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Original Communications

DIFFUSE ADENOMYOMA OF THE UTERUS: CONDITIONS INFLUENCING ITS DEVELOPMENT*

BY OTTO H. SCHWARZ, M.D., AND F. POWELL MCNALLEY, M.D.,
ST. LOUIS, MO.

From the Department of Obstetrics, Washington University School of Medicine.

ADENOMYOMA forms one of the most interesting chapters in gynecologic pathology. Its distribution and classification, both uterine and extrauterine, have recently received much attention. Of all types of adenomyoma there is none so common as diffuse adenomyoma of the uterus, and the frequency of the lesion can only be realized by those who study uteri from a microscopic standpoint. When one examines a stained section of uterine wall in which there are present numerous penetrating islands of uterine mucosa several questions immediately present themselves. Several of these are most important. First: What is the origin of the glands? Secondly: What is responsible for their presence in this abnormal situation? Thirdly: What is the nature of the diffuse thickening of the uterine wall and what are its chief characteristics? Fourthly: Is it a tumor, or how should it be classified?

The question as regards the classification of the lesion, particularly whether it deserves the name of tumor or whether it should be considered as a type of hyperplasia has received considerable attention. As a result of various views, apparently the same lesion has been assigned several different terms. Frankl, in 1914, points out that adenomyoma is frequently confused with so-called adenometritis,

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adenomyositis, adenomyometritis and adenoma diffusum. He suggests that the term adenomyoma should be reserved for those lesions which are definitely circumscribed and contain glands; adenometritis for those conditions in which the diffuse thickening with its contained glands is associated with inflammation, which Robert Meyer feels is the basis of explanation for most cases. Frankl states that he has seen cases in which there was absolutely not the slightest evidence of inflammation and suggests the term adenomyosis for such cases.

Strong, of New York, in a recent paper, discusses the same question and points out similarly the shortcomings of the term adenomyoma, and although the title of his paper is adenomyometritis, not adenomyoma, he does not suggest adenomyometritis for general application. Strong also refers to irregular penetrations of the uterine glands of the basalis into the myometrium. He tells us that these are quite common and are most important because they have a distinct bearing on the causation of so-called adenomyoma. These penetrations according to this author, are present to a greater or lesser degree in all uteri, and are extensive in proportion to the amount of inflammation, hyperplastic, or sometimes atrophic change that is present in the endometrium or the myometrium. It has been our experience also, that the endometrium has a very definite tendency to penetrate the myometrium in a large percentage of cases. This is strikingly brought out in the routine microscopic study of uteri removed at operation. Our experience has been that this occurs to a more marked degree in uteri of women that have borne children. Just how extensive this penetration should be, as to whether it should be disregarded or the lesion classified as a so-called adenomyoma is difficult to say. Perhaps an additional factor to consider would be the reaction of the myometrium in the vicinity of this penetrating tissue, in other words, the degree of the myometrial hyperplasia.

It is not our purpose in this paper to review the various theories as regards the origin of the glands in adenomyoma. First, because Lockyer has done this so ably in his recent monograph, and secondly, because we are not dealing with adenomyoma as a whole, but have confined our study only to the diffuse type of the uterine wall.

Although earlier there was a good deal of discussion as regards the origin of the glands in diffuse adenomyoma of the uterus, at the present time the mucosal origin which was first suggested by Cullen and definitely proved by him, is generally accepted. Frankl, in 1914, states other sources of origin for this type of lesion need scarcely be considered. Lockyer in his recent comprehensive review of adenomyoma, discusses at great length the etiologic theories which have been suggested and emphasizes particularly Cullen's mucosal theory. Of particular interest in this connection is the abstract which he gives of

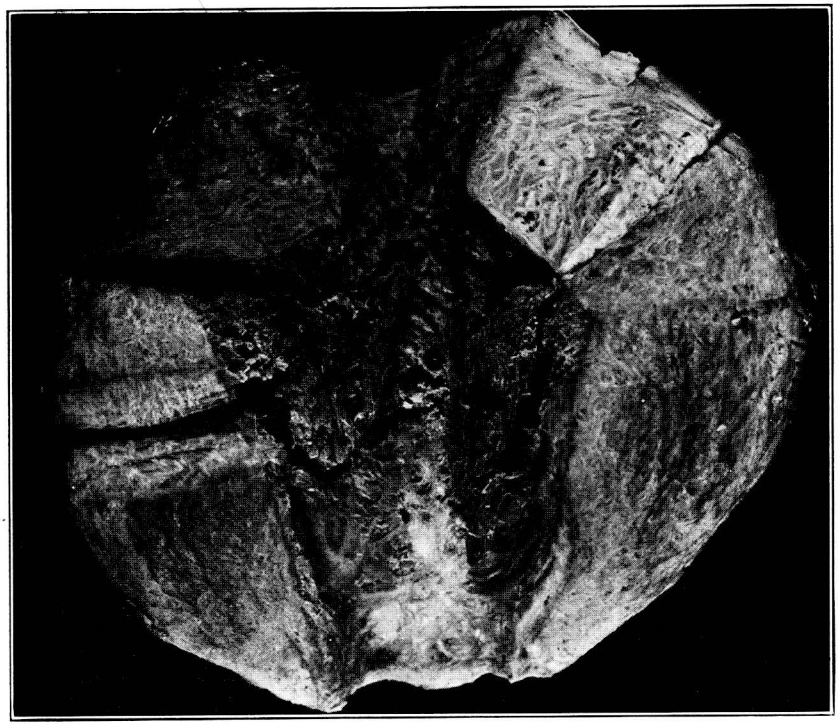

Fig. 1.—Diffuse adenomyoma associated with hyperplasia of the endometrium. Case 1299. Nulliparous uterus, supravaginal portion. Marked diffuse thickening of uterine wall—numerous dilated glands present in uterine wall in upper right portion. Only slight penetration in lower half. Marked hyperplasia of the endometrium.

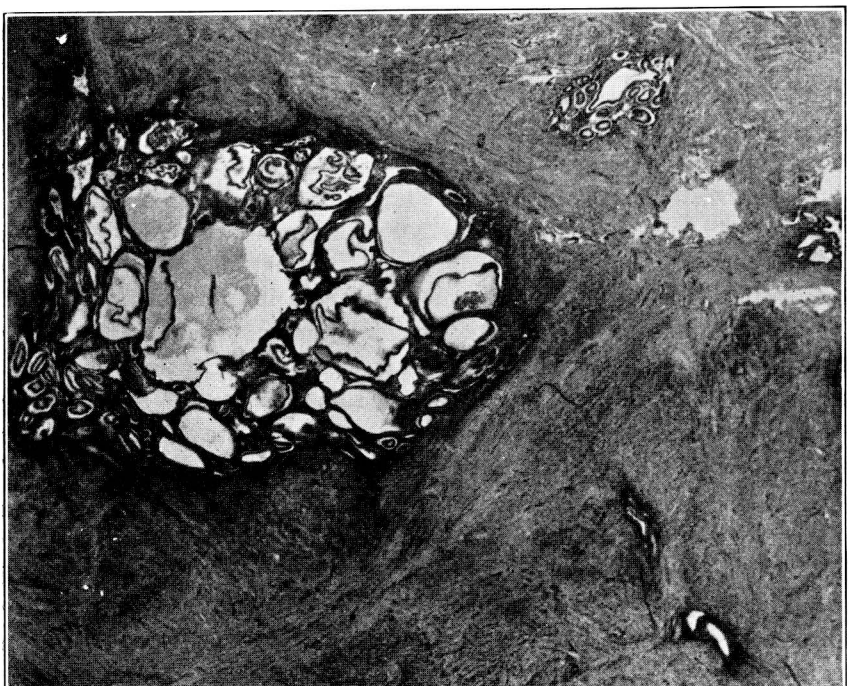

Fig. 2.—Section taken from upper right portion of Fig. 1. Shows numerous glands similar to glands in hyperplasia of the endometrium, which was very striking in this case.

