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A Study of

ENDOMETRIOSIS

Endosalpingiosis, Endocervicosis and Peritoneo-ovarian Sclerosis

by

JAMES R. GOODALL, M.D.

The first time the whole subject of endometriosis and its allied diseases has been collected and presented

140 Pages

13 illustrations in black and white and 17 subjects in full color on 6 plates

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A Study of Endometriosis, Endosalpingiosis, Endocervicosis, and Peritoneo-ovarian Sclerosis

A Clinical and Pathologic Study

BY

JAMES ROBERT GOODALL

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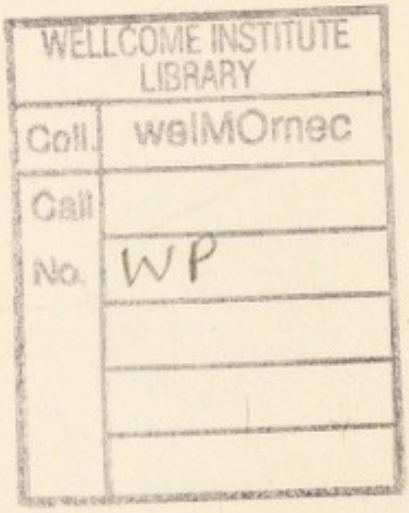


PRINTED IN THE UNITED STATES OF AMERICA

THIS BOOK IS DEDICATED
TO
DR. JOHN A. SAMPSON
IN RECOGNITION OF HIS
WORK AS A PIONEER IN
THIS FIELD AND AS A
TOKEN OF GRATITUDE
FOR HIS GENEROSITY

Preface

This book has been written in order to bring the whole subject of endometriosis and its allied diseases under one cover, and to add several chapters of new work upon this topic. Some of this new work has already been published in various journals. Other material appears in this volume for the first time: the chapters on endometrial endometriosis, peritoneal and ovarian sclerosis, new phases of stromatous endometriosis, and the cases of persistence of endometriosis after both ovarian extirpation and x-ray and radium treatment. The theories upon causation and prevention are interesting both as facts and as speculation.

This study has for its object the presentation, in a concise form, of the past history and the present status of this difficult subject. In this it will be endeavored, by a study of symptoms and signs: (1) to make it possible for the clinician to hazard a tentative or probable diagnosis; (2) to present the latest developments in research upon this subject; (3) to make it clearly understood how the disease spreads; (4) to outline the involvement of organs juxtaposed to the uterus, and the symptomatology arising out of these; (5) to speculate upon causation; and (6) to place before the reader the best means to meet the situation in any given set of circumstances.

A great deal of new knowledge has been forthcoming of late, much of which comes from the research laboratory and wards of St. Mary's Hospital—work that, as yet, has not been published. From this study it can be definitely stated how endometriosis spreads, and the consequences which devolve from the different modes of propagation. It will be shown that, in this respect, endometriosis has much in common with infections, and obeys the same rules; that, in this respect also, it has much in common with malignant growths of the pelvis, but that, unlike both of these conditions, its spread is restricted to the genital organs, and to those in close approximation to them. Remote metastases in endometriosis are extremely rare—in fact, they are limited to about four cases on record.

It is also now clear from recent discoveries that endometriosis may involve the endometrial stroma cells only, and never reproduce any glandular elements either in the intramural primary extensions from the endometrium, or in their remote extensions in neighboring organs. This fairly common type has heretofore been diagnosed as sarcoma in the

rapidly growing cases, and as fibromata in the chronic types. It will be demonstrated that in endometriosis, as in most of the types of new growth, there is a concomitant development of the fixed tissues of the organ involved. Sometimes these fixed tissues in their growth overshadow the endometriosis, hence the compound designations of fibro-adenoma, myo-adenomata, etc. In other instances the endometrial growth preponderates, and the surrounding tissues are soft and succulent in their reaction, thereby favoring the spread of the primary endometriosis. How like acute and chronic infections it is in this respect also!

It will be shown also that whatever the cause of endometriosis, it is an agent which operates in most of the cases not only upon the endometrium, causing it to proliferate and infiltrate, but also exercises a stimulating proliferative influence—though, of course, to a lesser degree—upon other tissues of the generative organs, such as those of the uterus, ovaries, cervix, and vagina. Until the present the endometrial overgrowth, being the dominant development, has completely overshadowed these other hypertrophic changes.

It is also now known that the agent of endometriosis exercises profound changes upon the lower abdominal peritoneum, not in the nature of endometriosis, but characterized by a diffuse sclerosis which is usually most pronounced in the posterior and anterior pelvic pouches. These changes also frequently involve the anterior parietal peritoneum as high as the umbilicus. In many cases, when opening the abdomen, owing to this manifest sclerotic change in the parietal peritoneum it has frequently been possible to diagnose endometriosis when this condition had previously been unsuspected. These peritoneal changes also constitute a new chapter in the disease, and shed a great deal of new light upon some of the characters of the causative agent or agents of the disease.

It will be made clear also, that, though the ovarian function may be necessary as an intermediary to start the disease, it is not an essential intermediary for its continuation, once its inception has been brought about. Other organs can adopt a substitutive rôle in the absence of the primary sex organs. What are these substitutes? Some of our knowledge upon the subject is factual, some is still in the delightful realm of speculation. Nature seldom is harried by having but a single track; she is always prolific in switches. So it is in endocrinology, where there are activators, inhibitors, and substitute-vicarious functions. Spontaneous arrest of endometriosis occurs in about 60 per cent of cases, showing that nature, when subjected to sudden endocrine changes which she cannot meet at the moment, can overcome this sudden change in the internal milieu if given time and sufficient individual reserve with which to work. The natural tendency is toward *restitutio ad integrum,* provided conditions are propitious. That about 60 per cent of cases undergo spontaneous

arrest is proof of that statement. How do we know that there has been spontaneous regression? That is a most interesting subject, and the reader is referred to the chapter which deals minutely with it.

The work is very largely based upon personal experience. The practical research upon the subject was done in the research laboratories of St. Mary's Hospital, Montreal. The cases were drawn largely from my own private practice, but also from the public wards of St. Mary's, the Homeopathic, and the Royal Victoria Hospitals. However, whatever theories have been expounded or whatever opinions have been expressed are entirely my own, and I take full responsibility for them.

It gives me great pleasure to express my gratitude and indebtedness to my predecessors in this field of work, and especially to Dr. John A. Sampson for his willing generosity in permitting me to draw so liberally upon his many beautiful illustrations; to attempt to improve upon them would be futile.

I am also indebted to Dr. Emmet Mullally for performing his uninteresting task of proofreading, and to my assistants, Drs. R. H. Power, F. O. Anderson, G. T. Altimas, and others of my associates for their co-operation in listening to, criticizing, and adding to my views and tenets upon this interesting subject.

J. R. G.

Contents

1

History

It is proposed to sketch the history of endometriosis merely in its broad lines, reserving the finer details of historic interest and discussion for the individual subdivisions as they come up for consideration. It is quite unnecessary to outline, except cursorily, the theories that from time to time have been propounded to explain the origin of endometriosis. Many of these, owing to the light of more profound research, have had to be abandoned for other hypotheses of a more comprehensive nature. Even today the cause or causes of endometriosis are still shrouded in mystery. Most of the polemics of past years, however, arose over the subject not of causation, but of origin and mode of spread. These two latter phases of the subject have now reached a stage of definitiveness which precludes many of the more abstruse and purely speculative theories.

The disease, that is, the most striking pathologic entity of the disease —the ovarian invasion—was first described by Russell in 1888, in a case of growth of "endometrioid" tissue in the ovary, with its extra-ovarian extensions. For a long time very little notice was taken of this discovery, as is so common with any discovery which requires the mental effort of readjustment. Russell's classic description was followed in 1896 by an article by Ludwig Pick, in which a case was described where the ovary was permeated by a growth which had characters simulating in every detail those of the normal uterine mucous membrane. In 1896 Von Recklinghausen, endeavoring to explain the presence in the uterine wall of structures of close similitude to endometrial tissue, propounded the theory that these were inactive embryonic rests derived from the remnants of the wolffian ducts. A similar contention was advanced by Martin in 1891 to explain the presence of a glandular growth—an adenoma—in the groin, attached to the round ligament, in which blood cysts were found, lined by a columnar epithelium with endometrioid characters. Until this date there seems little evidence to show that the writers associated the blood collections in ectopic endometrial tissue with the menstrual cycle. This was a later development. However, the proponents of the wolffian theory are few at the present day, though as late as 1920 Cuthbert-Lockyer contended that the wolffian theory of origin presented a ready explanation for these growths.

Near the break of the present century, Ivanoff proposed the theory that extra-uterine endometriosis might arise from a metaplasia of the pelvic peritoneum—a theory that found a stout advocate at a later date in Robert Meyer. According to Meyer, the impulse that starts the peritoneum on its wayward changes and wanderings is attributed to an antecedent inflammation of the peritoneum or its immediate neighborhood. Once the peritoneum has departed from its normal structure and normal function, there would seem to be no limits to its digression in respect to these two factors.

This theory finds its chief base of support from the embryonic history of the peritoneum—celomic epithelium—which is the ancestor of most of the abdominal structures, and therefore, being almost totipotential, may, in an abnormal or in a new set of circumstances during adult life, revert to its embryonic potentialities and reproduce these structures *de novo*. Whether such reversions are possible in an adult peritoneum, and whether, granting such reversions possible, these embryonic cells could reproduce such highly specialized tissues as the endometrium and endow them with full function, will come up for further discussion under the heading of "origin of endometriosis." This peritoneal metaplastic theory of the origin of endometrial growths was later emphasized by Gough, and still later by Spencer and Cullen.

For a clear understanding of another theory—the germinal epithelial origin of endometriosis of the ovary—we must revert to an earlier date in the history of this disease. In 1870 Waldeyer sought to explain the origin of epithelial new growths of the ovary by invasions of the ovarian stroma by its covering germinal epithelium, which under the stimulus of unexplained causes might take on invasive and vitiated growth by reverting to the properties of its embryonic phase. This theory was later adopted to explain the origin of endometrial invasions of the ovary. Here, again, no account was taken of the menstrual function. How could such tissue take on hemorrhagic characters? Whitridge Williams added his support to this theory by finding tall ciliated columnar epithelium on the surface of the ovary in adults.

In his early work Russell attributed the origin of endometrial tissue in the ovary to ectopic or misplaced müllerian rests, either on the surface of the ovary or within its tissues, and Blair Bell, in support of this theory, described a case of endometrioid tissue of the ovaries which was associated with marked hyperplasia of the involuntary muscle, giving to this condition the descriptive name of endometrioma. This müllerian theory also found support in the work of Janney in 1922, and of Blair in 1923. As a stimulus activating these müllerian embryonic rests, they inculpate general corporeal changes and local modifications of environment, activating the quasi-quiescent embryonic tissues.

In 1921 Sampson first elaborated his "spill" and "implantation" theory. He maintained that during menstruation, and possibly during the interval, uterine contents escape from the abdominal ostia of the tubes, and that in the "spill" are lining cells not only capable of implanting themselves, but also, in suitable soil, of reproducing the menstrual cyclic changes synchronously with the uterine menstrual phases. These implants from the "spill," Sampson contended, have the power to invade the organ-host upon which they are implanted, and can not only multiply but also, under favorable circumstances, have full functional capacity. These invasions by glandular elements, being closed cavities, menstruate into the cavities each month, causing dilatations into cystic collections varying in size from those of microscopic dimensions to growths as large as a grapefruit. The contents are either liquid blood or blood of tarry consistency, named "tar" or "chocolate" cysts.

In 1925 Sampson further demonstrated the possibility of extension of the outgrowths from the endometrium into the submucosal lymphatic channels and blood vessels, into the lumina of which he was able to demonstrate endometrial emboli. Sampson also showed that under abnormal stimuli the mucosa of the fallopian tubes was capable of shedding its epithelium, which, escaping from the fimbriated ends, could implant itself upon contiguous pelvic structures and invade contiguous organs. He also demonstrated that under similar abnormal circumstances the tubal epithelium could invade its own tubal muscular wall, and spread itself in the lymphatics of the mesosalpinx and into other parts of the subjacent broad ligaments.

2

Nomenclature

Names have a habit of multiplying rapidly when a discovery is made, with endometriosis no exception. Its defining terms have increased with its authors. Finally, when all the characters of a disease are known, a common basis of denomination develops by common usage. Endometriosis is still in the formative stage, but sufficient, I think, is now known about the disease to permit one to attempt a common denominating technology.

In the first place, there are three places from which infiltrating and implantation diseases may start; namely, the endometrium, the endosalpinx, and the endocervix. These terms, therefore, ought to denote the source of origin of the disease. This, I think all will agree, is sound logic. Then, to denote the type of infiltration, whether diffuse or localized in the form of a tumor, we may add a suffix of "-osis" or "-oma," respectively, to these two different forms of invasion, such as: endometriosis, endometrioma; endosalpingiosis, endosalpingioma; endocervicosis, endocervicoma. Thus we have origin and type of invasion denoted. We have ample precedents for the suffix in fibrosis and fibroma, diverticulosis and diverticuloma, etc. To these may be added prefixes to denote the type of stroma in which the mucosal tissue is proliferating (such as fibro-, myo-, or fibromyo-), and if the disease is made up wholly of endometrial stroma cells or composed of both elements of the endometrium, the terms stromatous or mixed, respectively, may be used for further definition of the cellular characters. Lastly, the organ invaded may denote the site of the chief expression of the disease. Therefore, we may have endometrial, uterine, ovarian, peritoneal, etc., endometriosis or endometrioma, and the cellular elements may be further defined by qualifying adjectives. I see no good reason for using the terms "interna" and "externa" for denoting that the growth is confined to the uterine wall or cavity, or that it has spread beyond the confines of the uterus.

The following division of the invasive diseases of urogenital origin is comprehensive and scientific:

Endometriosis
- 1. Mixed
  - Benign
  - Malignant
- 2. Stromatous
  - Benign
  - Malignant

Endosalpingiosis

Endocervicosis

It follows that we may have such definitions as endometrial intrauterine endometriosis, in which the growth-stimulation spends itself chiefly upon the endometrium, causing it to become thickened and often of the Swiss-cheese type of growth. Or the pathologic invasion may proceed from the basal layer of the endometrium and invade the uterine parietes and become a parietal endometriosis. Or again, the disease may spread beyond the confines of the uterus to contiguous organs and become ovarian, peritoneal, rectal, or a plastic combination of all of these locations. The common association of endometriosis with fibroids, myomata, etc., gives scope for a nomenclature to designate this symbiosis.

