe was not determined, as the specimens were considered valuable and could not be sectioned. The remaining ninety-seven prostates all had definite middle lobes.

dle lobe, the ejaculatory ducts and utricle prostaticus, mesially by the urethra and anteriorly by the anterior lobe and a considerable area of stroma, although in the lower or outermost portion anterior branches of the lateral lobes approach each other rather closely. Two large tubules in the outermost or caudal portion of the lateral lobes send branches in a caudad direction, all of the others extending cephalad or toward the bladder. This fact is of interest surgically because in nearly every successful enucleation it is necessary to cut these forward branches, as they seem to be particularly adherent to the capsule. The posterior borders of these lobes are separated from the posterior lobe by a rather dense layer of connective tissue, which also separates the latter from the middle lobe and ejaculatory ducts.

The course of the posterior lobe tubules follows rather closely the dorsal aspect of the ejaculatory ducts until

the latter structures ascend almost vertically toward the urethra, immediately caudad to which there is a small area free from glandular elements. Some of these tubules have extended toward the bladder until they are almost as far back as the ends of the middle-lobe tubules. This lobe fits over the posterior surface of the gland like a cap, being definitely and strongly separated from the other parts by a fibrous portion already referred to. This is the part of the prostate

until the incision is made into the part of the gland that contains them.

In the new-born, as shown on the reconstruction (Fig. 1), there are two very small tubules composing the anterior lobe. Occasional hypertrophied anterior lobes of considerable size have been found by Dr. Hugh H. Young and other operators. Two of our specimens showed hypertrophied anterior lobes, and Kuznitzky found a persistent ventral lobe in one out of every fifteen adult prostates. The total number of prostatic tubules opening into the urethra in the specimen under consideration is fifty-six, which is much greater than that usually mentioned in text-books. The number in six fetuses varied between fifty-three and seventy-four, the average being sixty-three.

TABLE SHOWING NUMBER OF TUBULES OF EACH LOBE OPENING INTO PROSTATIC URETHRA, THE NUMBER OF ALBARRAN'S TUBULES AND THE NUMBER OF SUBTRIGONAL TUBULES

Size of Fetus, Crown-Rump Measurement	Middle Lobe	Lateral Lobes	Posterior Lobe	Anterior Lobe	Total Number of Prostatic Tubules	Subcervical Glands of Albarran	Subtrigonal Glands
7.5 cm.	12	39	11	12	74	0	0
8 "	27	0	0	13	53	0	0
12.5 "	10	46	4	14	74	8	0
19 "	0	42	10	7	59	11	5
27 "	11	36	0	8	55	9	4
36 "	9	34	11	2	56	19	9
Averages*	10	37	8	9	63	12	6

* The averages are taken from the specimens in which the structure is present in case of middle lobe and the group of Albarran and the subtrigonal group.

A study of the embryology of the prostate gland that I have recently completed has brought out the following facts: The prostate begins to develop at the twelfth week of fetal life. It originates from five groups of tubules which begin as solid epithelial outgrowths, and which later develop lumina. These various groups arise from

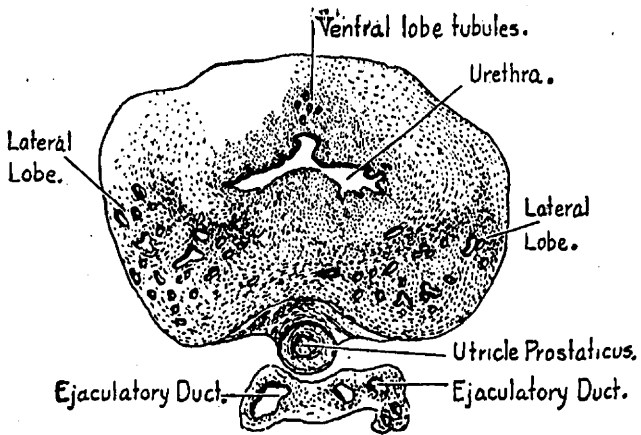


Fig. 3.—Prostate of human fetus (10 cm.) of 5½ months, showing absence of middle lobe.

the floor of the urethra between the ejaculatory ducts and the bladder, from each prostatic furrow, from the floor of the urethra outward from the ejaculatory ducts, and from the ventral wall or roof of the urethra, and become the middle, right and left lateral, posterior and anterior lobes, respectively. The tubules grow, with few exceptions, back toward the bladder, and by the sixteenth week are surrounded by developing muscle fibers which in later stages become quite thickly dis-