Robert Meyer's latest views regarding the causation of uterine adenomyoma. Meyer tells us that the mucous membrane sends hyperplastic and hypertrophic glands into the uterine muscularis. While the surface layers as a rule are not hyperplastic, and frequently even atrophic, according to Meyer these bits of invading mucosa follow the muscular interstices and the lymph vessels, but do not penetrate the lymph spaces. The invasion, he states, is postfetal, and is a disease of the adult uterus. In this connection Meyer studied one hundred uteri from fetuses, newborn, and girls up to fourteen years of age, and stated that the mucosal projections are seldom seen, and when they do occur it is only singly. We, personally, have examined a great number of similar uteri but have never been impressed with any definite tendency of the endometrium to penetrate the myometrium in such cases. It is quite characteristic of the endometrium of the fetal uterus of about thirty-six weeks' gestation to show only a few layers of cells lining the cavity, from which are differentiated the endometrium, both stroma and uterine glands. There is usually at this time of development no evidence of gland formation. Meyer feels that the invasion of the mucosa is favored by the absence of a true submucosa in the uterine wall and suggests that as a result, mechanical lesions such as might occur after therapeutic means, gestation and inflammation, the intrafascicular connective tissue is incapable of resisting the entrance of the mucosal element.

Cullen, in his elaborate monograph of 1908 on uterine adenomyoma, discusses the question of the causation of diffuse adenomyoma in one short paragraph. He mentions that probably pregnancy with its incident extensive stretching of the uterus might leave crevices in the uterine wall into which the mucosa could later flow. He states, however, that fifteen out of forty-nine patients were never pregnant, and with pregnancy as a possible factor, other causes must be considered for the appearance of the lesion in the nulliparous uteri. Cullen remarks that a number of cases gave a decided impression that the diffuse myomatous growth was the primary factor. He refers to this as a myomatous tendency by the almost constant presence of discrete myomatous nodules in these cases. He emphasizes the fact that the only pathological change in some cases lies in the extension of the normal glands into crevices throughout the diffuse myomatous growth.

Novak, in a recent paper, mentions the fact that hyperplasia of the endometrium is frequently associated with myoma of the uterus, but even more frequently with adenomyoma. Novak's statements made in a discussion of Dr. Cullen's latest paper on the distribution of adenomyoma are of considerable interest in connection with conditions influencing the occurrence of adenomyoma. Novak has been struck with the relationship which appears to exist between adenomyoma of the

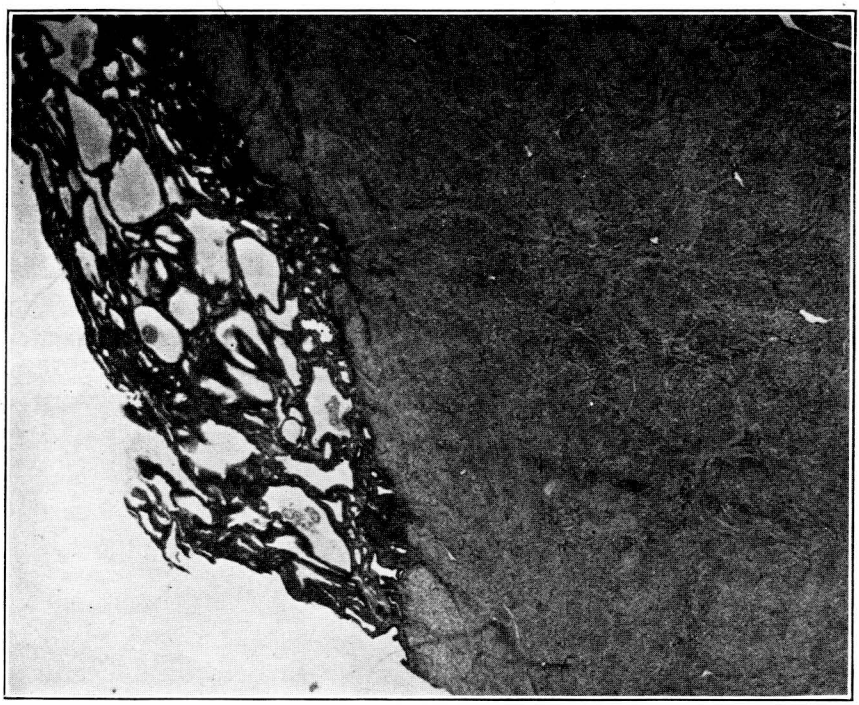

Fig. 3.—Section taken from lower left portion of Fig. 1. Marked hyperplasia of endometrium, shows only a slight tendency to invade. Hypertrophy of myometrium.

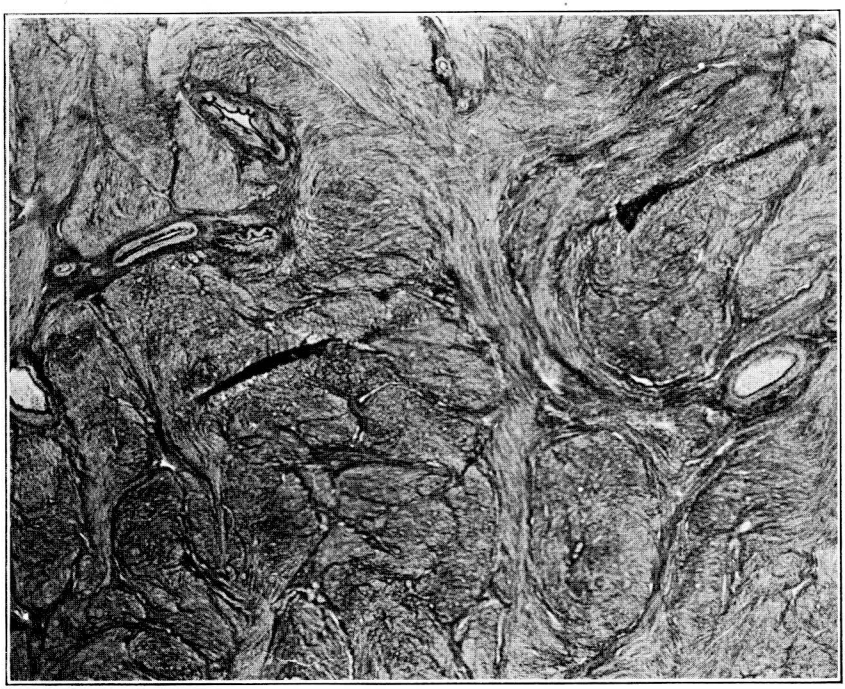

Fig. 4.—Myometrium, higher power; same area of myometrium from which Fig. 3 was taken; orcein-Van Gieson stain. Shows nulliparous distribution of elastic tissue. The internal elastic membrane of the arteries stands out well in this picture. The connective and muscle tissues show prominently. The connective tissue is the fine darker tissue between the lighter muscle bundles.

uterus and the condition known as hyperplasia of the endometrium. He points out that hyperplasia of the endometrium was first accurately described by Cullen in 1900. In many cases of adenomyoma of the uterus, according to Novak, the mucous membranes, both of the surface and deep down in the muscular tissue, show the characteristic pattern of hyperplasia. He mentions that both these conditions are characterized clinically by extensive menstruation, and the apparent connection between the two conditions suggests various interesting possibilities. Hyperplasia of the endometrium, as the term indicates,