3

The Invasive Diseases of the Urogenital Type

This term is used to comprise the diseases that arise from abnormal invasion of the pelvic tissues by cellular elements derived from one or more of the specific genital organs. These ectopic elements frequently carry over to their abnormal terrain their secretory or cyclic functions, thereby causing not only a definite constructive pathology of cellular dislocation, but also a destructive pathology arising out of a dislocated function. These latter are commonly retention cysts with bloody or secretory contents. The tissues of the urogenital ridge have a strong tendency to take on aberrant growth under abnormal circumstances. Some of these aberrations are prone to develop during the sexual age, from which it may be inferred that it is a response to overstimulation. Such, for example, are the endometriotic and allied overgrowths. Other growths from specific elements of these organs are more especially restricted to the postfertile period, from which it may be inferred that the aberration is due to the withdrawal of some restraining influence. Such, for example, are the common malignancies.

The specific structures of the first type, from which these ectopic cells are primarily derived, are, in the order of their frequency, (1) the endometrium; (2) the endosalpinx; (3) the endocervix; (4) the germinal epithelium covering the ovary; and (5) the peritoneum. In addition, the new growth may contain only the stroma cells of the parent structures, or may be made up of both stroma and glandular elements. Particularly does this last differentiation apply to those derived from the endometrium and endosalpinx. Whether the new growth will reproduce all the elements and normal construction of the parent structure will depend upon two factors: (1) rate of growth, and (2) environment (meaning soil, endocrine, age, and other ancillary factors). The cell elements which initiate the new growth are centrifugal as regards the parent organ, and centripetal in the organ of their adoption.

The new growths are limited in their field of spread. In the vast majority of cases the invasion is limited to the pelvic organs (more particularly to the organs which may show decidual changes during preg-

nancy), and this applies to the appendix and to the abdominal peritoneum, both visceral and parietal, below the level of the umbilicus. It will be shown later that endometriosis and decidual change, though somewhat similar in their zone of influence, have nothing in common except that the causative agent acts with greatest vigor at the site or origin of the cause, and fades as one recedes from this center of production. The cases in which metastases have been found in regions remote from these structures are so few as to be pathologic curiosities.

It will be shown that the ectopic growth of the invasive elements is only one small phase of these diseases. All other structures, both müllerian and celomic, usually participate in a great hyperplasia in response to the common stimulus. It may be noted incidentally that two disease processes are in operation in endometrial ectopias; namely, a foreign invasion by endometrial cells, to which is added the destructive influence of hemorrhagic extravasations of the menstrual cycles. In endosalpingeal ectopias, on the other hand, menstrual destructive cyclic changes and consequent hemorrhages are absent. Instead, one has a tendency to cystic formations, owing to the absence of outlet for the secretions of the epithelial elements. But, singularly enough, both of these invasive and functional processes, though subversive to normal relations and contiguities, are not destructive to, but act rather as a stimulant to the natural functions of the invaded organs. So one usually encounters on the same slide the appearance of normal or quasi-normal functions going on beside foreign destructive invasions. It will be pointed out later, however, that these natural functions, though excessive, are nearly always appreciably vitiated. Whether this appearance of deranged function is the cause of the aberrant growth or a sequence of it, will be dealt with at some length when discussing causation.

It cannot be overemphasized that the most apparent clinical manifestation of any endometriosis is the striking response in the form of a generalized urogenital hyperplasia to some (as yet unknown) causative agent. As a consequence the pathologic picture may vary considerably in different cases, depending upon which structure responds most perceptibly to the stimulation, in other words, the local manifestations of the disease depend for their effect upon three factors: (1) the mode of spread of the disease; (2) the characters of the invaded soil; and (3) the place of origin of the ectopic cells.

4

Uterine Endometriosis

Uterine endometriosis can now be divided into two distinct, though often combined, expressions of the disease. They are:

1. Endometrial intra-uterine endometriosis or Endometrioma — Mixed / Stromatous
2. Parietal uterine endometriosis or Endometrioma — Mixed / Stromatous

A word of explanation is necessary. In endometrial endometriosis the most apparent pathology is a great overgrowth of the endometrium which often may assume great thickness. This overgrowth may be diffuse, involving the whole of the uterine mucosa; or it may be localized to a portion of the uterine lining, producing a definite tumor growth. It then becomes an endometrial endometrioma. It may be sessile or polypoidal. This endometrial overgrowth is generally composed of both the glandular and stromatous constituents of the endometrium in normal relations, but these two elements often lose their normal relative proportions and at times we may find such endometrial hyperplasia made up chiefly of glandular elements with a minimum of stroma, while in other cases the growth may be made up wholly of stroma cells. These two types were formerly designated as glandular and interstitial endometritis before their true pathology was known.

And it may also be pointed out—a fact first noted in a previous paper—that nature by her own vis medicatrix strives, always within the limits of her reserve, to restore the vitiated function to the normal by correcting the underlying endocrinologic imbalance. As a consequence arrests and even spontaneous cures are common end-results.

5

Endometrial Intra-uterine Endometriosis and Endometrioma

Diffuse endometrial endometriosis is common, but rarely diagnosed. There are various reasons for this. First, it cannot be diagnosed except tentatively, unless the uterus is removed and studied *in toto*. In cases where tissue is obtained by curettage one obtains merely a quantity of endometrium in excess of the normal. It has very definitely the appearance and palpable qualities of nonmalignant tissue.

MIXED ENDOMETRIAL ENDOMETRIOSIS

This is the type which in past years was diagnosed microscopically as hypertrophic endometritis. Though the mucosa is greatly thickened, the glands and stroma retain more or less their normal proportions and relations. We know now that this overgrowth is a response to hormonal overstimulation. The glands are frequently cystic, giving the sections the characteristic Swiss-cheese appearance. The lining of these cysts may show various degrees of pressure atrophy. In other cases the hypertrophy may manifest itself in a marked degree of reduplication of the columnar lining of the ducts—conditions which are frequently designated as consequences of hyperestrinism. In many instances the glandular elements may almost completely outgrow the stroma cells, giving the tissue a honeycomb appearance—a condition characteristic of glandular endometriosis. It will be readily understood in this latter type that a correct diagnosis cannot be made from a biopsy, but curettings may be suspected from the abnormally large quantity of mucosa obtained. Quantity is the yardstick of hypertrophy, but by the microscope one cannot estimate the quantity of mucosa removed by curettage. Yet overgrowth is the dominant factor in endometrial endometriosis. It is only when hysterectomy is performed without curettage that the true significance of this endometrial disease can be evaluated.

Examination of many uteri removed at operation reveals certain other characteristics. The stimulus to overgrowth may not involve diffusely the whole endometrium. On the contrary it may be restricted to a special area of the uterine mucosa, causing at that spot either a

pedunculated or a sessile polyp, with microscopic characters similar to those of the diffuse type. Of course, such localization of overgrowth may not be appreciable by curettage, but it is a common finding when one studies the mucosa of uteri removed for causes other than the endometrial disease, or for uncontrollable hemorrhages arising in conjunction with the endometriosis. It will have been seen, therefore, that the endometrial endometriosis may be diffuse or local, and we wish to show that this difference is a product of biologic cell selectivity for which our crude methods of biochemistry upon dead tissue can offer no adequate explanation.

In the majority of instances the overgrowth of the endometrium is restricted to one part of the endometrium only, or at least becomes locally predominantly obtrusive in the form of endometrial polypi. They may be large or small, multiple or single, sessile or pedunculated. Their structure is usually that of the endometrium from which they stem, but it often shows the cystic formation and hyperplasias already described. This is the type of tissue which, in former years, was diagnosed as polypoidal endometritis. However, there is seldom any evidence of inflammation unless there happens to be a concomitant infection. The tissues involved in this overgrowth are, it is now believed, the expression of a prolonged excessive overstimulation by the follicular hormone; but this does not exempt these tissues from a degree of change incidental to luteinization when the corpus luteum is in operation.

STROMATOUS ENDOMETRIAL ENDOMETRIOSIS

In the above descriptions of endometrial overgrowth we have dealt chiefly with tissues composed of mixed glands and stroma. There are, however, cases of stromatous endometrial endometriosis or endometrioma. In curettings from such a case the stroma cells have responded to the stimulus, so that glands are conspicuously rare, or absent, in a tissue composed exclusively, or almost exclusively, of endometrial stroma cells. These, like the stroma cells of the normal endometrium, may vary in shape and staining properties, assuming now the normal round-cell with an oval nucleus with discrete nuclear membrane and chromatin in necklace arrangement; or the cells may be streamlined, resembling somewhat young fibrous tissue in characters; or they may be dividing so rapidly as to approach the size and character of lymphocytes. When curettings of these types are sent up for a diagnosis, the absence of glands almost invariably suggests the diagnosis of sarcoma, with a modifying prefix to designate the dominant cell type. Several such cases have come under observation where hysterectomy has subsequently been performed, upon the diagnosis of the pathologist, only to reveal either a perfectly normal or somewhat enlarged uterus, with or without concomitant signs of

endometriosis of some other organs in the pelvis. Curettings from stromatous endometriosis were formerly described as interstitial endometritis, before their true nature was known.

It must be understood that the division of endometrial endometriosis into mixed and stromatous is purely a relative one. In some instances of great overgrowth of the endometrium the relative quantities of gland and stroma may not be disturbed at all. What constitutes the normal relative quantities of these two structures is hard—yes, impossible—to define so that each pathologist will have his own mental estimate of this relationship. However, in other cases the glandular elements may be so preponderate as to reduce the stroma to the merest necessary supporting structure. And in others there is such an overgrowth of stroma that glands are conspicuous by their absence. Between these three cited types there may be all degrees of variations.

Of course, all of these various types of endometrial endometriosis respond to the changes incidental to the menstrual cycle, and the tissues will therefore show the changes characteristic of the menstrual phase of the patient at the time of operation. Polypoidal endometriosis, either mixed or stromatous, composed as it is of the superficial layers of the endometrium, often shows a decidual change of its interstitial cells when in the luteal phase of menstruation. Many of these polypi, whether glandular or stromatous, are prone to undergo vascular disturbances (such as thrombosis, or infection causing necrosis and a consequent unpleasant discharge, thereby increasing the probability of a tentative microscopic or clinical diagnosis of malignancy).

In all these cases of endometrial endometriosis there is an invariable increase in size of the uterus due to a proliferation of its normal cellular elements to which may be added some abnormal invasion of the muscularis by endometrial elements. It is rare that endometrial endometriosis, of whatever kind, occurs without one or both of the above added concomitants. When the abnormal growth of the endometrium described above occurs, the normal musculofibrous elements of the uterine wall undergo hypertrophy similar to that of early pregnancy. This is a response to the same agent as brought about the endometrial pathologic change.

Not infrequently the basal layer of the endometrial mucosa answering to the same stimulant penetrates more or lessly deeply into the muscularis beyond the normal limits of the ordinary basal layer of the mucosa. It is only in the active stage of the endometrial disease that these added complications can be detected. When hormonal balance is spontaneously re-established, these hypertrophic changes regress, and as a consequence uterine hypertrophy disappears and the ectopic intramural elements also disappear quickly and completely. The re-establishment of the hormonal balance may be only partial and the tissues may remain *in statu quo ante,*

with a degree of permanency proportionate to the stationary state of a minor hormonal imbalance. It is not possible to determine why some growths proliferate outwardly along the line of least resistance, while others invade the underlying tissues, even though they may be dense and resistant.

In connection with the hypertrophy of normal tissues which accompanies any form of acute endometriosis, a very interesting case recently came under observation, that of a married woman aged 42 years. She had had menorrhagia and metrorrhagia for the past three months. On bimanual examination the cervix, bilaterally torn, was greatly hypertrophied and soft. The uterus was the size of a three-months' pregnancy, symmetrical and soft—uncommonly like a pregnancy. The Aschheim-Zondek was negative. At operation the right ovary contained several cysts, the largest the size of an English walnut. Its walls were sclerosed and rigid. The smaller cysts were similarly, though less, affected. The left ovary was small and atrophic.

The uterus, the size of a three-months' pregnancy, was so like a pregnant uterus that I was in grave doubt about removing it. Trusting, however, on the accuracy of the test, I did a total hysterectomy. Upon opening the uterus there was a most beautiful specimen of diffuse endometrial endometriosis. There were nine polypi—some small, others large and broadly sessile—upon an endometrium fully one-half inch thick throughout. One of the polypi was hemorrhagic, and was the source of the uterine bleeding. But the most interesting feature was the tremendous muscular hypertrophy of the uterus. The walls were two inches thick, soft, succulent, exactly like the hypertrophy of pregnancy, and of a consistency indistinguishable from that of pregnancy. The ovarian cysts were follicular, and the largest had a thin sickle of internal-capsule-lutein cells covering about one-quarter of the circumference of the sclerosed cyst wall.

My assistant pithily said, "A beautiful case of endocrine imbalance ovarian in origin. There is everything here that you would find in a pregnancy—except a fetus and a corpus luteum. The fetus in pregnancy does not directly cause the uterus to grow, it just changes the endocrine functions of the ovary, and it is the endocrines of this organ which cause the hypertrophy." His statement was true. Microscopically the uterine wall was indistinguishable from the hypertrophy of pregnancy. This softness of the uterus in acute endometriosis is in sharp contrast to the hardness of the hypertrophied uterus in chronic endometriotic states.

6

The Vagaries in the Response of the Endometrium to the Cyclic Influences

I wish to emphasize the futility of attempting a diagnosis from curettings, and particularly from small portions of endometrium obtained by suction. Anyone who is conversant with endometrial conditions must know that the uterine lining is in a constant state of flux in response to the menstrual hormonal influences, and that in these there is not only a quantitative element, but a qualitative synchronism of the greatest importance. There is not only quantity, but timing. Moreover, the endometrium, as regards the influence of the hormones upon it, displays a specificity and selectivity most astounding.

There are two known ovarian hormones which play the principal rôles in the uterine menstrual cycle, and in the uterine changes of pregnancy. These are the follicular hormone (estrin), and the agent of the corpus luteum (progesterone). The former, estrin, is the growth hormone, causing hypertrophy and multiplication of the uterine cellular elements. Its action is normally limited to the superficial two-thirds of the endometrium. It is only when this hormone is in excess of the non-pregnant or prepregnant needs that its action extends beyond these limits. Let me clarify this matter, for it is essential to an understanding of the sequel.

In the menstrual cycle, nature does not expend any more energy than is necessary to bring about a certain physiologic result. The result to be achieved, and the *raison d'être* of this cycle, is to prepare the endometrium to a suitable state of semifluidity to permit nidation and nutrition of the ovum. As nidation of the ovum in its initial stages involves only the surface layers of the endometrium, we find that the cycle prepares only the surface third—and, to a lesser degree, the middle third—but does not perceptibly affect the basal third. This is a conservation of energy on the part of nature. And when conception does not take place, the inner third of the endometrium (which has gone a long way in a specific differentiation) cannot revert, so it is cast off. During the follicular stage

hypertrophy is the predominant feature. In the luteal stage secretory development is the striking feature to produce a succulence that makes for easy nidation and nutrition. Having considered the functions of these hormones, it may be added that their action may be intensified or weakened by the actions of other extrapelvic hormones, such as, for example, the thyroid, adrenal, or pituitary.