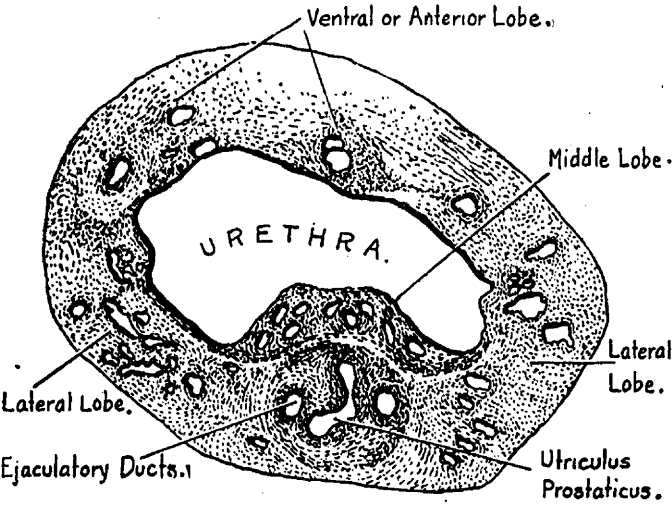


Fig. 2.—Prostate of human fetus (12.5 cm.) at 4 months, showing rather definite separation of the middle lobe from the lateral lobes.

which is palpated by rectum, and presents in the middle of its posterior surface a slight depression which is ordinarily termed the median furrow. This depression in the specimen under discussion is more pronounced in the region of the apex, gradually becomes shallow at the middle of the gland, and at the base assumes a rounded contour. It is produced by transmitted pressure from the lateral lobes. In this case the posterior lobe is made up of eleven tubules which open on the floor of the prostatic urethra anteriorward from the entrance of the ejaculatory ducts, and grow back toward the bladder behind these structures forming the main mass of the apex of the gland.

This lobe is of considerable importance for several reasons. Dr. M. L. Boyd and Dr. J. T. Geraghty in their studies on the pathology of the prostate have found that hypertrophy rarely or never occurs in this part of the gland, and that primary cancer of the prostate rarely or never begins in any other portion. These findings, considered with the fact that the posterior lobe is thoroughly separated from the other portions of the gland by a firm, thick fibrous capsule, suggest the possibility of there being some functional difference between it and the rest of this organ. In doing Young's perineal prostatectomy, operators find it necessary to make their two parallel incisions entirely through the posterior lobe, which in hypertrophy is usually flattened out, owing to increased pressure within the capsule, and the partition between it and the lateral lobes; otherwise the enucleation of the hypertrophied portions is impossible. In case the incisions are made only through the capsule of the gland into the posterior lobe, an attempted enucleation leads the operator's instrument or finger laterally into the outer capsule again where the partition between the posterior and lateral lobes becomes lost in it, and removal of the real offenders in hypertrophy, lateral and middle lobes, is not possible

posed. In early stages the five lobes of the prostate are well separated from one another, but later development decreases the separation between the lateral and middle lobes, although in every case but one, in which the middle lobe was entirely lacking, the independence of these lobes is discernible. The lateral lobes make up the largest portion of the gland. The posterior lobe grows back behind the ejaculatory ducts, and becomes separated from these and the middle and lateral lobes by a plane of connective tissue. The tubules making up the anterior lobe are at first as large as other tubules, and are quite numerous; but at the sixteenth week they are reduced in size, comparatively speaking, and after this time appear to shrink into insignificance. All of the tubules of the prostate seem to be firmly bound together within its capsule with the exception of those of the middle lobe, whose upper ends in some cases seem to extend beyond the capsule, lying freely between the vasa deferentia and the bladder.

There exist in close relationship with the prostate tubular structures which might be called accessory glands. These are the subcervical group described by Albarran,³ and a subtrigonal group, the development of which I have described elsewhere.¹

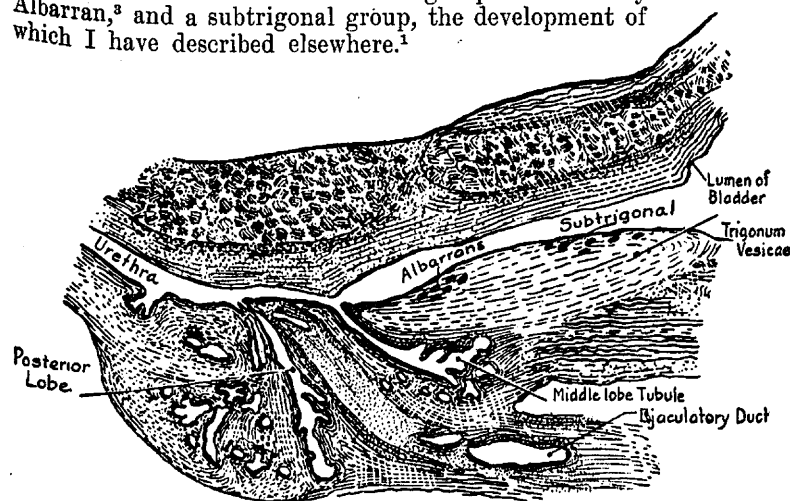


Fig. 4.—Sagittal section of prostate of 16-cm. human fetus of 5 months; X 15.