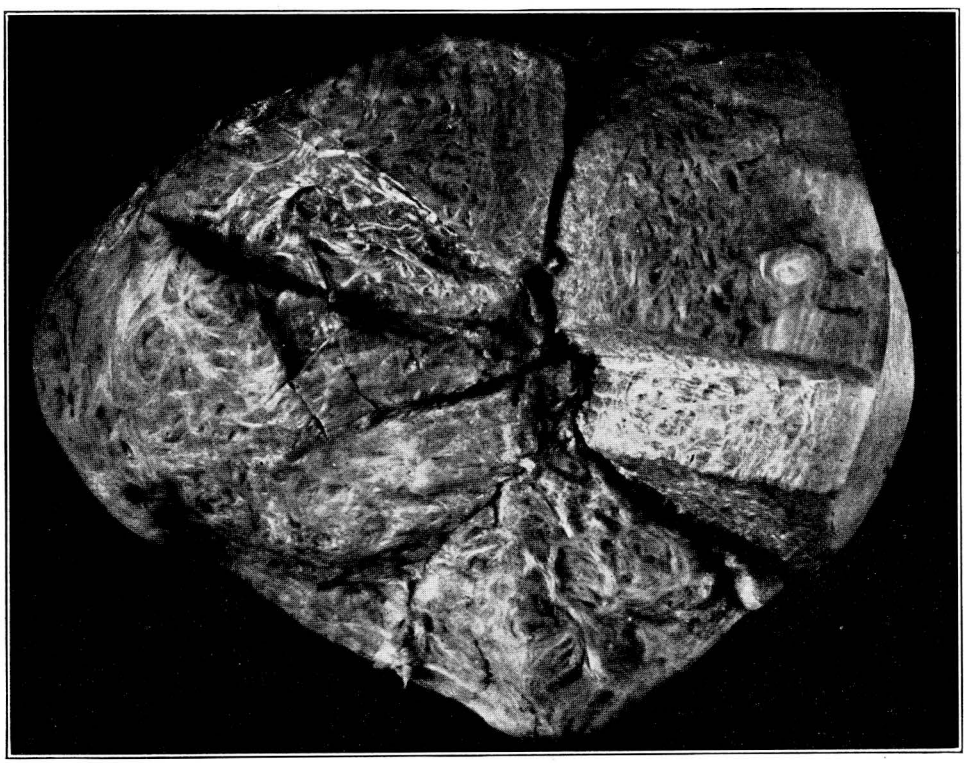

Fig. 5.—Diffuse adenomyoma associated with hyperplasia of the endometrium. Case 1323—similar to Case 1299 except for one full term pregnancy. No evidence of subinvolution. Marked hyperplasia of the endometrium. Marked diffuse thickening of the uterine wall throughout. Lowest portion of the uterus to right—fundus to left.

is characterized by a genuine increase in epithelial and stromal elements of the endometrium, while adenomyoma, in a broad sense is a hyperplasia of the muscular element. Novak feels that both may be produced by the same underlying cause. He calls our attention to the fact that in recent German literature the inflammatory theory of origin is by far the most popular. This is particularly emphasized as regards the causes of adenomyoma of the recto-vaginal septum. He closed by stating that he merely mentioned these facts in order to lure

Dr. Cullen into a discussion of the cause of these interesting lesions. In closing Dr. Cullen merely stated that the cause of adenomyoma is unknown and that there is no evidence that it is due to inflammation as has been suggested by numerous observers.

We feel rather strongly, that on account of the fact that there has been considerable confusion as regards our knowledge of pathological lesions of the uterine wall, that conditions, if any, favoring the development of diffuse adenomyoma would likewise be more or less confused. In our opinion, however, the recent work of Shaw has definitely cleared up certain types of lesions of the uterine wall. Shaw discusses

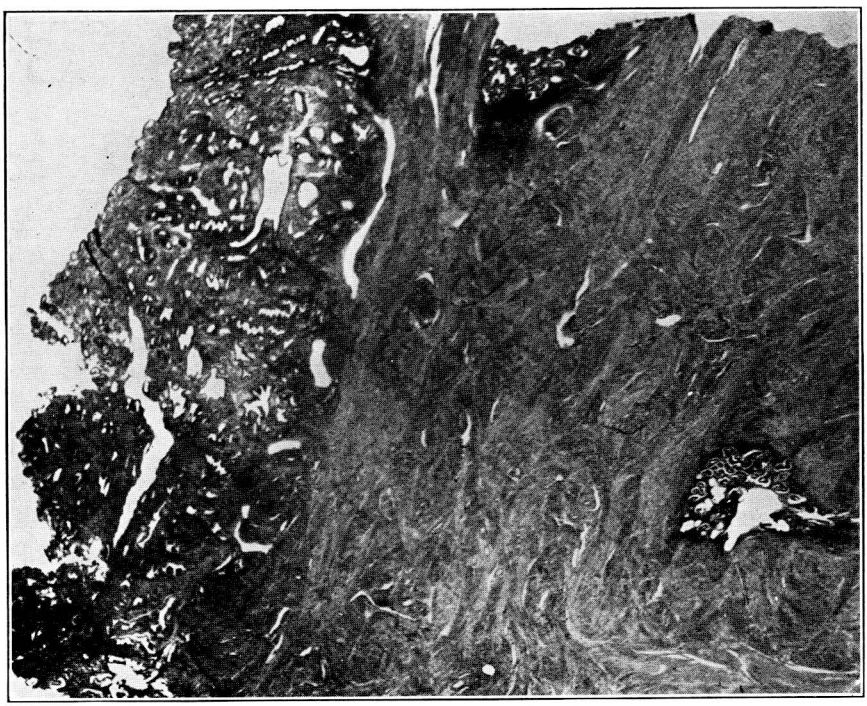

Fig. 6.—Case 1323—low power; showing hyperplastic endometrium and penetration of glands. Structure of myometrium similar to Case 1299, except separation of muscle bundles are more prominent and myometrium coarser looking in the gross.

three lesions, namely, chronic subinvolution, chronic metritis and hypertrophy. Briefly, chronic subinvolution consists of subinvolution of the circulatory system characterized by a diffusion of dead elastic tissue around the walls of the arteries. This material in addition contains unabsorbable portions of the old vessels, a smaller and newer vessel having developed within the old lumen. The veins, particularly the larger ones in the middle third, show a marked increase in this diffused elastic tissue, which has a tendency also to be present between the muscle bundles directly adjacent the veins. Reduplications of the internal elastic membrane in the larger arteries are also a striking

Fig. 7.—Case 1790. Diffuse adenomyoma associated with myomata. Nulliparous uterus. Note the diffuse thickening in the extreme upper portion of the picture.

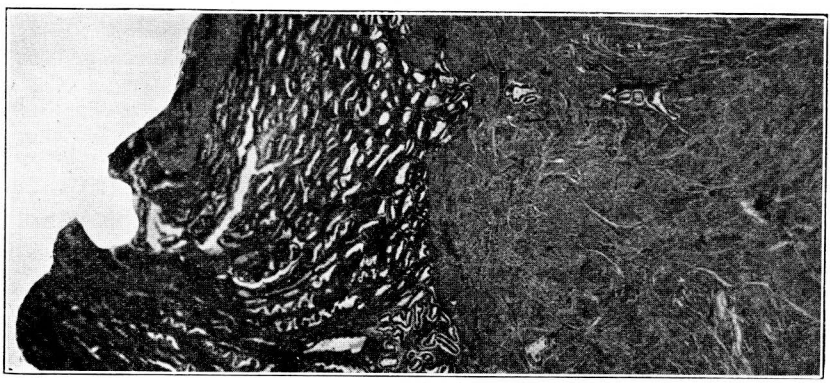

Fig. 8.—Case 1790. Section from area of diffuse thickening in upper portion of Fig. 7. Includes endometrium, which shows definite hyperplasia, and myometrium with several invading glands. Note the definite separation of the muscle bundles.

feature. In the outer third of the uterus between the muscle bundles there is present also a definite increase of this black stained tissue, which, in some instances, is quite excessive. More or less edema is also constantly present. Chronic metritis is a lesion which results from previous active inflammatory process within the uterine wall, and is characterized by a definite increase in connective tissue and small round cell infiltration in the myometrium. If this lesion is present of itself the uteri in most instances are not particularly enlarged and the walls are usually quite firm and cut with considerable resistance. Hypertrophy of the uterine wall is characterized by an increased thickness due to both hypertrophy and hyperplasia of the muscle cells and connective tissue of the uterine wall. This condition is in the nature of a work hypertrophy and, perhaps, is somewhat analogous with hypertrophy of the myocardium under certain conditions. Hypertrophy is chiefly associated with hyperplasia of the endometrium, myomata and also forms a part of the lesion of adenomyoma even to a more marked degree.