Let us now bring this knowledge to bear upon this group of endometriotic diseases. The selectivity of the ovarian hormones for the surface layer of the endometrium has been noted. But there are other points of hormonal or endometrial selectivity that are not so commonly known. One of these is: one may find in a single microscopic field of the endometrium a cyclic reaction which is intense and may extend through all the endometrial depth down to the muscularis, and in close proximity to this there may be another area which exhibits complete immunity to the hormones, from the surface of the endometrium down to the deepest layer. Such islands of lack of response are extremely common, but have seldom, if ever, been described.

This same specificity of tissue is often seen in glandular endometrial endometriosis. Islands of the endometrium may exhibit a massive glandular-tissue development, and in its immediate neighborhood there may be a quiescent normal area. The same has been found in cases of very early, microscopic endometrial malignancy, where the margin between new growth and unaffected tissue is as clean-cut as if done by design.

In a previous work, entitled "A Clinical and Pathological Study of the Permanently Enlarged Uterus," I stated that this clinical selectivity is just as inexplicable as bacterial tissue selectivity, but that basically both are chemical affinities. But why should an island of tissue differ from its immediate environment? One may be even more specific in one's observations. I have seen a cross-section of an endometrial basal gland completely responsive to the follicular and lutein hormones in one-half its circumference, while the other half presented all the microscopic properties of an unresponsive normal glandular lining. I have seen the same conditions in early malignancy of the uterine tubular and cervical racemose glands.

There is something in the physiochemistry of these unaffected tissues which protects them from the glandular activators which bathe all these tissues in a common lymph and plasma. No one has fathomed the depths of this tissue individuality which seems to be determined not only by site and environment, but also by an obscure vital chemistry which is intimately bound up with our profoundest cellular idiosyncrasies. There is a strange anatomic arrangement of endometrial vascularity which may explain many of these vagaries.

The vascular distribution of the endometrium has been under intensive

study for years in the research laboratories of St. Mary's Hospital. We have found that the uterine arteries which emerge from the uterine muscularis to enter the endometrium have all the normal constituent coats of permanent blood vessels of similar size in other parts of the body. The endometrium is not pervaded by thousands of small vessels which emerge from the myometrium into the endometrium, but the plan generally is as follows.

One large vessel perforates the myometrium and ascends into the endometrial layers perpendicular to the endometrial surface. From this main trunk a very great number of branches, like those of a pine tree, run at right angles (that is, parallel to the surface). The trunk vessel usually has all the essential coats of an artery—adventitia, muscularis, elastica, and intima. As one recedes from the trunk the branches lose first the adventitia, then the elastica, and lastly the muscularis. The endometrial tissue in the immediate neighborhood of the main trunk behaves as does the basal layer of the endometrium. It does not respond to the hormones of the cycle. And, what is more interesting, is that it is not cast off like the rest of the endometrium at the menstrual flow.

In other words, these constitute the islands of quiescent endometrium which do not respond, except probably mildly, to the ebb and flow of the cycle. Here again we see a conservation of energy in that the endometrium of renewal after menstruation can proceed, not only surfacewards from the basal layers, but laterally also from these pillars of unaffected tissue. These main arterial branches have been seen quite unaffected in the height of menstrual changes, both before and after the onset of the flow. And from a careful study of these vessels one is convinced that this lack of response is not a fortuitous monthly arrangement, but that these islands have a vascular tree with all the hallmarks of permanency. It is my opinion that these endometrial insular trunks are those from which the placental sinuses derive their arterial blood supply, but of course it is impossible to prove that that is so.

I will have occasion throughout this book to point out how this selectivity in specificity operates in all the various types of endometriosis. It will be shown that this selectivity not only is local, but that cells derived from the surface layers of the endometrium, which responds to the hormonal influences, carry with them that same susceptibility and responsiveness when transplanted to any new area, and that endometrial cells not so endowed remain unresponsive when similarly transplanted. The importance of this broad statement will be accentuated when dealing with the separate regional plants of endometriosis. Were all the endometrial cells susceptible to the menstrual hormones, the destructiveness of endometriosis would be increased tremendously. Or were it possible

for active endometriosis and pregnancy to co-exist, the destructiveness of endometriosis would be inconceivably increased, owing to the great surcease of the ovarian hormones during pregnancy. Fortunately for womankind active endometriosis and pregnancy *never* co-exist.

7

Parietal Endometriosis and Endometrioma

Before entering upon a description of the pathology of this invasive disease, it will be advantageous to study certain normal and quasi-normal conditions that have received scant consideration yet must be understood in order to draw the line between physiology and pathology.

In a work published in the *Transactions of the American Association of Gynecologists, Obstetricians, and Abdominal Surgeons* in 1937, after an exhaustive study of interstitial or stromatous parietal endometrioma, I found that the stroma cells of the uterine mucosa normally permeate between muscle bundles—first in thick bands, but dividing into finer and finer ramifications like the roots of a tree, eventually losing themselves in the middle and outer thirds of the parietal thickness. (Fig. 1.) These strands can be recognized by their deep-staining properties with hematoxylin, and can be seen to advantage with a low magnification and with the slide held up to a window. The size of these roots differs in different uteri, not only in their thickness, but also in the depth to which they can be traced as they permeate the uterine wall. In a large percentage of cases, undoubtedly the permeation has reached proportions that are definitely pathologic, but, as it is a normal condition for the endometrial stroma to invade the interfasicular bundles, one is forced to ask oneself the question, "To what depth and in what quantity should we consider this of normal degree?" It is, as yet, impossible to give an adequate answer to this problem.

There immediately follows upon this a second question. Should the glandular elements of the mucosa cease abruptly at the basal layer of the mucosa, and not penetrate at all into the muscular tissue, or is a moderate degree of penetration normal? Until an answer to these questions is forthcoming it will be impossible to draw the line between incipient invasive parietal endometriosis and normalcy. However, there are certain limits, and these will vary with the interpretation and experience of each pathologist, beyond which the condition will be definitely set down as pathologic.

Parietal endometriosis implies a diffuse invasion of the uterine wall,

but not necessarily involving all the uterine muscularis, nor the whole depth of the uterine wall. The process may implicate only the anterior or the posterior wall, or only a portion of these. Several independent parts of the parietes may be affected simultaneously. The disease is characterized by an invasion of the parietes by cellular elements which normally compose the uterine mucosa. These invasions may be composed of both the elements, glandular and stromatous (in which these two may vary quantitatively in wide limits), or the pervasion may be composed solely of stroma cells.

The term parietal endometrioma, on the other hand, is applied to that type of growth which is restricted to a circumscribed area or areas, where it has developed into a definite local tumor resembling, in outline, ordinary fibromata. These again may be composed of all the cellular elements of the mucosa, and would then be designated as an endometrioma, prefixed by the dominant tissue in which it is embedded. On the other hand, the new growth may be made up wholly of endometrial stroma cells without glandular elements, to which the designation of stromatous or interstitial parietal endometrioma is applied.

The following classification of parietal endometriosis, therefore, can be differentiated:

1. *Mixed endometriosis* — in which the uterine wall is invaded (generally or locally) by both glandular and stromatous endometrial cells.
2. *Stromatous endometriosis* — in which the uterine wall is invaded diffusely to abnormal depths by the stroma cells of the uterine endometrium.
3. *Mixed endometriomata* — in which the parietal invasion by both endometrial elements is accumulated in localities in the uterine walls to form definite tumor growths causing asymmetry.
4. *Stromatous endometriomata* — in which these tumors are made up wholly of stroma cells of mucosal origin and devoid of glandular elements.
5. *Malignant stromatous endometriosis*

PARIETAL ENDOMETRIOSIS

As stated in the foregoing paragraph, the invasive process begins at the basal layer of the uterine mucosa, and gradually infiltrates into the spaces between the muscle bundles. The scheme is fairly uniform in its

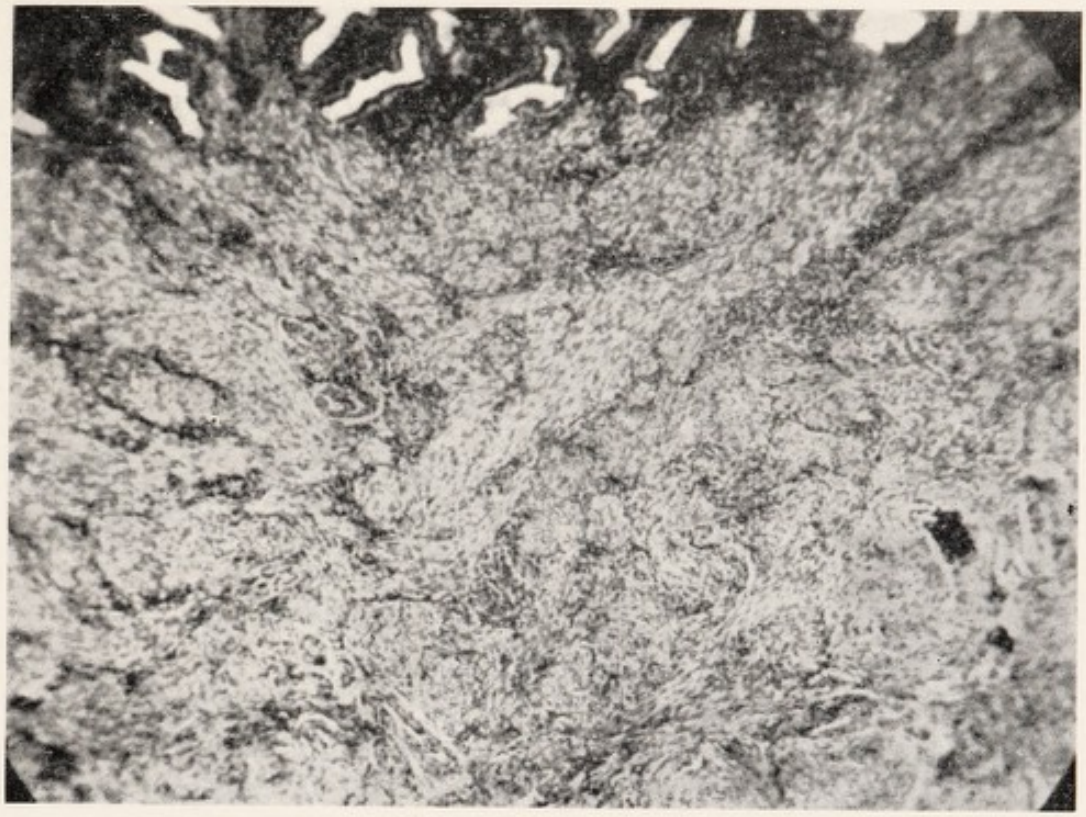


FIG. 1. Roots and rootlets of interstitial stroma pervading the muscular uterine wall, from the mucosa inward. One can trace them to the subperitoneal surface.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricians, and Abdominal Surgeons, *50*:197, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

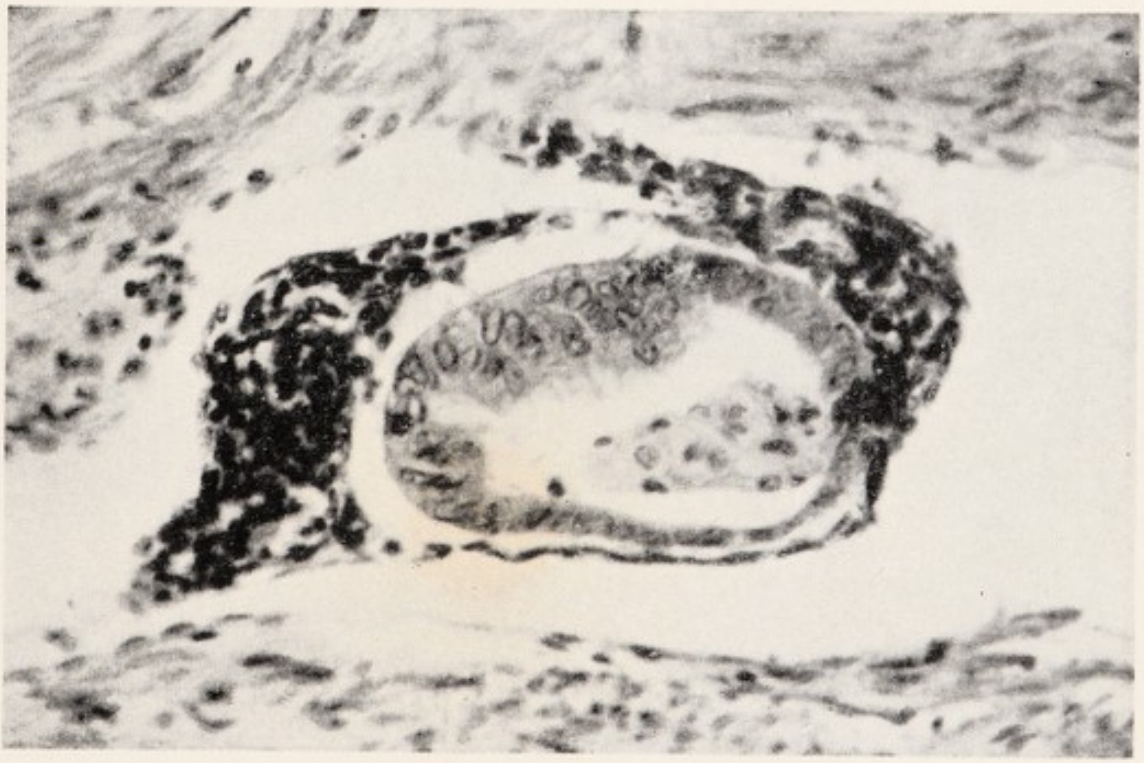


FIG. 2. Photomicrograph (× 310) consisting of an epithelial gland surrounded by endometrial stroma and the latter apparently covered by endothelium.

(Courtesy of John A. Sampson, M.D.: in Amer. Jour. Pathol., *3*: Plate 30, 1927, Cambridge, Mass., Harvard University Press.)

method. The advance is always along the connective tissue between the muscle bundles, in which the lympatic vessels and blood channels course to and from the periphery of the uterus. The usual arrangement is for the stroma cells to precede the glandular elements, so that penetration by the stroma is usually far in advance of the front-line attack of the glandular elements. The result is that each glandular tongue is clothed by a zone of stroma cells which insulates it from the fixed tissues of the uterine wall.