The subcervical group of Albarran is represented in the specimen of the new-born here described by nineteen simple tubular glands, lined with very small columnar epithelium, which do not extend very far beneath the mucosa. These structures are found in the mucous membrane commencing at about the middle of the vesical sphincter and extending down to its lower border. In a few instances they have smaller branches, some of which extend for a short distance into the musculature of the sphincter. None of these tubules is found in the ventral mucosa of the orifice except in one instance, but there are some very small evaginations in that region which may later develop into tubules of some sort. They are not surrounded by muscular tissue as are the prostatic tubules, but appear to be merely imbedded in the submucous structures. They open for the most part near the middle line on the floor of the urethra, but a few open in the angular depressions at the sides of the urethra which mark the beginnings of the prostatic furrows. Previous study on fetuses has shown that this group makes its appearance at the sixteenth week, being found in all specimens older than that, and in one case in the mucosa of the ventral wall of the urethra as well as the posterior. The position in which this group occurs is of the utmost importance because urologists

have found that a slight enlargement at this point causes grave obstruction to the passage of urine, more in fact, than great hypertrophy of any of the prostatic lobes, because the tubules grow back directly within the sphincter.

In the mucous membrane at about the middle of the trigonum vesicae are found nine delicately constructed tubules which are recognized as the subtrigonal glands. Most of them are simple tubules which extend down to the muscle, but a few of them have one or two small branches which extend for a short distance into the musculature of the bladder wall. The blind ends of these tubules are a little closer to the base of the trigone than their mouths. In the series of fetal prostates studied the subtrigonal glands were not found in any of the specimens younger than 20 weeks, but were found in all of those older than 20 weeks. They are apparently insignificant, but as in the case of the subcervical group occupy a strategic position. Cases have been observed by Dr. Hugh H. Young, Dr. John T. Geraghty and other surgeons in which this group of tubules had become enlarged, and a further growth had caused them to become almost free in the bladder lumen, being connected to the original site by a small pedicle. On attempted urination this globular mass would fall into

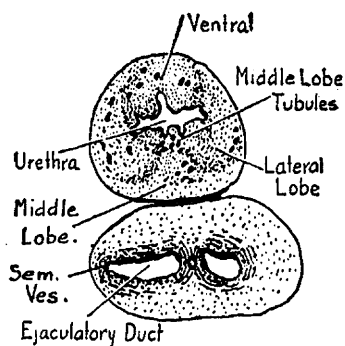


Fig. 5.—Prostate of human fetus (7.5 cm.) of 3 months; X 20.

the orifice of the urethra, and blocking it would cause more obstruction than an enormous adenomatous prostate.

In the mucosa of the prostatic urethra at the region of the apex of the gland and in the urethral mucosa just below this point there are noticed numerous tubular structures which are easily differentiated from prostatic tubules, being much smaller in size, having fewer branches, and lacking the muscular coats of the latter. The entire structures are contained within the muscular walls of the urethra, and their ducts open into it on all sides. These tubules are considered to be glands of Littré, and while numerous just below the apex of the prostate are comparatively few in number lower down in the urethra.

The seminal vesicles are made up of five divisions on each side; their walls are almost as thick as those of the vasa deferentia, and their uppermost ends reach a point behind the bladder and on a level with the base of the trigone. The lumina of these several divisions communicate lower down, the whole structure consisting of a main part which is convoluted and from which four short convoluted branches grow out as described by Pallin.⁴ They connect with the ejaculatory ducts just below the point where they become imbedded in

3. Albarran: *Maladies de la Prostate*, 1902, p. 520.

4. Pallin, Gustaf: *Arch. f. Anat. und Pchthol.*, 1901.

the musculature of the prostate. The ampullae of the vasa deferentia are easily distinguishable in this specimen, and are marked by a considerable widening and great increase in the size of the lumen.

A study of the embryology of the seminal vesicles discloses the fact that they begin to develop at the thirteenth week as lateral evaginations from the vasa deferentia, being surrounded by the same tissue that envelops the latter structures. They grow backward and laterally, their lumina becoming large and convoluted with branches as described above, and their openings into the ejaculatory ducts comparatively much smaller.