Three years ago one of us confirmed the work of Shaw, except that we felt that there was more overlapping of these conditions than his descriptions lead one to believe. Shaw, in a personal communication, referred to this article not as a criticism of his work, but stated that there was very little difference between this work and his, and suggested that it was due rather to the difference of conditions under which the articles were written than to any real difference of view. At the time Shaw wrote his article he used one heading, namely, chronic metritis, and placed the three above mentioned lesions under this one title. He mentioned the fact that the rigid classification which he adopted was due to the fact that he had to emphasize these very distinct types, but realized that there was frequently distinct overlapping. In our opinion Shaw clears up a rather confused subject which should result in the abolishing of a large list of terms referable to lesions of the myometrium.

We know that myomata and hyperplasia of the endometrium frequently accompany diffuse adenomyoma. We felt that a study of a series of cases in which particular attention would be paid to the presence of the conditions described by Shaw, in addition to the presence of myomata and hyperplasia, might lead us closer to an explanation of why the mucous membrane of the uterus penetrates the uterine wall in the lesion of so-called adenomyoma. We, of course, consider that the mucosal origin of the glands in this type of case is proved. This has been shown by serial section, and has been particularly emphasized by Dr. Cullen. Further, because in the early lesions it is very easy to see the connection with the mucosa in almost any single section. We have recently modeled the penetrating islands of mucosa in order to

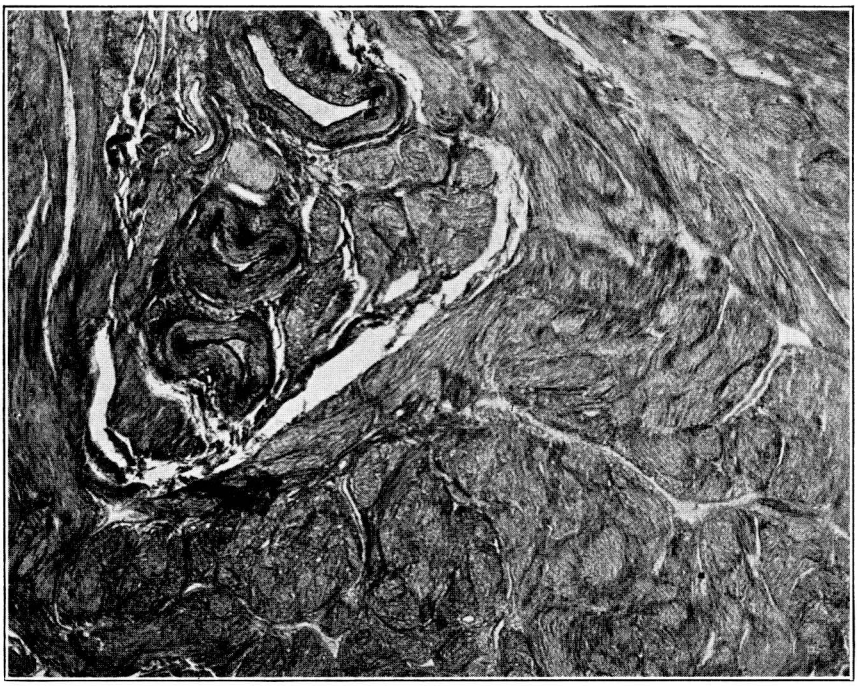

Fig. 9.—Case 1790. Myometrium (orcein-Van Gieson stain) higher power; shows a loose structure, muscle and connective tissue both prominent; nulliparous distribution of elastic tissue. The internal elastic membrane of the arteries stands out clearly; no other elastic tissue evident in the picture.

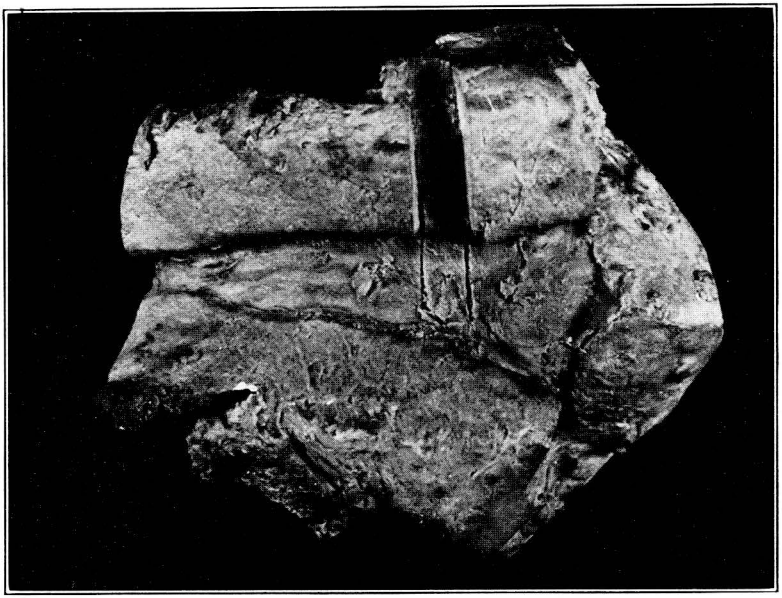

Fig. 10.—Diffuse adenomyoma of the uterus associated with chronic subinvolution. Case 480. Supravaginal uterus—wall 22 mm., thick, endometrium 1 mm. Diffuse thickening not prominent. Penetration of glands over 1 cm., in myometrium in places.

definitely show the relation to one another and also to the endometrium. Mr. Wm. D. Dieckmann prepared this model in the Obstetrical Laboratory. The model shows very clearly the tendency of the mucosa to invade the myometrium; it also shows how the islands communicate with one another. A large portion of the model, however, could be connected to the endometrium only by a very small strand of mucosa, and we have refrained from publishing this work hoping to use a case which shows the connecting links to a more marked degree.

The fact that we rather frequently made a diagnosis of early adenomyoma of the uterus in routine work caused us to become particularly interested in these early cases. We were also particularly interested in the circumstances under which these lesions started, and in the chief characteristics of the myometrium in these cases.

This paper includes the study of forty-nine uteri in which the lesion of adenomyoma exists, apparently, of itself, or coincident with other lesions. The material for this study was chiefly obtained from the Barnes Hospital. However, we are indebted to H. S. Crossen, Lee Dorsett and George Ives for a considerable number of cases. These were divided into two groups. The first group were those cases in which a definite diagnosis of adenomyoma could be made, the lesion, however, still comparatively early. The second group were those cases in which the lesion was well advanced. In the first group there were twenty-three cases and in the second group there were twenty-six cases. These cases were carefully described in the gross, and celloidin sections were studied, stained with hematoxylin and eosin and also with orcein and Van Gieson's stain. The clinical histories were available in all but four of these cases. Careful attention was paid to the presence of hyperplasia of the endometrium, chronic subinvolution, chronic metritis, hypertrophy and myomata.