But this is not always the case. Occasionally one finds an isolated branch of a gland which has made a byway for itself and lacks the insulation of stroma. Whether the insulation is merely reduced to a minimum, or totally absent, is a point which I have never been able to determine to my complete satisfaction. Upon this decision hangs a very important issue. There are those, on the one hand, who contend that in the invasion of ectopic endometrium, both glandular and stromatous elements must penetrate—not necessarily simultaneously—but must penetrate, nevertheless, to reproduce *in novo loco* the two endometrial elements. There are those, on the other hand, who maintain that the glandular elements of the endometrium are the progeny of the stroma cells, and that the metamorphosis is basically a question of suitability of milieu for this transformation. At the present date it is still a very debatable point, and until some more concrete evidence can be adduced we are compelled to leave this question *in statu quo*.

In my work previously referred to, it was shown that the uterine mucosal stroma cells normally pervade the uterine wall in fine ramifications. What depth or what size would be considered normal is a moot point, but it can readily be seen that, if these are the normal constituents of the uterine wall and if stroma cells are the parents of the glandular elements, stimulation of these resident parent cells would be all that would be necessary to awaken them into unusual activity of growth and differentiation. But against this theory are many factual evidences and arguments, though it is quite impossible totally to refute the arguments advanced above. To those who have profoundly studied the endometrial glands in the immediate vicinity of the placenta, it is evident that the columnar epithelial lining of glands so situated either reverts to the stroma-cell type, or is cast off and absorbed. That their reversion may occur in the unusual circumstances of pregnancy is not surprising, but under other circumstances I have never seen anything which had any semblance to such retrogression, though that does not necessarily imply that it cannot or does not occur. But there is considerable evidence to support the theory that stroma cells can and do metamorphose to glandular linings, and thereby become elevated in the scale of cell society.

In the first place it will be proved that endometriosis of the uterine wall is an infiltrating disease, and not an activation of normal mural

constituents; that these infiltrations penetrate beyond the walls of the uterus into areas where, so far as we know, müllerian tissue does not normally exist; and that endometriosis often is composed of only one element of the uterine mucosa. It will be shown that penetration of the uterine wall may be made up wholly and solely of stroma cells. And yet, concomitant with this, there may be a mixed glandular and stromatous invasion of the ovary. This change in the characters of the invasive elements might be advanced as an argument in favor of a metaplasia based upon differences of environment and soil. But such is not the case, for it will be shown more clearly later, and at greater length, that when conditions are favorable to invasion by the endometrial elements, various routes are open to the endometrial cells, and that the routes determine the origin and composition of the migrating cells, and also their potential functional response to hormonal influences.

Ovarian endometriosis is commonly transplanted thither by the "spill" method of cells derived from the surface of the endometrium, which are both glandular and stromatous and possess the highly specialized property of responsiveness to the cyclic hormones; whereas uterine parietal endometriosis, derived from the basal layer of the endometrium, is decidedly unresponsive. Uterine parietal endometrial invasions may be mixed glandular and stromatous, or each singly, but ovarian endometriosis is preponderantly mixed, because ovarian endometriosis is largely of "spill" origin and sequestered masses of surface epithelium from the endometrium during menstruation are invariably made up of both endometrial cellular elements.

Endometrial penetration of the parietal wall, it has been stated, may begin simultaneously over the whole basal layer of the endometrium, or it may be restricted to one wall or to only a portion of one wall. This is a process of selectivity which we do not understand. The penetration between the muscle bundles may be shallow or deep—even to the broad ligaments, uterosacrals, ovaries, round ligaments, and parietal peritoneum. If the invasion is diffuse, arising over the major part of the basal layer, the uterus will be uniformly enlarged, symmetrical, soft or hard, and the vagina and cervix will be bluish by venous congestion. This condition is frequently confused with pregnancy on the one hand, or with a fundal fibroid or a diffuse fibrosis on the other. The uterus may still retain its symmetrical character when the anterior or posterior wall is thickened to two or three times its normal thickness, and the opposite unaffected wall may retain its normal proportions or be thinned out by the intrauterine bulge of the invaded wall.

The invasion, if acute, will usually reveal an enlarged, soft uterus resembling pregnancy, and just as in pregnancy there will be a great hypertrophy of all the normal elements of the uterine wall, muscle, con-

nective tissue, blood vessels, and lymph channels. Whether this is a reactionary process in response to the pressure of a foreign growth or whether it is a concomitant response to the same hormonal vitiation that initiated and maintains the endometrial invasion, is a subject of great debate which will be dealt with at some length under general discussion. It is of importance, however, to note here that when the abdomen is opened in cases of advanced parietal invasion (even without adnexal involvement), it is found that the veins of the pampiform plexus are hugely dilated and the tissues in the immediate neighborhood of the uterus present an appearance of deep anoxemia, as already noted in the cervix and vagina.

When the penetration of the uterine wall by the endometrial elements has reached the limits of the uterine musculature, the progression from this point on depends upon the location at which the endometrial tissue reaches the uterine boundary. If it should reach the free peritoneal surface of the uterus, then implantation may take place by particles of endometrial tissue set free in the peritoneal cavity. The susceptibility or nonsusceptibility of the peritoneal organs or the ovary to the free particles will determine whether these will implant themselves immediately, or whether, like tubercular invasion of the peritoneal cavity, the particles may sink by gravity and peristalsis to the pelvic pouches or to any other shelf of quiescence, there to set up the process of infiltration.

When, on the other hand, the disease reaches the uterine limits at a spot at which the uterine wall is covered by supporting tissues or by a contiguous organ, the infiltration extends into these by direct extension or by lymphatic metastasis. The structures that may become involved in this way in the order of their frequency are: the broad ligaments, the uterosacrals, the rectovaginal septum, the perivaginal supporting tissues, the round ligaments, and other less frequently involved parametrial extensions.

MIXED PARIETAL ENDOMETRIOSIS

This is the commonest type of ectopic invasion. The process starts as an invasion of the normal parietal tissues by the two normal cellular component elements of the endometrium. (Fig. 2.) The disease arises out of the basal layer of the endometrium where the mucosa normally is in contact with the muscularis. It is seldom recognized macroscopically except when well advanced. But there are all grades of parietal permeation from quasi-normal limits to extensive infiltration to and beyond the outer limits of the uterine wall. Not only do cases vary greatly in the depth of the invasion, but they vary greatly also in the quantity of this ectopic growth, and in the relative quantities of glandular and stromatous elements in these ectopias. The disease may be restricted to a very small

segment of the uterine wall, or the process may begin seemingly all over the musculomucosal layer at the same time, thereby involving the uterine wall not segmentally but diffusely. These are vagaries that are met with in all disease processes. The uterus is enlarged symmetrically to a degree which depends upon the extent of invasion of its walls.

But there is another factor of primary importance which contributes largely to this increase in size of the uterus. It is the concomitant hypertrophy of the musculofibrous elements of the uterine wall in response to the same agent which caused the endometrial elements to pervade the tissues beyond their normal confines. In the mixed endometrial invasion, the stromatous elements always invade more deeply than do the glandular elements. It is common to find the gland surrounded by a layer of stroma cells, but at times these latter may be reduced to an almost imperceptible minimum. This is relatively rare.

On the other hand, the stromatous elements may largely predominate, and the glands consequently rare and small. Between these two extremes are all quantitative and qualitative varieties. In the vast majority of cases, however, the disease, for reasons which will be described later, remains restricted to the immediate neighborhood of the musculomucosa line. But in others the infiltration may reach the confines of the uterine wall, and invade the neighboring tissues. As explained above, if it reaches the free peritoneal surface the cellular elements may be set free in the peritoneal cavity, and transplant themselves upon any pelvic tissue upon which sufficient quiescence permits lodgment and infiltration. Then the process of invasion in this new soil continues apace if the urge is still in operation. If, on the other hand, the invasion should reach the nonperitonealized surface of the uterus, further invasion of contiguous tissues by lymphatic and blood-vessel extension is the rule. In cases of peritoneal soiling, as described above, adhesions must necessarily follow by virtue of the intraperitoneal implants. But in the second type of invasion of the neighboring organs by lymphatic and blood-vessel extension, the newly invaded tissues become thickened, enlarged, and pervaded by the endometrial elements.

Finally, however, the two types in the end-results are frequently similar. For example, in the cases of direct peritoneal invasion the cells usually gravitate to the pouch of Douglas. In this locality they penetrate subperitoneally and invade the subjacent connective tissues, causing dense adhesions which are indistinguishable from a local direct extension through the uterine wall in this region.

In both these types of extensions the adhesions may be restricted to one area where the sedimentation has occurred, or where the direct extension has broken through, and in many of these cases the ovaries and tubes may be found quite free from any involvement. This is, of

course, not the rule, but such cases are very instructive in that they indicate very emphatically how the extension has taken place.

Once the extension has gone beyond the uterine wall there may be no limit to the involvement of the subjacent tissues, though like all endometriotic ectopias the disease is restricted to the body below the level of the umbilicus as an upper limit, and to the level of the vulva as the lower limit. Within this segment of the body the disease may be widespread and may cause not only serious new growth, but also synechias which destroy contours and impair normal function.

PARIETAL OR INTRAMURAL MIXED ENDOMETRIOMA

Endometrioma, if studied carefully by serial sections, will show in a goodly percentage of cases the line of glandular endometrial structure which unites them with the basal endometrium of the uterus, though in many instances it is quite impossible to demonstrate this continuity. And that is as one might expect, for it is well known that ectopic tissue may spread by direct continuity or by lymph-channel metastasis.

Endometriomata may vary in size from microscopic to large dimensions, and clinically are usually mistaken for fibroids. The quantity of endometrial tissue in endometriomata varies within wide limits. In most instances the amount is small, and is usually sparsely scattered in a matrix of fibrous or muscular tissue or of both of these, so that the endometriosis may be absent from many sections and present in others. The glands usually have a minimum of stroma cells about them, and therefore present a picture closely resembling an adenoma—hence, the designation fibromyo-adenoma that has frequently been applied to this type of intramural growth. Macroscopically the tumors of this type are indistinguishable from fibromyomata. In others of a different type, the ectopic endometriosis is more abundant and the hypertrophic fixed tissues of the uterus are less dense, more edematous, and the endometrial stroma cells are much more abundant. Not infrequently, when the uterine wall is cut through, the islands of endometrial tissue are of a yellowish color and of a softer consistency than the surrounding matrix. In many instances there are evidences of small cystic degenerations presenting a lemon-pulp appearance and consistency. Small pin-point old hemorrhagic areas are common, and are diagnostic. Usually the bloody contents are blackish and granular, but never coagulated.

It is generally thought that endometriosis, wherever found, responds to the hormones which govern the cycles. This is not true, however. One may state as a general physiologic law that only certain cells of the endometrium are hormone-sensitive to a degree which elicits cyclic changes, and that cells so sensitized retain those characteristics wherever and whenever transplanted, and transmit those properties to their de-

scendants. This law is now stated for the first time. It has a profound and wide bearing upon the destructiveness and spread of endometriosis. Let me repeat here that only the surface layers of the endometrium respond to the cyclic changes. The deepest layers are immune. Therefore, according to this law, only susceptible surface layers can beget susceptible cells, and conversely, only immune cells can beget immune cells. It is therefore easy to see that parietal invasions of the uterine tissue are invariably derived from the deepest layer of the endometrium, which is nonsensitive to the ovarian hormones. Consequently, the parietal invasions do not bleed at menstrual epochs, and therefore do not produce intra- and periglandular blood and chocolate cysts, such as occur in *most* instances in ovarian endometriosis.

I emphasize the term "most" in the foregoing sentence because it will be pointed out later that most cases of ovarian endometriosis are derived from a tubal "spill," in which the cells are offcasts from the surface of the endometrium and therefore hormone-sensitive. But in a few cases the ovary becomes invaded by the endometrium by direct lymphatic extension from a parietal endometriosis, and in these instances the ovarian ectopias do not menstruate and are at times indistinguishable from ovarian endosalpingiosis. It is therefore clear that the ovary may be invaded by surface contamination; or through the lymphatics or blood stream by endometrial cells with very different susceptibilities, but having one common property—that of invasiveness. It may again be emphasized that only surface endometrial tissues and their derivatives are hormone-sensitive. And this constitutes one of the strongest arguments against the peritoneal origin of endometriosis, in that peritoneal cells never menstruate and cannot be made to menstruate, no matter what their environment may be.

If parietal endometrial invasions responded to the hormone of menstruation, then in all cases of parietal endometriosis we would find the uterine wall riddled with blood cysts of all sizes and ages, and the uterus would reach enormous dimensions. We would expect conditions to parallel those that usually occur in ovarian endometriosis. But we know that parietal endometriosis very rarely produces blood cysts, and that when these occur they are usually of pin-point dimensions and are atrributable to an entirely different cause. To clarify this point it may be stated that only a percentage of cases of unusual uterine hemorrhage is due to defective ovarian function. In a large percentage such hemorrhages are due to extrapelvic causes that may be toxic or metabolic. Under these circumstances the uterus bleeds more frequently than other organs because it is an organ that bleeds easily—it has the habit of bleeding. And at the premenstrual congestion and in the menstrual flow the pelvic organs would be more susceptible to the bleeding tendency than would other

extrapelvic organs not susceptible to these environmental changes. The mucous membrane of the nose is the one membrane that is subject, to a slight degree, to these sexual changes of congestion and diapedesis. Hence the frequency of nosebleeds at menstrual periods, the recognition of vicarious nasal menstruation, the intractability of nasal infection during the menstrual phases, and the nasal erectile influence during sexual excitement.

Let me detail a recent case of parietal endometriosis with small hemorrhages. A woman aged 37 years, married 15 years and sterile, consulted me for metrorrhagia. She had been previously regular and normal. She had been bleeding steadily and profusely for 18 days. On examination I found the uterus hard, and symmetrically enlarged to the size of a two-months' pregnancy. Intramural fibroid was suspected, but there was a distinct infiltration of the tissues posterior to the cervix. The bleeding stopped spontaneously, and menstruation recurred normally twice afterwards. As I had recommended operation at her first visit, she insisted upon that policy being carried out.

Upon opening the abdomen the uterus was found enlarged, symmetrical, and fixed at its vaginal attachments. The peritoneum was free everywhere, and the ovaries normal except for a small cyst on the left. But the posterior wall of the enlarged uterus showed blue-black subperitoneal spots which were at once diagnosed as uterine endometriosis with hemorrhagic cysts. Consequently both ovaries were removed, and a total hysterectomy was performed in which the cervix was bound posteriorly in dense endometrial invasion. On section of the uterine wall, the whole was disseminated with endometriosis and small endometriomata, with small hemorrhages of various sizes from microscopic points to that of a pea. The blood was old and black. Under the microscope only about one cystic cavity in 50 had bloody contents, and there were evidences in the ovary of old interstitial hemorrhages that had occurred synchronously with the metrorrhagia. The ovaries were otherwise normal and absolutely free from endometrial invasions.