The ejaculatory ducts surrounded by their thick muscular walls, which become intermingled one with the other, lie quite close together in their passage through the prostate. Their course through the gland is interesting. They begin well within the tubular region of the prostate by the junction of the vasa deferentia and the seminal vesicles. They pass anteriorly on a gradual slant, assuming much the same direction as the middle lobe tubules until they reach the verumontanum, at which point they turn sharply and run almost parallel with the axis of the urethra for a distance equalling one-half of the length of the verumontanum. They then turn sharply lateralward and empty on the sides of the verumontanum; their lateral openings, which seem to be protected by a small valve-like membrane, make for an effectual closure of their outermost portions in the case of distention of the posterior urethra from any cause; this probably accounts for the fact that few posterior urethral infections are transmitted through the ejaculatory ducts to the seminal vesicles and epididymides.

The utriculus prostaticus is found in the uppermost or bladderward portion of the verumontanum. It runs parallel with the long axis of the urethra for a short distance, and then the main part of it ascends rather abruptly toward the crest of the verumontanum, while a small part of it continues on for a little way in its original direction. It opens through a rather large mouth in the middle line at the summit of the verumontanum, a considerable distance above the mouths of the ejaculatory ducts, which is an unusual arrangement, as in nine fetuses this structure opened immediately below the openings of the ejaculatory ducts. There is no evidence in this or in any of the other prostates studied that either the ejaculatory or the prostatic ducts open into the utricle.

The utriculus prostaticus is found in the 13-weeks-old fetus, being observed as a small tube between the vasa deferentia. In all specimens older than 22 weeks the utricle appears only in the verumontanum, which is formed by the growing in and further development of the ejaculatory ducts, and the utricle, as shown in Figure 2.

I wish to express my sincere thanks to Drs. Hugh H. Young, Franklin P. Mall and E. R. Clark for the use of material at their disposal and for many valuable suggestions. This research was done in the anatomic laboratory of the Johns Hopkins University.

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ABSTRACT OF DISCUSSION

DR. HUGH H. YOUNG, Baltimore: Dr. Lowsley's work was undertaken at my suggestion. I felt that the literature in regard to the embryology and histology of the prostate was very much at sea. This material which he has presented represents a tremendous amount of work. Dr. Lowsley kept at it for about a year and a half, almost every day, and the formation

of this wax reproduction of the prostate is masterly. I think that he has solved some interesting and troublesome problems in regard to the prostate. We have known for a long time that in doing a perineal prostatectomy an incision merely through the capsule very quickly leads one entirely outside of the prostate. Further investigation showed that it was necessary to cut a certain distance, from 5 to 8 mm., before the real capsule of the prostate was reached, there being an entirely separate and distinct fascia. Dr. Lowsley has demonstrated why in the pathologic prostate we find the conditions we do and how essential it is to observe them during operation.

We have now seen twenty or thirty cases in which hypertrophy was associated with carcinoma; we have found hypertrophy of one part and carcinoma of the other. The two have gone hand in hand, and absolutely distinct, and the capsulation of this lobe is often so distinct as to prevent the invasion of the carcinoma. The carcinoma would involve the seminal vesicles and ejaculatory ducts without involving the lateral lobes. We have also seen at operation a number of anterior lobes. Dr. Lowsley's demonstration that there is a peculiar ventral group of glands which later on may atrophy, but which is constant in the new-born, is an interesting explanation of it. His division of the various parts of the prostate is, I think, original and very important, especially the trigonal group as separate from the middle lobe, and I think a great many of the mooted questions of prostatic hypertrophy will be solved. There is certainly a great deal of doubt now as to how these things do develop.

A CASE OF BILATERAL URINARY LITHIASIS

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This case is of sufficient interest to be reported because of the following facts:

1. The long interval between the present symptoms for which the patient sought relief, and the original onset of his trouble—sixteen years.
2. The necessity of subjecting patients to a radiographic examination of both kidneys and both ureters although the symptoms at the time of examination may be unilateral.
3. The value of the shadowgraph catheter in the diagnosis of ureteral calculi.
4. The fact that in this case the only pain of which the patient complained was right-sided, yet he had bilateral calculi in the upper urinary tract.
5. A simultaneous right-sided ureterotomy for stone and a left-sided nephrectomy.

REPORT OF CASE

Present History.—The patient states that he had always been well until February, 1911, at which time he passed bloody urine for about two days. The urine then remained clear until April, 1911, when he had a second attack of hematuria which lasted for twenty-four hours. These are the only two attacks of hematuria which he has had. The blood was well mixed with the urine. The hematuria was painless. There were no urinary symptoms, no frequency, no pain.

Pain in the back had been present only for the past eight hours. The pain was localized in the region of the right kidney, mostly posteriorly, and it did not radiate into the bladder, testicles, scrotum or penis.

Previous History.—At the age of 17 he lifted a heavy weight which was followed by pain in the back on the right side. This was not very severe and remained localized in the right kidney. At the age of 21 the patient entered the Greek army,