The hyperplastic myometrium which is present more or less marked in most cases of adenomyoma attracted our attention first. We shall briefly mention some of the impressions that this study made. In the first place the tissue involved has more the characteristics of hyperplasia than of new growth. These lesions of themselves do not reach the limitless growth that the ordinary discrete myomata do. If they reach any considerable size it is due to a dilatation of the contained glands rather than the result of any enormous hypertrophy of the uterine wall. The hypertrophy of the wall is due both to hypertrophy and hyperplasia of the connective tissue and muscle tissue of the uterine wall. This in the gross appears very much coarser than the normal, and in the gross the individual muscle bundles appear much larger. The amount of connective tissue varies. In almost all cases it is definitely increased. This is most striking, perhaps, in the cases in which intramural myomata are associated with the lesion.

This is prominent in both parous and nulliparous uteri. It is also quite marked in cases which are accompanied by hyperplasia of the endometrium. With this condition the connective tissue content of the wall seems to be more prominent in cases in which the patient had

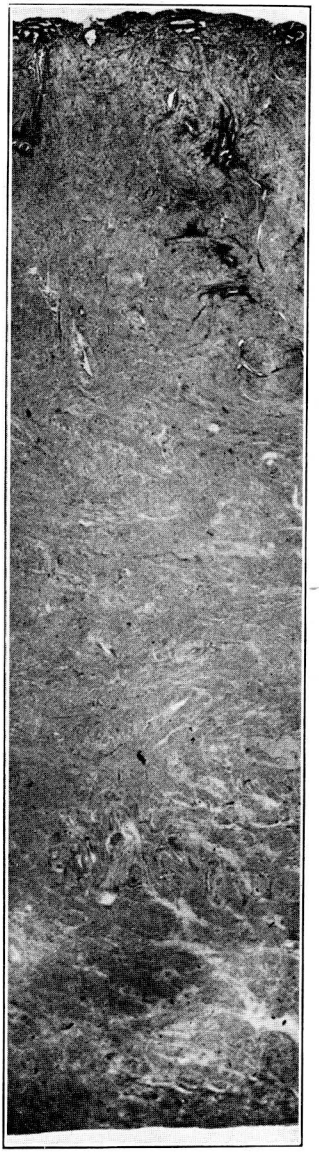

Fig. 11.—Case 480. Entire wall—low power—Hematoxylin-eosin stain. Shows an atrophic endometrium with glands penetrating one-third of the distance to the serosa.

Fig. 12.—Case 480. Same field as Fig. 11. Orcein-Van Gieson stain. Marked evidence of subinvolution throughout wall, collars of diffused elastic tissue about arteries of inner third, marked amount of diffused elastic tissue between muscle bundles of outer third.

had no children, or, perhaps only one. The same fact may be noted in ordinary hypertrophy of the uterine wall in the absence of adenomyoma. The connective tissue increase is less conspicuous in cases which have had numerous pregnancies and where the invasion of the glands is not particularly marked. In such cases also the entire thickness of the uterine wall may not be markedly increased. It is also quite clear that the increase in connective tissue is in no way referable to the inflammatory process such as we see in chronic metritis because we see no accompanying round cell infiltration in this hyperplastic tissue. We do not recall a clear cut case of chronic metritis which

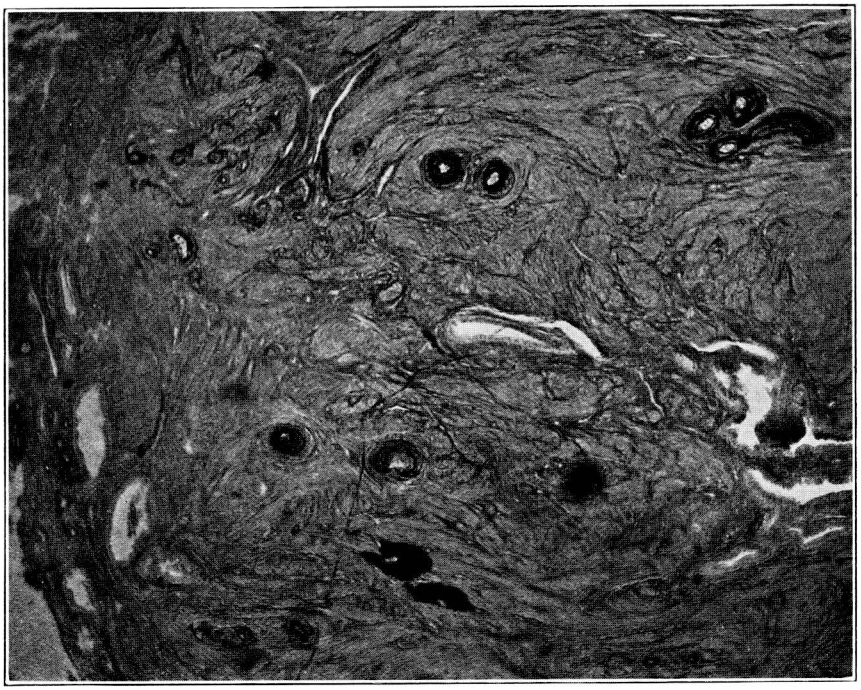

Fig. 13.—Same as Fig. 12. High power. Extreme upper left portion. Shows black collars about numerous arteries; also prominence of connective tissue associated with hypertrophy of the wall.

did not show some definite round cell infiltration in the myometrium.

The individual cells of both muscle and connective tissue are usually somewhat enlarged but are in no way suggestive of being atypical or tumor cells. We have never observed any evidences of degeneration in this tissue. This is in striking contrast to ordinary discrete myomata. This increased connective tissue relation is present in the early lesions and the point which differentiates this tissue from that of early myomata which are noted for their lack of connective tissue in early stages of their development. We have had the opportunity recently to observe the uterus of a nineteen-year-old girl which was

riddled with countless small myomata, from microscopic size to as large as 5 mm., none larger. The absence of fibrous tissue in the smaller tumors was quite striking. Comparing these young tumors with the myometrial hyperplasia of ordinary adenomyoma suggests very strongly that their origin has nothing particularly in common and suggests an origin outside of the muscle or connective tissue of the uterine wall. This strongly suggests the origin from blood vessels, as some writers point out. Our case also points strongly to this source. Dorsett and one of us will report this case in detail at a later date.

In short the condition of the myometrium is a definite hyperplasia of all its constituents quite similar to the lesion of ordinary hypertrophy of the uterine wall. This hyperplasia may be present primarily as a result of the presence of discrete myomata, or due to an accompanying hyperplasia of the endometrium; it may be considered a work hypertrophy. In other instances the glands may invade the myometrium primarily and the hyperplasia result from the presence of the glands, and may be considered an expression on the part of the uterine wall to rid itself of the invading tissue. This involves particularly cases in which subinvolution is the only accompanying lesion.

In classifying the forty-nine cases which were selected in this study, seven groups were arranged. They consisted of groups in which chronic subinvolution, hyperplasia of the endometrium and myomata existed alone; the remaining four groups representing various combinations of these lesions. In the group where subinvolution was present alone there were placed twelve cases. The striking feature of the chronic subinvoluted uterus was very marked in all of these cases with one exception in which it was quite definite. Chronic subinvolution occurred in combination with hyperplasia of the endometrium in eleven cases; in five instances chronic subinvolution and myomata were present and in six instances there was a combination of chronic subinvolution, myomata and hyperplasia. There were four cases in which hyperplasia occurred alone—in each of these instances the hyperplasia was very striking. Two of these cases were classified as early adenomyoma (one perhaps questionable) and the other two were very well advanced cases. Hyperplasia occurred in connection with myomata in five instances—in four of these cases it was quite striking and very definite in the fifth. Myomata occurred alone in six cases. The cases of the last group as a whole were uteri which were studded with numerous small myomata, many nodules being between ½ and 3 cm. in diameter, just the type of uterus in which the accompanying hyperplasia of the myometrium is most strikingly seen. In thirty-four instances subinvolution was present of itself or with these various combinations. Hyperplasia was present of itself or in combination with other lesions in twenty-six cases. Myomata were present of

Fig. 14.—Diffuse adenomyoma with marked chronic subinvolution. Case 1984. Section of inner third of uterus—low power—hematoxylin-eosin stain. Endometrium atrophic. Note the marked irregularity of the endometrium with very marked penetration of strands of mucosa in numerous places; also the numerous blood vessels with thickening walls.