This case, and a few others with somewhat similar experiences, emphasize the rarity of intramural endometrial hemorrhages. Parietal endometriosis, however, I consider one of the commonest gynecologic diseases, outnumbering ovarian and other forms of endometriosis in the ratio of about three to one. And yet intramural hemorrhages in these cases are quite exceptional, whereas in ovarian endometriosis hemorrhages are the rule and not the exception. In all cases of active parietal endometriosis there is hypertrophy of the normal muscular and connective-tissue elements of the uterine wall; in the third and fourth decades the coincidence of tumors of these elements in the form of fibromata, myomata, and fibromyomata is frequent; and endometrial elements are

frequently incorporated in these to constitute mixed tumors composed exclusively of uterine mucosal and parietal tissues.

Endometriomata cannot be differentiated except in rare cases where complications have occurred. In about 30 per cent of cases of endometriosis, of whatever type, there are also fibromata and myomata. These associated complications, though rare between 18 and 30 years of age, grow more frequent in the later years of the third decade. This association will be dealt with under the chapter on associated diseases.

8

Diseases Caused by the Invasion of the Uterine Parietes by the Stroma Cells of the Endometrium

GENERAL

In my papers on stromatous (also called interstitial) endometriosis, published in 1937 in the *Transactions of the American Association of Gynecologists, Obstetricians, and Abdominal Surgeons,* and in 1939 in the *Journal of Obstetrics and Gynæcology of the British Empire,* I presented 14 cases grouped as follows: 2 cases of stromatous endometriosis, and 12 cases of stromatous endometriomata. This grouping was correct up to a certain point. Later developments and the careful examination of many new cases, as well as more precise distinctions in growth-study, require that I should revise the groupings then made. The endometriomata are as heretofore described, but the cases of endometriosis fall into two categories which are quite distinct, both in manner of growth and in courses of the diseases. So, with our present knowledge, we can distinguish the following types:

1. Chronic uterine stromatous endometriosis.
2. Chronic uterine stromatous endometriomata.
3. Acute endometriosis with restricted malignant characters.

The chief difference in this new classification consists in placing two cases of stromatous endometriosis in a separate group—a restricted malignant group. Whether these cases are really malignant in their characters is doubtful, but you can judge for yourself by the description (which is now complete, because both cases died of endometriosis, or rather, of the consequences of endometriosis). Both became x-ray–fast over a long period and would not respond to treatment, and became metastatic outside the pelvic limits—in the lungs—only just before death. So much for these two cases which are so parallel in all their characters and course as to be a disease entity.

The division of the other cases into chronic stromatous endometriosis and endometriomata is purely an arbitrary one. In the endometriosis

cases the disease is an infiltrative process without definite tumor formation, and therefore without loss of symmetry on the part of the uterus. In the endometriomata the growths have become isolated like fibroids, and may vary in size just like fibroids, usually with loss of symmetry of the invaded organ. Of course, it will be readily understood that both types may be found coincidental, just as fibroids and fibrosis are commonly associated, but as we distinguish between fibrosis and fibroids so it is thought proper to retain the same distinction between stromatous endometriosis and stromatous endometriomata.

Most of the cases described presented stromatous invasions almost completely devoid of glandular endometrial elements, but in subsequent studies many cases have been found with mixed elements. In these the glands have been few and scattered, so that an isolated gland was frequently found only after careful search in many sections. The glandular elements, though usually few, may vary considerably in numbers.

So also in the slowly growing invasion the component stromatous cells may vary in shape and arrangement, depending upon the rate of growth, the soil, degeneration, and regression. These will be dealt with more minutely in the definition of the cases.

In these articles there are descriptions of 14 cases of chronic stromatous endometriosis and endometriomata. It will readily be understood that the division into acute stromatous endometriosis and chronic stromatous endometriomata is an arbitrary one. Rapidity of growth is purely a relative term, and endometriomata of all kinds are relatively slow in development. The extremes of these two diseases are vastly different, but intermediate cases are also found where there is a combination of diffuse infiltration and of aggregate growth in the form of tumors, just as we find cases of diffuse fibrosis uteri, cases of fibroids, and combinations of both conditions.

The interstitial or stroma cell of the endometrium is a highly endowed structure with a potentiality for differentiation which makes it a close second to the interstitial cells of the ovary, with which it has much in common. Ordinarily, and under normal stimulation (and therefore when in normal function), its activity is restricted to a fixed rate of division. This may be physiologically accelerated by the hormones which determine the menstrual cycle, pregnancy, and postconceptual periods. Its activities are usually reduced to a quasi-quiescence before puberty and after the menopause. During the sexual age, the stroma cell is in a fairly constant state of change—a state of flux—and in this restless state it is prone to pass over into aberrant activity, and take on invasive properties. In the opinion of some investigators, a stroma cell is always a stroma cell. Others claim that it is the progenitor of the gland cells of the endometrium, in the same manner that ovarian stroma cells may become

granulosa and lutein cells. If and when so raised in its social class, it may revert only with great difficulty to its former state, I think, under the potent influence of the pregnancy hormones. Especially is this true in the region of the placental implantation. These, its chief properties, it possesses and elaborates under the domination of the ovarian hormones which play with it as with a bauble, though ordinarily the play is restricted to certain well-defined limits.

Frequently, however, such is not the case, and under excessive stimulation, or due to the withdrawal of a restraint upon cell division, the endometrial stroma cell becomes an invasive agent, frequently mildly invasive, at times almost sarcomatoid in its appearance and spread. Certain it is, that in its invasive properties the stroma cell retains many of its normal physical appearances. Uterine glands are totally absent in the majority of instances, though occasionally a stray acinus may be found—usually in the periphery of the stromata. This latter statement applies only to the stromatous endometriomas, and not to the more acute stromatous endometriosis. In the latter group glandular elements are wholly absent. Those who maintain that stroma cells differentiate themselves into glandular lining might here contend that division in these acute cases is too rapid to permit of normal differentiation, and that the law that differentiation is inversely to division still holds true; whereas, in the more chronic endometriomas, occasionally a gland may be found. This was true of Casler's case of stromatous endometrioma, in which an occasional gland was seen. This, however, is not true of 11 of my 12 cases of stromatous endometriomata. It is not known whether, under normal conditions, these cells possess a function other than responses to the ovarian hormonal influences. But in the new growths under description it is never found that there is any response to these influences. It is a typical new growth, varying in different cases in physical characters much like other new growths.

Chief among these recognizable differences is cell morphology. In the rapidly growing endometriosis and endometriomata the component cell is small, rounded, and presents a nucleus which stains deeply with hematoxylin and has a definite nuclear membrane. The protoplasm is clear and scanty, such as one finds in round-celled sarcomata. In the more chronic growths the cell takes on varied degrees of spindle-shape and streamlined configurations, much as one finds in corresponding sarcomatous types.

CHRONIC PARIETAL STROMATOUS ENDOMETRIOSIS AND ENDOMETRIOMATA

The first case of this type of invasive disease was described by Casler in 1919. The condition is characterized by local invasions of the uterine

wall by the stroma cells of the endometrium—of such a nature as to produce either diffuse infiltration (endometriosis) or a single or multiple intramural tumors (endometriomata) resembling, more or less closely, fibroids (but, unlike fibroids, frequently associated with endometriosis of the appendages or other pelvic organs, causing what is known as conglomerate tumors).

In a work read before the American Association of Gynecologists, Obstetricians, and Abdominal Surgeons in 1937, 12 of these cases are reported with two cases of acute endometriosis. At that time it was not known by me that Casler had described such an endometrioma, and his description kindly being called to my attention, I immediately acknowledged it, according him priority. I owe this courtesy to Prof. Daniel Dougal of Manchester, England, who later kindly sent me a report and photomicrographs of an undoubted similar case that had just come under his observation.

Since my cases were reported in the *Transactions* of the Society in 1937, and later in the *Journal of Obstetrics and Gynæcology of the British Empire,* several other surgeons have written me of cases of this nature that have come under surgical treatment, and many others have been found in my operative clinic at St. Mary's Hospital. There are 12 cases reported in the *Transactions*. The description of the cases of endometriosis given in the previously mentioned articles will be reviewed in part and a few more recent cases which add to our knowledge will be added.

Case I. Mrs. G., aged 35 years, a mother of three children, with nothing in her history referable to pelvic disorder, came complaining of general weakness and fatigue. She could "scarcely drag herself about." The menstrual function was normal in every respect, except that she had a copious leukorrhea. On physical examination there was a severe chronic endocervicitis and cervicitis, with a large, globular, superimposed uterus.

Operation. Operation for total hysterectomy and ovariotomy was performed in October, 1933. The peritoneum was free from adhesions—except on the left side of the posterior leaf of the broad ligament where the ovary was densely adherent—and, when separated, there was shown the presence of old blood and cicatricial puckering of the ovarian capsule so characteristic of endometriosis.

Pathologic Report. Sections of the uterus revealed a penetrating growth with the diagnosis of diffuse, small-celled sarcoma of the uterus. Unfortunately, sections of the ovary were not preserved. Revision of this case and its sections elicits the typical characters of an endometrioma interstitiale. There is widespread invasion, without destruction. Changes of a hyaline nature with dilated lymphatic spaces exist, but these, it is

thought, are co-existing rather than associated changes. They are found so commonly in all pathologic uterine states.

The arrangement of the growth is strongly suggestive of malignancy, however, and the arborizations stain most intensively with hematoxylin, in marked contrast to the surrounding hyaline-infiltrated fixed tissues that take the pink eosin. There are not any glands present, and the individual cell morphology differs in different portions of the uterine wall, due more to compression and probably nutrition conditions. The general type of cell is the hematoxylin-stained clear protoplasm, with a large oval nucleus, granular and filamented with a deeply stained nuclear membrane. Mitotic figures are relatively rare. The patient is alive and well at the time of writing.

Corrected Diagnosis. Ovarian endometriosis and uterine interstitial endometrioma.

Case II. Mrs. W., aged 43 years, consulted Dr. J. Quinn on February 16, 1936, complaining of fatigue, brown vaginal discharge, loss of weight, and nervous instability. She stated that with the exception of a "flooding" three years ago, her menstruation had been perfectly normal until January 1936, when she noticed that for about three days prior to the onset of her period she had a thin brown odorless discharge and a similar discharge for the same period after her last menstruation. Her periods lasted from four to five days, and were not excessive. For the past 18 months the patient had not felt well, she tired very easily, and became unusually upset for no apparent reason. She lost approximately 15 pounds in weight in the past 12 months. The bowels were regular and there were no urinary symptoms. She had four normal pregnancies and four miscarriages. The youngest child was 12 years of age. Two miscarriages preceded, and two closely followed the last child. Her periods had always been regular, with the one exception mentioned previously. Her family physician said at that time he thought she had a small pelvic tumor, but that he was not certain. The writer saw the case in consultation on February 18, and found a large fibroid filling the pelvis, and a copious, yellow, watery, vaginal discharge (a mass of which came away in the examining hand in the form of a vaginal mold—obviously coagulated lymph). Malignancy was suspected.

Operation. At the operation, which was difficult owing to her obesity, the uterus was symmetrical, free from adhesions, and the size of a four-months' pregnancy. The ovaries, enlarged and cystic, were adherent. Total hysterectomy and removal of both appendages was performed. Her recovery was uneventful. When the uterus was incised there was what was considered a large fibroma filling the fundus, and encroaching

markedly upon the cavity of the uterus. At this point the uterine wall was thinned out and the mucosa atrophied by pressure. When the tumor was incised it cut easily, was the size of a grapefruit, and was filled with a clear fluid which coagulated upon cooling. The inner surface was very shaggy, with numerous pockets. The ovaries were markedly cystic, and considerably enlarged. There were two cysts filled with old blood.

Pathologic Report. Specimen consisted of a large globular uterus, 11 cm. in diameter. The uterine wall was 2.5 cm. thick. The cervix had been mutilated (sections having been removed), so a description cannot be made. Growing in the fundus and posterior wall was a globular tumor impinging upon the whole canal. The external surface was smooth, and matted with adherent blood clot. This tumor had already been opened, and presented a shaggy broken-down center with pockets filled with a clear yellow fluid. On anteroposterior section this growth blended almost imperceptibly with the uterine wall; there was no line of demarcation. The tumor, except in the edematous areas, had a slight yellowish tinge, and could be seen irregularly infiltrating the uterine wall.

Microscopic Examination. Sections taken through the tumor and uterus showed hypertrophy of the myometrium. As this was followed centripetally, the well-differentiated muscle gave way to a dense, closely cellular mass. At this boundary zone there was a rather sudden transition of the muscle cells into tumors. This line of demarcation was irregular, and islands of well-differentiated muscle could be seen lying within the tumor. Throughout the tumor mass there were numerous wide spaces filled with albuminous coagulum. This indicated edema of the tumor. Many of the vessels consisted of an endothelial wall only; others were surrounded by muscle, which indicated that the tissue was growing in preformed tissue. The cells of the tumor were large, elongated, with pale cytoplasm with indistinct margins, and the cells fused with one another. The nuclei were large, with a distinct nuclear membrane and pale nucleoplasm, with numerous dots of chromatin. A few contained nucleoli. Mitotic figures were relatively few, and there were no giant cells.

Diagnosis. Sarcoma of the body of the uterus.

Today, three years after operation, the patient is in excellent health. Re-study of these specimens showed them to be of the interstitial endometrioma type that was undergoing degeneration and liquefaction. This is a common complication of endometrioma, as will be shown in subsequent histories. The lymphatics deep in the uterine wall showed invasions by masses of endometrial cells, and accompanying the uterine endometrioma was a diffuse adenoma of the cervical canal originating from the racemose cervical glands and a precancerous state of both the

cervical epithelium and of the squamous epithelium of the portio, all of which are frequent concomitants of endometrioma and endometriosis, and are due to a common underlying stimulant.

Corrected Diagnosis. (1) Chronic degenerating uterine interstitial endometrioma. (2) Adenoma of the cervix. (3) Precancerous cervical changes.

Case III. Mrs. de V., aged 50 years, entered St. Mary's Hospital on April 30, 1936. Her complaints were loss of appetite, swelling of the ankles, menorrhagia, and metrorrhagia. She stated that she was well until one year previous. Until that time her periods were always regular, duration four days. It then changed to the ten-day type, the flow becoming excessive. One month ago she had a flooding ten days after her regular period, preceded by the expulsion of a quantity of watery fluid. The same condition of watery discharge followed six days of bleeding. Ankles had swollen for the past year. She had had three normal pregnancies—the oldest child was aged 32 and the youngest 22 years—and she thought she probably had one miscarriage between them. She had always enjoyed the best of health, except for an operation for umbilical hernia 18 years ago. On physical examination there was a large mass filling the lower abdomen, the size of a five-months' pregnancy. She said that it seemed to vary in size daily, and was exquisitely tender.