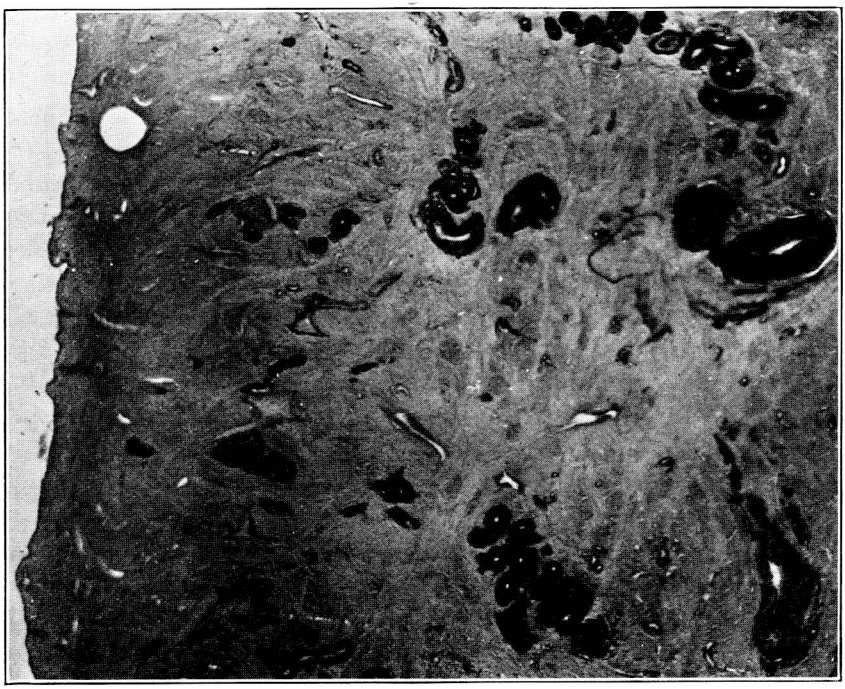

Fig. 15.—Same as Fig. 14. Orcein-Van Gieson stain. Almost every artery in the field shows the characteristic black collar of chronic subinvolution. No hypertrophy of myometrium.

themselves or in combination with other lesions in twenty-one instances. In every one of the forty-nine cases it was possible to place the case under one of these headings. It is readily seen that subinvolution and hyperplasia are by far the most frequent accompanying lesions in this series, subinvolution alone and in combination with hyperplasia occurring in twenty-three cases, and in forty-three cases either one or the other of these lesions existed. In six cases myomata alone were present and in five out of these six cases the patient had borne children. There was not sufficient evidence microscopically of chronic subinvolution but enough to stamp them as parous uteri.

Clinical histories were obtainable in all but four cases; in two or three others it was incomplete. We were particularly interested in the frequency of menorrhagia. In these forty-nine cases there was a definite history of menorrhagia in thirty-one instances. In the chronic subinvolution cases alone out of the twelve cases there were eleven with complete histories, of which six gave a history of menorrhagia. In the cases where subinvolution and hyperplasia existed, histories were obtainable in eight out of eleven cases; in six cases there was a definite history of menorrhagia, in one case the information was doubtful and in another it was negative. In the case of doubtful history the hyperplasia was fairly striking, whereas in the case which was negative there was only a moderate hyperplasia. In five cases of subinvolution and myomata the history was complete in four, of which two were positive for menorrhagia and two were negative. In the cases where all three lesions occurred there were four positive histories and two negative histories as regards increased menstrual flow. In one of these cases the lesion was quite moderate and in the other it was not particularly striking. In the cases of hyperplasia alone there was marked menorrhagia in all four, two of these being nulliparous women, one uniparous and the fourth having had two full term children. In the five cases in which hyperplasia and myomata were present together the history was complete in four cases and showed menorrhagia in all four instances. Where myomata occurred alone four out of six cases had menorrhagia and two gave negative histories.

This résumé as regards the frequency of hemorrhage associated with cases of adenomyoma seems to us to show that those cases which are combined with hyperplasia of the endometrium are most apt to show a definite history of menorrhagia. This is so in our series of which there were twenty-six cases, in all but three instances. In two of these instances the lesion was not particularly striking and in the third instance in which it was fairly striking there was some doubt about the history. It also shows that the cases associated with subinvolution alone or in combination with myomata may quite frequently not be

associated with menorrhagia. Two cases with myomata alone showed no increased bleeding.

So we feel we can say that adenomyoma of the uterus may or may not be accompanied by profuse menstruation. The largest percentage of adenomyoma which consistently gave a history of menorrhagia are found to be accompanied by hyperplasia of the endometrium. We feel that this series shows very strikingly that adenomyoma is very clearly accompanied by other uterine lesions. We thought, however, that a series of forty-nine cases, a few of which were quite early, could not be considered too seriously. We, therefore, thought it a good plan to go over the cases of diffuse adenomyoma of the uterus in Cullen's monograph and see how many could be placed more or less definitely according to the accompanying lesions. This, of course, was difficult because one could not study cases of subinvolution with a special stain. However by placing all cases which showed no other lesion and had a definite history of having had full term children under the heading of subinvolution fairly accurate conclusions could be drawn.

In going over the cases in Cullen's text book, there were forty-seven cases of diffuse adenomyoma, which we reviewed. The placing of these cases in definite groups as in the series just described is obviously difficult and perhaps in a few instances inaccurate, but we felt, perhaps, some comparison and some conclusions could be drawn. There were four cases which were not classified according to this scheme:—Three of these gave no history, and the fourth will be considered by itself. The remaining forty-three cases were placed as follows: Subinvolution alone, five; subinvolution and hyperplasia of the endometrium, four; subinvolution with myomata, five; subinvolution with both myomata and hyperplasia, four; hyperplasia alone, four; hyperplasia and myomata, ten; myomata, eleven. These groups showed that hyperplasia of the endometrium occurred eighteen times of itself or in combination; myomata occurred in all combinations thirty times. The inferential diagnosis of subinvolution in all combinations was made in eighteen cases. This series showed a definite increased incidence of myomata, while the frequency of hyperplasia was slightly less striking and the subinvolution incidence was also less. In these forty-seven cases there were a greater number of nulliparous women. In the hyperplasia cases only one out of the four had no children; in two cases there was no available data. In the hyperplasia-myomata cases there was a definite history of no pregnancies in seven cases, while in the cases of myomata alone two had had children, one case none, and in the remaining cases the clinical data was incomplete.

It was quite evident that menorrhagia was present to a more marked degree than in our series. It occurred in thirty-one instances in Cullen's cases. It was negative for menorrhagia in eight instances and

in the remaining cases no history was obtainable. In the cases of hyperplasia alone it occurred in fifteen instances, one case negative and two gave no histories. In the six subinvolution cases alone, all showed increased bleeding; and in the myomata alone, six out of eleven were positive, three negative and two gave no information. There was a striking difference as regards the frequency of nulliparous women in the series. Nine cases with no pregnancies and ten cases where this information was not obtained—only six cases in our series were nulliparous. We might add that the age incidence of our series compares very favorably with Cullen's series—our youngest patient was nineteen, as was his. He states disease is most prevalent between thirty and sixty years; chiefly near or just past forty is the most frequent time our series shows.

Cullen's case 5768, is quite remarkable. In this case the patient was single and was thirty-eight years of age. The menses at fifteen were regular, profuse and accompanied by clots. She has had a severe dysmenorrhea as long as she can remember, this being more pronounced during the first three days. The uterus amputated at the cervix measures $8 \times 9 \times 8$ cm.; the endometrium is of normal thickness and seems unaltered; the increase in thickness of the uterine wall is due entirely to the diffusely thickened myometrium. No discrete nodules were present. The invasion of mucosa in this case was very marked and was literally falling in the uterine wall through clefts in the myometrium.

This case suggests, first, that myometrial hyperplasia might have occurred before the invasion of the glands. Then the question comes up: what was the cause of the hyperplasia? It seems to us that it is reasonable to assume from the fact of the history of profuse bleeding with this case, that it represents a case of hyperplasia of the endometrium in a young girl which caused this myometrial hyperplasia to develop as a work hypertrophy, the hyperplasia of the endometrium subsequently disappearing. On the other hand, long continued dysmenorrhea may be explained in this case, on mechanical grounds, or to an increased density of the compact portion of the endometrium. In either case there would result a definite increased effort on the part of the uterine wall, which in turn would result in a work hypertrophy.

SUMMARY

Our study of forty-nine cases of diffuse adenomyoma of the uterus brings out a few rather definite points. In the first place it shows that diffuse adenomyoma of the uterus in almost every instance is present coincidently with one or more other lesions. That these lesions are fundamental in influencing the development of this condition is

quite apparent. It is rather difficult to say which one of these exerts a greater influence. It is quite evident that it rarely, if ever, occurs in a normal wall.

The lesion is explained chiefly on mechanical grounds. A parous uterus, or more particularly a uterus which shows the lesion of chronic subinvolution, favors the invasion of the mucosal elements. This invasion immediately causes a reaction on the part of the myometrium due perhaps, either to local irritation or an attempt on the part of the myometrium to withstand this invasion; in some cases this results in a marked hypertrophy of the wall and in other instances this hypertrophy is not particularly striking in this selected group. The explanation that this lesion does not occur in the subinvoluted uterus may rest in the fact that in these cases of subinvolution the endometrium is frequently atrophic and does not have the same tendency to penetrate that a more active endometrium might exercise. The mechanism in cases of hyperplasia alone is explained on an entirely different basis. In this instance the hyperplasia of the endometrium is the primary lesion; subsequently, as a result of the persistent hyperplasia of the endometrium, a work hypertrophy results in the uterine wall which gives it its coarse structure and allows the mucosal elements to penetrate between the widened interstices. In cases of myomata alone the thickened uterine wall exists before the invasion of glands and results from work hypertrophy in an attempt on the part of the uterine wall to rid itself of discrete nodules. That there may be an occasional case in which the explanation of the hypertrophy must be sought elsewhere is shown by the case in Cullen's series, and perhaps our explanation for these may prove satisfactory. As a whole, however, diffuse adenomyoma of the uterus occurs in almost every instance as a result of the presence of some pathological lesion of the uterine wall favoring its development.

That inflammation in the uterine cases is a definite factor in the production of the lesion as in the cases of tubal adenomyoma cannot be substantiated. Cullen has repeatedly remarked the same. In our series it was so inconspicuous that the number of cases was not even tabulated.

CLINICAL CASE HISTORIES

LABORATORY NO. 480.—*Typical case of subinvolution associated with diffuse adenomyoma.* No other lesion in uterine wall. Endometrium 1 mm. thick.

Patient forty-seven years of age, has had eight children, the last two years ago. Since her last pregnancy a partial prolapse of the uterus developed, with more or less constant pelvic discomfort and a marked increase in the menstrual flow. She menstruated every two weeks for the past two years, the flow lasting three to four days at a time. Vaginal hysterectomy was performed.

The uterus was considerably enlarged and measured 12x6x5 cm. There was no evidence of pelvic inflammation. The uterine wall at its thickest portion measured

21 mm.; the endometrium 1 mm., and was normal. There was no general increase in connective tissue but its presence was quite striking in the inner third. Blood vessels of the inner third show in most instances a very marked collection of diffuse elastic tissue around the outer portion of the new vessel wall. The vessels of the middle third, particularly the veins, show an immense amount of this diffuse elastic tissue. The elastic tissue between the muscle bundles and the outer third was also markedly swollen.

This case was reported previously as a typical case of chronic subinvolution which, to be sure, it is. The adenomyoma was discovered subsequently in studying further sections.

CASE NO. 1299.—*Diffuse adenomyoma of the uterus associated with marked hyperplasia of the endometrium in a nulliparous woman.*

Patient was thirty-four years of age. Menses had been three to four days in duration and appeared every 28 days up to about three years ago. Since then the flow has been increased, of long duration, frequently lasting two weeks. The last period has been three weeks in duration and there is still some flow on admission.

Supervaginal uterus is globular in shape and measures 10x10x8 cm. Uterine wall measures 4½ cm. in thickness in the left upper portion. The endometrium in the upper cavity has a shaggy, stringy appearance and is from 1 to 1½ cm. in thickness all over; the tissue hangs in shreds from a base and there are blood clots hanging to the shreds. Microscopically there are numerous glands present in the thickened uterine wall surrounded by a definitely hyperplastic myometrium. Section from the right uterine wall shows a very definite hyperplasia of the endometrium, with only a very slight tendency to invade.

CASE NO. 1323.—*Diffuse adenomyoma associated with a marked hyperplasia of the endometrium in a parous uterus which shows not the slightest evidence of subinvolution.* Specimen presented by Lee Dorsett.

Patient a married woman 48 years of age. One child seventeen years ago. Menses began at twelve and were profuse until twenty, normal to thirty, profuse after thirty, with flooding spells for the last five years. Specimen consists of a symmetrical uterus diffusely thickened throughout, removed by supravaginal amputation. The uterus measures 12x12x10 cm. The uterine wall measures 4.5 cm., in thickness and has a very coarse appearance. No discrete nodules present. Microscopic section shows a very marked hyperplasia of the endometrium, endometrium being 7 mm., thick. The muscle wall is 40 mm. thick. Glands are embedded in the myometrium 1.5 cm., from the base of the endometrium.

CASE NO. 1790.—*A nulliparous uterus with numerous small myomata, hyperplasia of the endometrium, diffuse thickening of the uterine wall and an early adenomyoma.*

Outside case, no history available but patient is single. The uterine wall is studded with numerous interstitial nodules, the largest 5 cm. in diameter. The uterine wall iteslf, outside these nodules, is very coarse and much thickened. The endometrium is thrown into numerous folds and is greatly thickened. Microscopically the endometrium shows definite hyperplasia and definitely invades the myometrium for a distance of 7 mm. Muscle bundles show a very definite tendency to separate.

CASE NO. 1984.—*An early penetration of the endometrium in the wall of a markedly subinvoluted uterus*

The patient forty-four years and has had twelve pregnancies, the last, a full term, three months before admission.

Specimen consists of a large subserous tumor 21x7x8 cm., attached by a small pedicle to the posterior wall, and a supravaginal uterus measuring 7x6x4 cm., which

DR. OTTO H. SCHWARZ, St. Louis, Mo., presented (by invitation) a paper entitled **Diffuse Adenomyoma of the Uterus: Conditions Influencing Its Development.** (For original article see page 457.)

DISCUSSION

DR. W. P. HEALY.—Adenomyoma is a comparatively rare lesion in our experience. In five years up to January 1, 1920, we had only 14 cases of the diffuse type in the Roosevelt Hospital service. We had a number of ectopic adenomyomata occurring in other places, but of the diffuse type we had 14, and these three conditions to which our attention has been drawn as being associated with it, are quite common lesions in the uterus; that is, myomata, chronic metritis and hypertrophy. It would seem to me that if we were to assume that they are an underlying cause for the development of adenoma or adenomatous changes passing out into the corpus uteri from the endometrium, that we would meet with the lesion more frequently.