Operation. Upon opening the abdomen the uterine tumor was the size of a 4.5-months' pregnancy. There were no adhesions. Both appendages were the size of a tangerine. A subtotal hysterectomy was performed, and total ablation of the appendages was done. Recovery was uneventful. It may be noted that she had only 53 per cent hemoglobin, but 4,390,000 red blood corpuscles, a fair degree of hypochromic anemia, and a high percentage of blood sugar of 180 mg. Transfusion and sugar control were practiced before operation.

Upon opening the uterus there was found a large tumor of the posterior wall, causing it to bulge into the cavity. Upon opening the tumor it was found filled with a pink grumous liquid in a shaggy cavity, with large cavernous spaces that could easily be broken into with the finger. The tissue was very friable. The line of demarcation between tumor and muscle varied. In places it was sharp, in others slowly transitional. The mucosa was thick and yellow.

Microscopic Examination. This showed a richly cellular fibroid undergoing red degeneration. However, there were numerous other spots in the uterine muscle filled with the same type of cell. Some of these were close to the mucosal interstitial cells with which they were continuous. Others were deep into the subperitoneal region. In this area there were

several distinct patches of glandular endometrial tissue. The mucosa presented the typical Swiss-cheese type. The ovaries were cystic, due to many unruptured graafian follicles.

On re-examination this case proved to be a typical interstitial endometrioma undergoing liquefaction, complicated by a hemorrhage into the cavity. There are the scattered associated nodules in the uterine wall near and far from the mucosa, and a glandular endometriosis near the peritoneum.

Corrected Diagnosis. (1) Chronic interstitial endometrioma. (2) Chronic uterine glandular endometriosis. (3) Liquefaction and hemorrhage.

Case IV. Mrs. G., aged 49 years, entered the Homeopathic Hospital in June 1935. She had had severe hemorrhages in all her labors to the degree that she was exsanguinated after each. She always menstruated for ten days, and abundantly. For the past three months there had been metrorrhagia, and severe dysmenorrhea during the first three days of the flow.

Mrs. G. was one of those individuals with overrefinement of their tissue, which makes them correspondingly unstable as to their functions. The sclerotics were pale and the skin of extremely delicate texture. She was a tissue aristocrat.

On pelvic examination the uterus was enlarged symmetrically and about the size of a two-months' pregnancy. The cervix was large and hard. The uterine body was soft, and Hegar's sign was marked, but there was no other sign of pregnancy. There was tenderness and fixation of both appendages. Her youngest child was five years of age, and the writer had sterilized her by sectioning the fallopian tubes shortly after her last pregnancy, owing to her hemorrhagic tendencies. At that time the pelvis was normal.

Operation. Median incision. A diffuse endometriosis of both ovaries with chocolate cysts was found, and a large soft uterus the size of a 2.5-months' pregnancy. Panhysterectomy was performed. Recovery was uneventful.

On opening the uterus there was a diffuse thickening of the uterine walls, and a tumor of a pale yellow color and softish consistency in the right posterior wall. Upon squeezing the wall numerous points of oozing could be seen upon the cut surface, and the tumor could be scooped with the finger. The fundus of the body of the uterus was filled with a shaggy growth of the endometrium springing from all parts of the fundus. This was thought to be cancerous. Sections showed a widespread endometriosis of the appendages, a typical infiltration of the uterine wall by interstitial endometrial tissue, concomitant hypertrophy of muscle, and

an interstitial endometrioma infiltrating the uterine wall. There was also a most marked benign endometrial mixed endometriosis of the uterine mucosa, and areas of adenoma of the cervical glands.

Corrected Diagnosis. (1) Endometriosis of the appendages. (2) Endometrial endometriosis of the uterine mucosa. (3) Adenoma of cervical glands. (4) Diffuse interstitial endometriosis of the uterine wall, and an interstitial endometrioma.

*Case VI.** This is the crucial case of the series that brought the subject of interstitial endometrioma into a clear perspective.

Mrs. D., a patient of Doctor Power's, entered St. Mary's Hospital with the preoperative diagnosis of degenerating fibroid with infection superimposed.

Her complaints were menorrhagia and metrorrhagia, and abdominal pain. The onset dated back seven weeks, was acute in character, and the patient was confined to bed for four weeks before Doctor Power saw her in consultation. The writer saw her in consultation two days later. She was a young married woman, aged 26 years. She had been married but a short time and had never been pregnant. There was a copious serosanguineous discharge, and a healthy pale introitus. There was a large mass filling the pelvis, rising to within an inch of the umbilicus, a diffuse infiltration of the pelvis which suggested a widespread infection.

Operation. Median incision. Great vascularity of skin and subcutaneous tissue. Widespread edema of the parietal peritoneum, and signs of subacute peritonitis that extended as high as two inches above the umbilicus, with recent adhesions. The uterus, when freed, was the size of a three-months' pregnancy. There was a diffuse endometriosis of the pouch of Douglas and of both ovaries. The rectum was solidly bound to the upper vagina and lower third of the uterus. Both appendages were liberated and removed. The uterus was then removed by supravaginal hysterectomy, most of the cervix being removed by coning deeply. An unusually smooth recovery followed.

When the uterus was opened the walls were diffusely thickened and the right upper cornu was filled by a tumor 3 cm. in diameter, with a cavity about 2 cm. across. The cavity wall was smooth and glistening, and the fluid was of a clear straw color. It coagulated on exposure. The cavity wall was grayish, about 0.5 to 0.75 cm. thick, and separated from the uterine cavity at the nearest point by about 0.5 cm. On further study of the uterine wall there were numerous other yellow areas, varying in size from a bean to a millet seed, with a granular appearance on the cut

* Case V, originally published in the *Transactions of the American Association of Gynecologists, Obstetricians, and Abdominal Surgeons* in 1937, is omitted from these case reports.

surface. These were most numerous about the isthmus, and extended from the mucosa right through to the outer limits of the uterine wall. The cervix was thickened, as was also the isthmus. The mucosa of the uterus was thin and hemorrhagic. At the upper margin of the posterior wall near the left fallopian tube was a subperitoneal nodule, sessile to its widest diameter, about the size of a marble, whitish at the periphery, but becoming bluish at the center and highest point as if filled with blood. This was interpreted as a uterine chocolate cyst. Its contents, however, were solid and granular, and of the same type as the others.

Microscopic Examination. Sections were taken from almost every part of the uterus, cervix, isthmus, ovaries, and fallopian tubes. There was a probable excess of interstitial tissue in the mucosa, and a corresponding paucity of glands. The interstitial cells of the mucosa dipped in broad strands into the intermuscular tissues, and in places stained deeply with hematoxylin but not at all with eosin, so that they could be traced with the naked eye quite easily, and, better still, with an inverted eyepiece of the microscope. These strands communicated directly, in places, with the islands of interstitial tissue. Some of these were immediately contiguous with the mucosa; others were deep-seated. The largest tumor was undergoing a coagulation necrosis. The small subperitoneal sessile tumor was of the same type but better preserved, and the cells were more uniformly characteristic of an interstitial endometrioma. The individual cells had a minimum of cytoplasm, which stained very faintly with hematoxylin; a large oval nucleus with a clean-cut, deeply stained nuclear membrane; a nucleolus deeply stained; and a great deal of granular and filamented chromatin. The degeneration process was of a hyaline type, and involved both tumor cells and uterine connective tissue and muscle, both of which latter were greatly increased in association with the new growth. The upper portion of the cervix showed a widespread adenomatous overgrowth of the cervical glandular structures.

Diagnosis. (1) Adenoma of the cervix. (2) Mixed endometriosis of the appendages. (3) Endometrioma interstitiale of the uterine wall.

The following cases so far have not been reported, and each adds something to our knowledge of stromatous endometriosis. They accentuate an endometrial polypoidal stromatous-endometriosis, involvement of all the endometriomata in a uniform degeneration and a diffuse pelvic sclerosis, all of which will be shown to have a direct connection.

Case VII. Mrs. M., aged 45 years, married 15 years, no children, came complaining of general abdominal malaise, weakness, and menorrhagia which had lasted six weeks. Prior to this she had been regular. She had lost about 15 pounds in weight in the past year. On physical examination

there was a mass the size of a three-months' pregnancy rising out of the pelvis, and on bimanual examination this proved to be a symmetrically enlarged uterus sensitive to the touch, and a large nodular cystic cervix definitely the seat of a chronic cervicitis. Owing to this finding the superimposed enlarged uterus was looked upon as the seat of a chronic metritis, probably incorporating a small fibroid.

Operation. Upon opening the abdomen a sclerosis of the anterior parietal peritoneum was encountered, and there was a free, clear, straw-colored fluid in the pelvis—I should judge about 50 cc. in all. It was collected for study. I had been interested in this type of peritoneal sclerosis for some months. Here was a clear-cut case. Upon studying this condition it was found to affect all the anterior parietal peritoneum as high as the umbilicus. As one ascended the abdominal wall the condition grew less marked. But as one descended into the pelvic regions it grew more pronounced, so that in the vesico-uterine and Douglas' pouch the sclerosis reached parchment whiteness and great thickness. So sclerosed were the tissues in these areas that as one cut across the vesico-uterine peritoneal reflexion the scissors emitted a crunching sound, as if cutting semicartilaginous tissues. The posterior wall of the uterus was similarly though less affected, and the peritoneum of Douglas' pouch was white and semirigid. The abdomen was found free from adhesions, except for a few dense adhesions about the right ovary. The uterus was found symmetrically enlarged as described above. The ovaries were about the size of a hen's egg and were filled with follicular cysts. Both ovaries and tubes were removed and a total hysterectomy was performed. Recovery was uneventful.

Pathologic Report. On opening the ovaries there was a general sclerosis of the tissues to such a degree that the cyst walls were white and retained their shape when evacuated. On palpation the cyst walls were almost cartilaginous and were almost entirely cortical. The largest was the size of a white bean. The uterus when opened presented a strange appearance. There was a marked thickening of the mucosa to a degree of three-eighths of an inch, and the surface was masked in great part by several sessile and pedunculated polypi. One of these latter was the cause of the hemorrhage, for apparently its vessels had undergone a thrombosis, and the tip of the polyp was infiltrated with blood. The uterine wall was greatly thickened in places to 1.5 inches, and was studded by numerous tumors, each filled by a yellow mustard-like paste. The largest of these was about the size of a filbert nut, the smallest microscopic. One could count 13 such discrete tumors, all presenting the same yellow pasty contents. These were scattered indiscriminately throughout the wall and some had invaded the isthmus and cervix.

Microscopic Examination. The description of the microscopic appear-

ance of the peritoneal sclerosis will be reserved for the section which deals at some length with that subject. The uterine mucosa was greatly thickened by an overgrowth of the stroma cells of the endometrium. These were all oval-shaped, large, and clear-cut, like those of a woman in early sexual life. There were relatively few glandular elements, and many of the polypi were made up exclusively of stroma covered by a single layer of columnar cells. The mucosal blood vessels were unusually large, and presented to a much greater degree than any normal mucosa all three component coats of the average permanent artery. One polyp was decidedly hemorrhagic. The uterine wall was greatly hypertrophied, and was transversed in all directions by strands of stromatous tissue. Some of these communicated freely with tumor masses of the same type of cell. These small tumors were without capsule, and blended almost imperceptibly with the surrounding tissues. The component cells of these tumors presented an appearance closely resembling a large round-celled sarcoma. The inner wall of each tumor ended in a shaggy surface with strands of tissue extending as a scaffolding into the homogeneous center. These strands showed various stages of degeneration of a hyaline type, each ending centrally in a homogeneous mass, in the edges of which phantoms of cell and strand formation could in places be made out. The cervix presented a great deal of overgrowth of its component tissues into a chronic cervicitis, and an adenomatous overgrowth of its glandular elements.

Diagnosis. (1) Endometrial stromatous endometriosis. (2) Polypoidal stromatous endometriosis. (3) Uterine parietal stromatous endometriosis and endometriomata. (4) Peritoneal sclerosis of an advanced degree. (5) General degeneration of all the intramural endometriomata.

The next case is of interest in that it brings forcefully to our attention certain poorly understood complications of stromatous endometriosis.

Case VIII. Mrs. E., aged 38, mother of three children, the youngest 12 years of age, no miscarriages, came complaining of metrorrhagia (slight in amount but continuous), weakness, leukorrhea of a watery character, and severe backache. The onset of symptoms had been slow and insidious.

On physical examination of the abdomen the fundus of the uterus could be felt just on the level of the symphysis. It was tender. Bimanual examination revealed a large cervix, hard and cystic, with a superimposed large tender symmetrical uterus. There was considerable fixation of the uterus, and pain on imparted movement. The fornices were rigid and fixed, and the appendages could not be defined. The case, clinically, was looked upon as one of chronic metritis and cervicitis of long standing,

from previous infection years ago, leaving an old cellulitis of the broad ligament.

Operation. Upon opening the abdomen there was a pronounced sclerosis of the peritoneum, extending from the umbilicus to the pelvic pouches. The uterus was enlarged, fixed at its isthmus, and presented several sessile fibroids on its surface. The broad ligaments were thickened and shortened and tense, and the ovaries (enlarged, fibrotic and cystic) were bound with dense adhesions to the posterior surfaces of the broad ligaments, by fully organized tissue union. I was still of the opinion that this was the result of a chronic inflammatory change. The ovaries were liberated, and a panhysterectomy was performed. Recovery was uneventful.

Pathologic Report. Upon cutting the ovaries open they were found much sclerosed, filled with follicular cysts with rigid walls. There were numerous atretic follicles and corpora. The broad ligaments were fibrous and tough. The uterus, when opened, presented greatly thickened walls containing innumerable small tumors without capsules. Their cut surfaces were lemon-yellow in color, with strands of whiter tissue containing a paler pulp in the interstices. The mucosa of the uterus was greatly thickened, and there were numerous polypi large and small, two of which filled the cornua. A breaking-down process affected one polyp. There were many cystic cavities in the mucosa. The cut surface of the uterine wall was very fibrous and the tissues were under great tension. The cervix was filled with nabothian cysts, and the cervical canal contained several polypi.

Microscopic Examination. Sections of the mucosa showed a diffuse polypoidal overgrowth composed mostly of stroma cells. Glandular elements varied much in number in different parts of the uterus, but the polypi were made up almost exclusively of stroma cells, of the large oval type with round clear nuclei.

Sections of the uterine wall showed a widespread permeation to various depths by large and small strands of mucosal stroma cells. Their departure from the basal layer, and their continuity through depths of the wall, could be seen with the naked eye. There were no glands in these permeations. The morphologic characters of the cell strands varied greatly in different parts. In some areas they had much the same characters as those of the mucosa; in others the cells had become streamlined, due to pressure, and often difficult to differentiate from connective tissue except by more intensive avidity for the dyes.

These strands had reached the broad ligaments, and there were seen to fill the lymph spaces, coursing outward toward the pelvic wall. The small multiple tumors of the uterus were stromatous endometriomata,

and in the cellular elements the same morphologic changes were seen as in the strands.