DR. J. O. POLAK.—The first thing that impresses one, in looking at the slides which were shown, is that adenomyoma is a distinct entity which has nothing whatsoever to do with the myomatous uterus. The second point which the doctor has brought out, and which is a point I think he makes clear, is the fact that the normal uterus is not subject to these invasions from the mucosa.

While the diffuse adenomyomata which the doctor describes and the cases he

reports are relatively few, I feel certain that were we to make serial sections of our cases we would find them more frequently than we do. It has been surprising to find that where this has been done in cases which did not show definite evidence grossly of such lesions, microscopically the lesion was found.

Now, all adenomyomata do not occur as diffuse tumors. The class to which the doctor has called attention is easily explained by the invasion theory which was suggested by Cullen and which the doctor has shown so clearly in these cases of metritis, of subinvolution and of hypertrophy, where the fibers are actually spread and the uterus is relaxed to a greater or lesser extent. Again, we know that this invasion takes place along the blood vessels, particularly in cases associated with inflammatory lesions, and while it does not invade the blood vessels, you will find that these invasions of the mucosa and these causal rests are present in the blood-vessels. But there are several adenomyomas that are not explained, those of the rectogenital space, which Cullen has attempted to explain by an inversion of the peritoneum and that the peritoneal covering can take on the same characteristics as the cells lining the interior of the uterus. It seems at first hand that that is a rather improbable theory and still it is a fact that the large majority of the myomata which I have seen have been located in this region. The next most frequent location, in my experience, is at the cornu of the uterus, usually posterior; and whether the old theory that the wolffian duct and the müllerian (duct) crossing at that point, causing relaxation, has been the etiologic factor of the development (of the condition) at that point, or whether it is purely inflammatory and the result of an invasion and inclusion of the mucosa, as one expects to find at that point in chronic inflammations of the tubes, is the etiologic factor, it is difficult to say. Yet those are two very common locations in which we find adenomyomata. How can we explain on this invasion theory the adenomyomata that we find, for example, in the round ligament, in the broad ligament, and in a case that Dr. Pomeroy reported and one I reported of the umbilicus? It is hard to think of the invasion of the mucosa to such points as that.

This paper has been very illuminating, because, first, it has brought out so clearly that a healthy uterus seems to be protected; secondly, it is a distinct entity from fibroid of the uterus; and, thirdly, there is a relaxation, so to speak, and a broadening of the muscle fibers which allows of invasion of these mucosa rests.

DR. HERMANN GRAD.—In a study of a series of 100 uteri to find the cause of bleeding, I found that in only 3 of the cases had the pathologist reported penetrating uterine glands, and that was the only lesion that we found to account in some way for this bleeding, and in all there was this marked condition of subinvolution. In one of the 3 cases, in addition to the subinvolution, there was also what the pathologist, Dr. Strong called a myometritis.

DR. S. H. GEIST.—I have had the opportunity of looking at a great many uteri in the last ten or twelve years and have been struck with the comparative rarity of this condition. At Mount Sinai Hospital, where we have a fairly large service, we see not more than 6 to 10 cases of diffuse adenomyoma cases a year. We see more frequently adenomyoma, a distinct tumor, in which there are islands of uterine mucosa.

It is not my recollection that the lesions which Dr. Schwarz describes are always present. We have diffuse adenomyomata without any type of lesion, either fibroid, hypertrophy or the condition which he describes as subinvolution. The hypertrophied condition of the mucosa, I believe, is an entirely different problem. That is a condition which we find associated, as the doctor has stated, with fibroids, and particularly with the types of cases that are called "essential bleeding." I

believe that the lesion in the mucosa has nothing to do with the process in the uterus, and that it is probably an expression of some other factor. However, I think that there is undoubtedly a great deal to be said in favor of the invasional theory, in view of the fact that in the presence of chronic irritation, whether because of subinvolution or the rare finding of a chronic metritis there is a stimulus to the normal uterine mucosa which has no submucosa to protect the uterine wall and allows this so-called invasion. I think invasion is a badly chosen term because it gives one the impression of a malignant tumor, and these conditions of adenomyomatosis are not malignant; they are benign and simply give rise to the local symptoms which we deal with in these cases.

I think that in the presence of an inflammatory process or some other irritative factor, we might have one possible etiology for the infiltration of the so-called normal mucosa into muscularis or fibrous tissue wall of the uterus.

DR. H. B. MATTHEWS.—It seems to me that this invasion of the endometrium might be looked upon as the precursor, as it were, of cancer. It seems strange that this tissue can migrate out of its normal habitat into the interstices of this muscle tissue without finally acquiring some characteristics of malignancy.

DR. W. S. STONE.—Apropos of the remarks of the last speaker regarding the development of cancer in such a tumor, I have seen two cases of uterine cancer in which such a sequence of lesions seemed probable. Both of them were operated upon under the diagnosis of fibromyoma with the probable complication of some tubal disease. At operation, in both cases, the uterine tumors were found densely adherent to all the surrounding structures and the removal of the tumor was extremely difficult. Instead of an inflammatory cause for these adhesions we found a diffuse infiltration of the uterine wall with a malignant neoplasm which extended directly to the peritoneal surface and perimetrial structures, differing in its mode of distribution entirely from that which we see in the ordinary adenocarcinoma of the uterine body, and illustrating nicely how the anatomy of cancer is determined by the type of lesion that has previously existed. In both of these instances it seemed most probable that the cancer had its origin in a diffuse adenomyoma. Its diffuse distribution and its extent was such that it could not be accounted for in any other way.

DR. R. L. DICKINSON.—The clinician would ask the writer of the paper to carry the study further, if his histories admit, to tie his pathology to his symptomatology and treatment, whether the pain, the dysmenorrhea, the intermenstrual pain, the bleeding can be grouped as definitely with his pathology, so that we can fit our treatment to them.

DR. OTTO H. SCHWARZ.—It appears from the discussion that others do not feel that the lesion is as frequent as I indicate. I think the frequency in which this lesion is found depends directly upon the interest one has in the specimen, whether it is the operator or the pathologist. It has been my experience that most general pathologists are not particularly interested in this special field, and a man who is particularly interested in this subject will give more accurate data as regards the frequency of this lesion.

Inflammation accompanying this lesion in my series was not at all striking; it was so slight that we made no table of the cases in which this lesion occurred. However, in the case of cornual or tubal lesions, inflammation is present in almost every instance.

The term "invasion" was used in this paper in a mechanical sense, merely a flowing in of the endometrium between the muscle bundles, and in no sense invasive as compared to the invasion of a malignant growth.

As subinvolution is very frequently present in large uteri removed at operation, one might also ask the question, "If this condition has anything to do with the causation of adenomyoma, why do we not find it more frequently?" I feel that this might be explained by the fact that frequently in subinvoluted uteri we have an endometrium which is rather atrophic and it might be expected that such an endometrium would have less tendency to invade these clefts than a normal or more active endometrium might have.

In regard to the clinical aspect considerable data are embodied in the paper which I neglected to mention. In our series there were only six nulliparous uteri; in Cullen's series there were fifteen.

Menorrhagia was found most frequently in those cases with hyperplasia of the endometrium, which occurred in about twenty-six cases of my series. In every instance where hyperplasia was very definite the menorrhagia was quite profuse. This was also true of the cases of hyperplasia in Cullen's series. In the cases of subinvolution in my series only one-half gave a history of increased bleeding. In the cases of myoma alone, both nulliparous and multiparous, there was no hemorrhage in several.