Sections of the ovaries showed this same permeation of their substance by strands of uterine stroma cells, and in two places there were stromatous endometriomata about the size of peas. Direct connection of these with the neighboring lymphatics was easy to establish. Sections of the cervix showed a widespread cystic cervicitis, diffusion of uterine stroma cells throughout the cervical musculoconnective tissue, and a great overgrowth of the cervical glands in the nature of a benign adenoma. The sclerosis of the peritoneum conformed to the type described under this heading.

9

Stromatous Endometriosis

GENERAL

A short description of recent changes in our concepts of the composition of the uterine wall is necessary to understand the genealogy and spread of interstitial endometriosis. The uterine mucosa is made up of two component cells—the stroma cell, and the gland columnar cell. Our teaching has been that these stop abruptly at the musculomucosal junction. This is not so. We have seen that the glands and interstitial cells frequently penetrate deep into the muscularis to constitute a parietal mixed endometriosis, and it was also stated that it is difficult to draw the line between a physiologic and a pathologic penetration of the supposed boundary between muscle and mucosa. If this is the case in mixed parietal invasions, it is even more difficult to determine the borderline between physiology and pathology in stromatous invasions.

In 1937 I wrote that in the normal uterine wall the stroma cells of the endometrium penetrate beyond the musculomucosal border into the intermuscular fasciculi, first as fairly stout bands, which ramify into finer and finer branches to various intramural depths. They constitute a normal component of the uterine wall, so that one has to reckon with this new element in all studies of the uterine physiology and pathology. I do not know to what depth these interstitial strands normally penetrate, but in a large number of cases they have been traced in fine strands as far as the peritoneal covering of the uterus. In the virgin uterus the invasions are slender and often difficult to detect. But in numerous sections taken from different parts of the uterine mucosa it was found that the penetration varies considerably in different parts of the uterine wall. In multiparae this is usually greatly augmented, and in interstitial endometriosis there is no limit to the degree of invasion.

So now we must regard the physiologic uterus as composed not only of muscle and adult connective tissue with its nerves and blood vessels, but also of various quantities of ramifying stroma strands. The characters of these intramural interstitial cells vary widely, especially in their morphology. As a matter of fact, their morphology and various tinctorial properties are about all we know of this interstitial cell. Of its function,

except as a scaffolding for the more specific glands, we know but very little. But that it has a responsive property to the hormone of menstruation and of pregnancy we see quite clearly in the changes which are known under the term "decidual."

If, then, the uterine stroma cell is a normal component of the uterine parietes, and if these vary quantitatively within wide limits at the different ages of women, must we then regard any gross pathologic invasion of the uterine wall as a local hypertrophy of the normal constituents, or is it a penetration *de novo* from the musculomucosal area? This is a question to which a convincing answer cannot be given, though opinion has taken it for granted that these disease processes are a new invasive disease in many ways simulating the familiar picture of sarcomatous penetration. I think we all agree that in carcinoma and sarcoma the disease is not general, but that certain cells take on aberrant growth and penetrate, and that the fixed cells of the infected area merely show reaction to the new uninvited guest. This idea has automatically carried itself into endometriomata, and we have accepted it almost without question. However, there is nothing factual to disprove that intramural stromatous endometriosis may be an overgrowth of the endometrial stroma cells normally found in the uterine wall. Interstitial penetration of the uterine wall may take on various characters. It may be a diffuse penetration in strands causing the uterus to become considerably, but nevertheless symmetrically, enlarged (endometriosis); or the growth may be more accentuated in one or several areas so as to cause definite tumor formations (endometriomata); and, lastly, there are various combinations of both these types.

In the endometriosis types, curiously, the invasions may affect the uterine wall diffusely, but in many cases the disease may affect only one wall—such, for example, as the anterior—and yet leave the posterior wall almost or quite immune. Or the penetration may be restricted to one or more areas of either anterior or posterior walls.

In all the cases of interstitial endometriomata there must be theoretically a degree of accompanying endometriosis, though it is sometimes difficult to demonstrate. The reason for this is found in the instability of these growths. It will be pointed out later that of all cases of ovarian endometriosis which come to operation for reasons of either adhesion pains or tenion pain, only about one-third of these are in the active stage of the disease. The other two-thirds of the cases are either in advanced retrogression or in complete quiescence. This question will be dealt with at greater length at its appropriate place.

But it may be stated here that endometriosis of whatever variety is an expression of vitiated endocrinology, and nature tries within the limits of her reserve to overcome this imbalance, and succeeds in the majority

of cases. So that endometriosis is but an expression of a more or less prolonged dyscrasia, but essentially a temporary one. The extreme limit of its duration would be the menopause, at which time, owing to the withdrawal of active ovarian functions, theoretically at least, all endometrial invasions which depend upon ovarian function for their continuance would undergo resolution. We find parallels to these pathologic variations in other gland functions, such as, for example, in the thyroid activities which undergo temporary dyscrasias under various forms of stress and of various durations, only to be restored to the normal when environmental harmony is restored. So it is with endometrial diseases of endocrine origin—the great *vis medicatrix naturae* asserts itself. Especially is this applicable to endometrial disease, which is essentially a disease of the most vigorous years of a woman's life—her sexual age.

The influence of these statements upon endometriosis is this: that, were it possible to examine all cases when in the active stages of the disease, we would find continuities and combinations which would facilitate study and promote understanding. But where regression and degeneration affect two-thirds of the cases that are operated upon, many links of continuity are broken, and in combinations of parietal endometriosis and endometriomata the strands of endometriosis may disappear completely, while the local growths (endometriomata) may show only degeneration changes. It does not follow, however, that it is necessary to trace a direct continuity by serial sections between an endometrioma and the mucosa of the uterus. It will be shown later that metastases by lymph and other channels are common, and that, therefore, direct continuity never existed. But in a goodly number of cases endometriomata are the result of an intensified local growth in a diffuse endometriosis, and in these cases the continuity is easy to establish. This has been done in several of my cases where the endometriomata were not too far removed from the musculomucous junction.

It is pointed out here that endometriosis of whatever kind is restricted to the pelvic organs. To be more exact, it is confined to those structures that are susceptible to decidual change. Any widening of this sphere of growth must be by direct continuity of growth. This is rare, and was seen in only two of my series of cases—cases that came under the heading of sarcomatoid endometriosis, a very rare occurrence. So we find that stromatous growths of the uterine wall are of two kinds: the diffuse strand-like invasions of the lymphatics (endometriosis), and the more local growths into tumors (endometriomata), and combinations of both these types.

Not infrequently the stromatous invasions extend beyond the limits of the uterine wall along the lymphatics of the two broad ligaments and invade the ovaries, uterosacral ligaments, and other parts of lymphatic

extension. These extra-uterine invasions are of great clinical interest inasmuch as removal of the uterus will not arrest the progress of an unrecognized extra-uterine extension.

The cellular morphology of stromatous endometriosis varies within wide limits. In this respect it closely resembles its parent cell in the endometrium. Just as in the endometrium the stroma cell (1) may be large and oval-shaped with a clear protoplasm, an oval nucleus covered by distinct nuclear limiting membrane, and distinct dark chromosomes with well-defined dark connecting skeins; or (2) may be small, deeply stained and so closely resemble a lymphocyte as to be indistinguishable; or (3) may take on characters resembling those of the senile endometrium (Fig. 3), streamlined and approaching the characters of a connective-tissue cell—so also may the component cells of an interstitial endometriosis vary in morphology. In many instances the strands stand out tinctorially and morphologically in marked contrast to the circumambient tissues. In others the new growth is distinguishable with difficulty. Not only are these differences met with in different cases, but also in different regions of the same case, showing that, independent of the common exciting cause, there are local causes inherent in the terrain which exercise a profound influence upon morphology.

It was pointed out above that regressions in endometriosis of all types are very common. The regression and consequent degenerative processes involving stromatous endometriomata are extraordinarily interesting. I look upon all these changes as degenerations preparatory to absorption. (Fig. 4.) They are a close imitation of those found in fibroids and myomata, but owing to the increased vascularity, less density, and absence of capsule, endometrial degenerations are more common, more rapid, but essentially the same. Vitreous degeneration with small and large cavities filled with clear or slightly blood-tinged contents is the rule. This is a preparation for absorption. The clear contents of the endometriotic cavities coagulate quickly when removed from the body and are rich in follicular hormone. At other times the tumors present small trabeculae of fibrous tissue in the interstices of which a lemon-pulp filler is found. Under the microscope these show all forms of colloidal degeneration. In a few instances the cavities of degeneration are filled with a yellow mustard-like paste the nature of which I have been unable to determine.

The amount of fibrous and muscle tissues which may be components of any endometrioid tumor varies greatly. In some tumors, like those of mixed endometrial parietal growths, they may be chiefly muscle or fibrous tissues or both, with small local discrete interstitial endometriomata incorporated within the fibromuscular tumor. In others the fibromuscular elements are conspicuously absent and the tumor presents

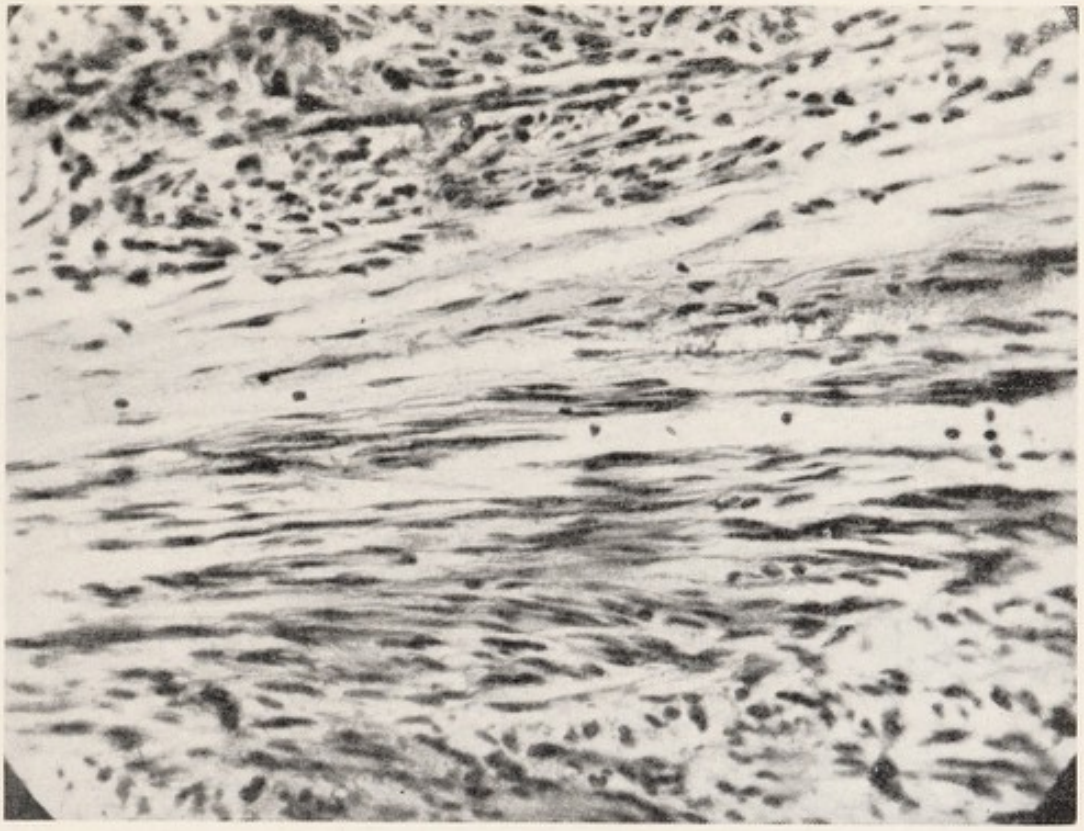


FIG. 3. Streamlined type of interstitial cell, representing the more chronic growth.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricans, and Abdominal Surgeons, *50*:193, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

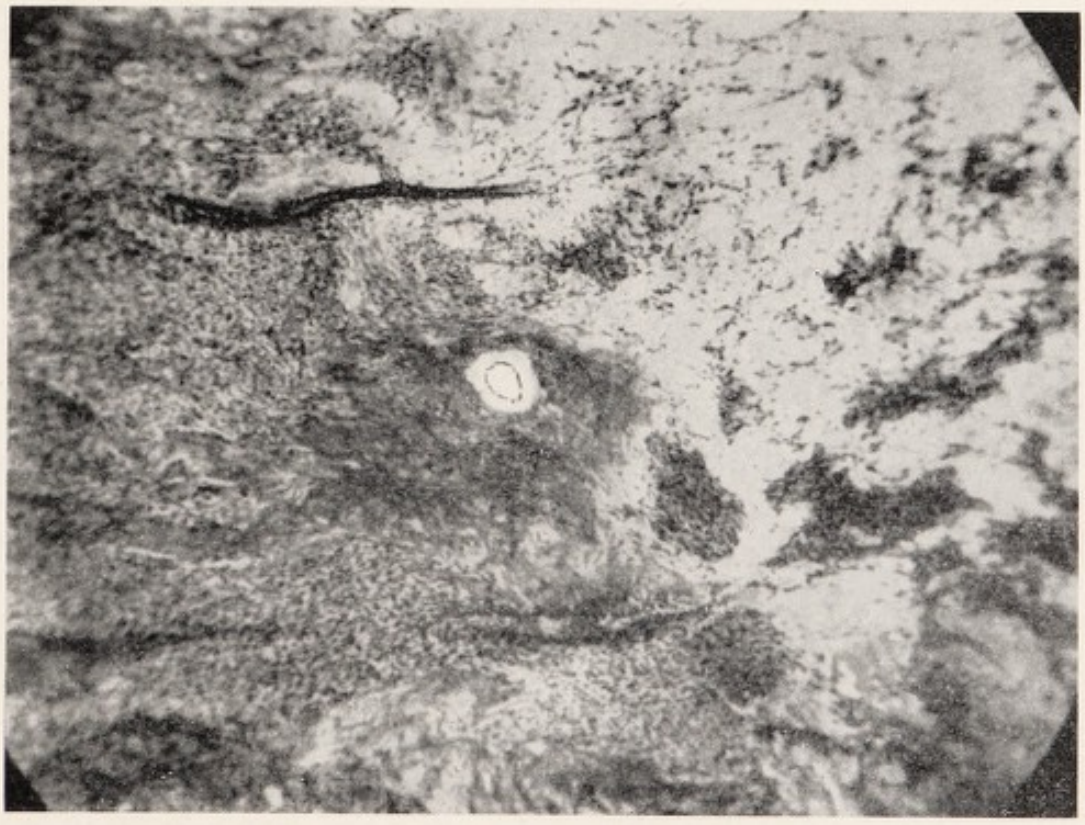


FIG. 4. Hyaline degeneration of interstitial endometrioma.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricans, and Abdominal Surgeons, *50*:211, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

characters indistinguishable microscopically from round-celled or other forms of sarcoma.

Interstitial endometriomata vary in size from the microscopic to that of an orange. Size does not seem to exercise any marked influence upon the incidence or type of degeneration. There is this, however, which is a very striking characteristic: when degeneration of whatever kind takes place in endometriomata, it affects all the tumors in the uterus at the same time, and this regardless of their size or number. I have seen as many as 13 stromatous endometriomata in one uterus, all filled with mustard-like pasty contents. Some of these were large, some small. The semiliquid contents in each were still surrounded by a capsule of the tumor, more or less broken down by the same process of degeneration. In other cases the contents are clear and liquid and are more or less universally distributed. From these observations certain logical deductions can be drawn.

Heretofore, degeneration of fibroids and such-like cellular tumors of the uterus was attributed to local vascular changes causing nutritional degenerations. We now know that such is the case chiefly in pedunculated peritoneal or mucosal tumors. Such is rarely the case in intramural growths. Practically all endometriomata are intramural, and, being without definite capsule (for reasons that will be given later), they seldom become pedunculated. When as many as 13 intramural tumors in one uterus are all afflicted with the same degenerative process, then the obvious conclusion is that the cause of the degeneration is not due to a local one, but to a cause operating generally.

Degenerations of this type, not being nutritional and not being sporadically topical, I therefore infer must be due to a cessation of the active agency that brought them into being, and also we must infer that these degenerations are an expression of an attempt to restore a normal status. If we are right in our inference that these growths of endometriosis of whatever kind are an expression of an endocrine imbalance, then their degeneration (if not due to some limited local vascular cause) must be due to a withdrawal of the abnormal stimulation and an attempt at restoration of a normal endocrine balance.

The similarity to degenerations of fibroids was dealt with in an article entitled "The pathology of the permanently enlarged uterus," published in the *Journal of Obstetrics and Gynæcology of the British Empire* in 1941. In this article I pointed out the rare association of pregnancy with endometriotic disease. In a previous work upon stromatous endometriosis, it was shown that there had been an average of 15 years of sterility in the 14 detailed cases. This was published in the *Transactions of the American Association of Gynecologists, Obstetricians, and Abdominal*

Surgeons, and later and more fully in the *Journal of Obstetrics and Gynæcology of the British Empire.* In a paper read by invitation before the Canadian Medical Association in Toronto in 1940, it was stated that one of the implications of endometriosis is sterility, and it was pointed out that this defect is due not to any physical cause of obstruction between the male and female factors of reproduction but to a biochemical cause, and that when pregnancy supervened in any case of endometriosis it could be interpreted as a restoration of normal or quasi-normal biochemical conditions.

Wherever there is *active* endometriosis there is also an associated enlargement of the uterus. This association is dealt with at some length in the above-mentioned article entitled "The Pathology of the Permanently Enlarged Uterus." The hypertrophy of the musculoconnective tissues of the uterine wall in association with endometriosis is not an expression of irritation by a foreign invasion, because parietal stromatous endometriosis is not a foreign invasion, as was clearly pointed out above. It is merely an expression of hypertrophy of the normal stromatous endometrial content of the uterine wall, plus an invasion by similar elements from the basal layer of the mucosa. The accompanying hypertrophy of the muscle and connective elements is an expression of the stimulating (endocrine?) fluid upon these intramural and endometrial cells. That this stimulating growth influence emanates from the ovary leaves little room for doubt, because removal of the ovaries almost invariably produces a regression in all endometriotic growths. Whether the abnormal stimulation is a direct and primary product of the ovary, or whether the ovary is merely an essential middle agent it is impossible in our present knowledge to establish. The removal of the stimulating agent also brings about an early regression in the uterine hypertrophy of all the cellular elements.

This subject of uterine enlargement and involution in pregnancy in relation to ovarian function is now under intensive study in the laboratory of St. Mary's Hospital. Certain deductions already substantiated are of great interest and have a direct bearing upon uterine disease processes. The first deduction is that, by a study of ovaries removed during the fifth and subsequent months of pregnancy, there is almost a complete quiescence of ovarian function; that this quasi-senility of the ovary continues during lactation. Any few ova which begin to ripen during the late months of pregnancy become abortive and end as early corpora atretica. This obvious quiescence of reproductive activity accounts for the rapid involution of the puerperal uterus simulating senility. When ovarian activity is re-established, there is normally a burst of ova developing and ripening simultaneously 14 days before the onset of the first menstruation—a superactivity which regenerates the tissues of all the pelvic

organs, especially the uterine and ovarian cellular elements. These facts are strikingly demonstrated by the microscope.

When, on the other hand, owing to a general debility or to a low ovarian reserve this postpartum response of the ovary cannot be elicited, then we find an explanation for the many cases of postpartum hyperinvolution of the uterus and vulva simulating a premature senility. So it is in endometriosis. The uterine and other hypertrophies are concomitant responses to a common ovarian cause. And just as endocrinologic dystrophies are an expression of a variance between the individual and her environment, restoration of a normal environment and a readjustment between the external and the internal milieu is the rule, so we find that diseases that are the expression of this dystrophy increase or diminish in accordance with the discord or harmony of the variables. And according to our records of ovarian endometriosis collected from cases operated upon, spontaneous cures outnumber active progressive cases in the ratio of two to one.

It is also believed that whatever has been written in the preceding pages concerning endometriosis applies, except in minor details, to fibroids. Endometriosis, when active, is invariably accompanied by a diffuse or local and diffuse growth of the musculofibrous elements of the uterine wall. The diffuse response of these elements resembles the same process as obtained in early pregnancy. The more chronic local growths are in the nature of fibroids and myomata. In 30 per cent of all our cases of endometriosis in St. Mary's Hospital, there were fibroids in association. Taking only those in the fourth decade of life, the association rose to over 50 per cent. When degeneration sets in in a case of endometriosis, the associated fibroids are almost invariably found to be undergoing degeneration characteristic of this form of tumor.

CLINICAL CHARACTERS OF STROMATOUS ENDOMETRIOSIS AND ENDOMETRIOMATA

The recognition of this clinical and pathologic entity is relatively new. It therefore behooves us to be more explicit than would be necessary in a common or well-recognized disease. The common type of stromatous invasion is confined to the uterine wall, and is seldom diagnosed, clinically or at the time of operation, though it should be suspected. On bimanual examination the uterus is found to be large, hard, and symmetrical if diffusely involved in an endometriosis, and symmetrical also in some cases of endometrioma where the normal uterine contour is not lost, but usually asymmetrical in local endometriomata. The enlargement of the uterus is due not only to the invading endometrial elements, but also to the hypertrophy of the other constituents of the uterine wall. Therefore, in symmetrical cases the clinical diagnosis is usually chronic

metritis or some one of the common terms used to describe this enlargement, such as chronic subinvolution, fibrosis uteri, arteriosclerotic uterus. The resemblance to this disease is heightened in that the cervix is usually involved in the hypertrophy and is in the state commonly described as chronic cervicitis—a large, hard, often cystic cervix. The portio may at times be so hypertrophic as to fill the vault of the vagina.

There are, of course, all degrees of parietal involvement, so that the involved uterus may differ greatly in size, depth of involvement of the parietes, accompanying hypertrophy, and in the number and size of the tumor formations. When the stromatous endometriosis expresses itself in tumors, the enlargement is generally diagnosed as fibroids, and the true diagnosis (though suspected by those who are familiar with this disease) cannot be established until biopsy has been performed. Heretofore these sections, on account of their cellular conformation and their close resemblance to sarcomatous tumors, have been almost invariably diagnosed as sarcomata, until their true origin and clinical properties were made clear.

The enlargement of the cervix is rarely due to invasion of the cervical tissues by stromatous endometrial cells, but is a simultaneous hypertrophy of its fixed elements in response to the growth-hormone stimulation which underlies the hypertrophy of the uterus and the invasion by the endometrial stroma cells. It is pointed out here—a matter which will be dealt with more fully later—that endometriosis of whatever kind is not purely a disease localized to the area most conspicuously involved, but is a general pelvic disease in which the other pelvic organs respond to the stimulus in a manner characteristic of that organ and in a degree varying with its susceptibility to response. Stromatous endometriosis like fibroids does not disturb the rhythm of menstruation, but may increase the flow proportionate to the enlargement of the uterine mucosa. Menorrhagia and metrorrhagia are not ordinary signs of endometriosis, but, just as in fibrosis uteri and fibroids, metrorrhagia is an expression of some complication of degenerative vascular change in the local growth, or—and this is more frequent—due to some hemorrhagic state of extrapelvic origin. The growths that are restricted to the uterus are singularly free from symptoms, and are generally accidentally discovered upon pelvic examination for causes other than uterine. Almost invariably disturbances of the rhythm and flow are attributed to the discovered uterine enlargement. Almost invariably also the hysterectomy which follows upon the discovery—for want of better—stops the disturbance in the rhythm and excessive flow, but, as Prof. William Fletcher Shaw has frequently stated, "It is a confession of failure and defeat."

When, on the other hand, the stromatous endometriosis has spread beyond the confines of the uterus, the broad ligaments become thickened

and shortened, and stromatous endometriomata may develop like mixed endometriomata in any organ that is within the pelvis, but with this great distinction: that stromatous endometriosis, spreading as it does by direct lymphatic continuity, rarely invades the peritoneal cavity but may involve any pelvic organ that has a connection by lymphatic channels with the parent organ of the disease, the uterus. Mixed endometriosis that has arisen primarily from the cells of the surface of the endometrium almost invariably contaminates the surface peritoneum by "spill" and later by invasion of the deeper subperitoneal lymphatics by invasion from the peritoneal implants.

When stromatous endometriosis affects extra-uterine tissues, the symptoms will depend upon the organs that are involved and upon the amount of disturbance these invasions set up in the normal functions of these organs. These disturbances, however, seem to be due exclusively to the pressure of the new growth and not to any destructiveness caused by the growth itself, or due to its function. It does not respond to the menstrual hormones, and therefore it does not menstruate, and is consequently devoid of the destructive influence of blood-filled cysts.

10

Acute Stromatous Endometriosis with Restricted Malignant Characters

Since the time that these two cases were described as Cases I and II in my original articles in the *Transactions of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons* in 1937, and later in the *Journal of Obstetrics and Gynæcology of the British Empire* in 1939, with added notes of the course of their disease up to that date, both these patients have died. Both were observed until they succumbed, and a complete autopsy was obtained upon one. Although an autopsy was denied upon the other, I had occasion to x-ray the lungs and bones two months previous to and just before death. In these above-mentioned articles I placed these cases among the group of stromatous endometriosis. The subsequent course of the disease was so different that they warrant a sub-group of this category. They exhibited such powers of division as to transcend the usual curative influence of ovarian removal. Though responsive to deep x-ray and radium in their early stages, after years of stunned somnolence the cells again took on growth activity, became x-ray–fast, and eventually caused death by occluding the ureters, and thereby bringing about destruction of the kidneys and death by uremic poisoning.

Case IX. Mrs. M., aged 57 years, was sent to the writer for hysterectomy for the cure of a fibroid. She had gone to her family physician, Dr. George Berwick, with the complaint of being "run down" and always tired, and had noticed some fulness of the lower abdomen during the past two weeks. Menstruation was normal, every 28 days, lasting from three to four days; no dysmenorrhea. Two children alive and well, a third died at birth; the youngest was aged 22 years. Systems were found normal except for a relaxed perineum and a globular mass in the lower abdomen, and on pelvic examination signs of a symmetrically enlarged, hard uterus, in size comparable with a three-months' pregnancy. It was somewhat fixed and drawn to the right. There was not the slightest doubt

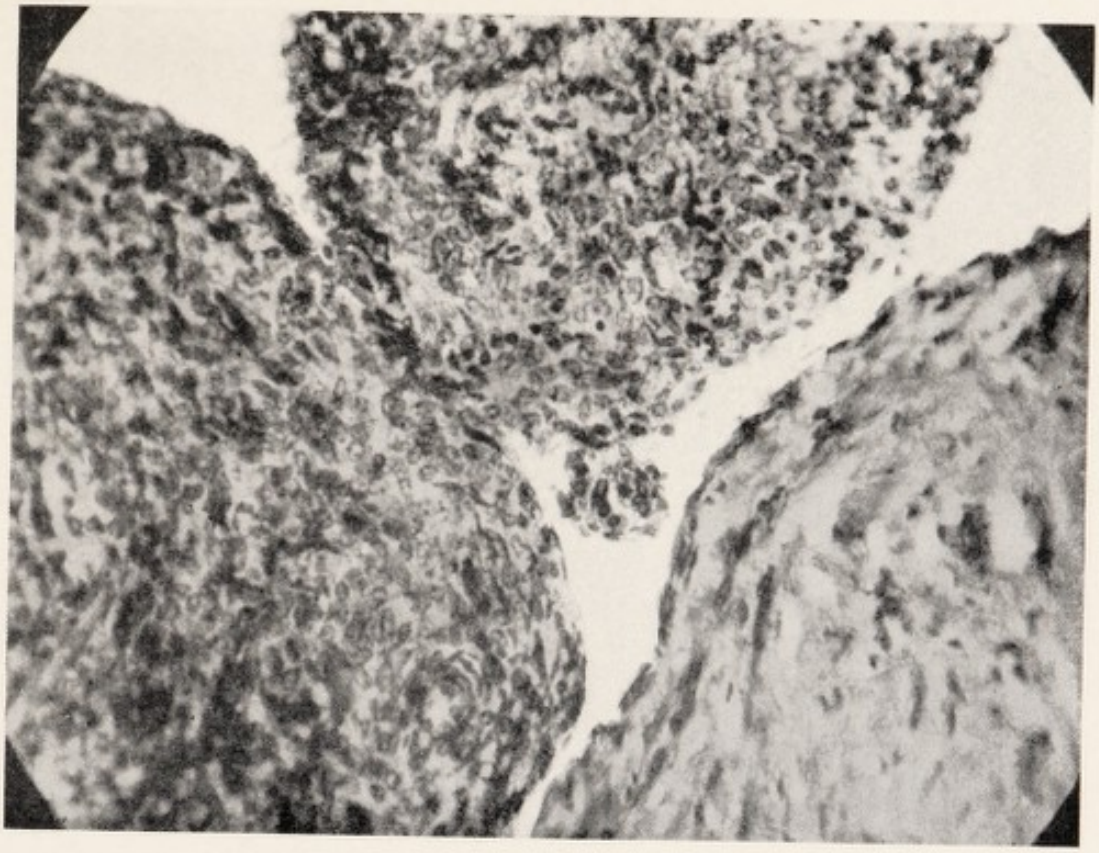


FIG. 5. Endometrial lymphatic embolus. Note that the lymphatic lining is intact.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricans, and Abdominal Surgeons, *50*:196, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

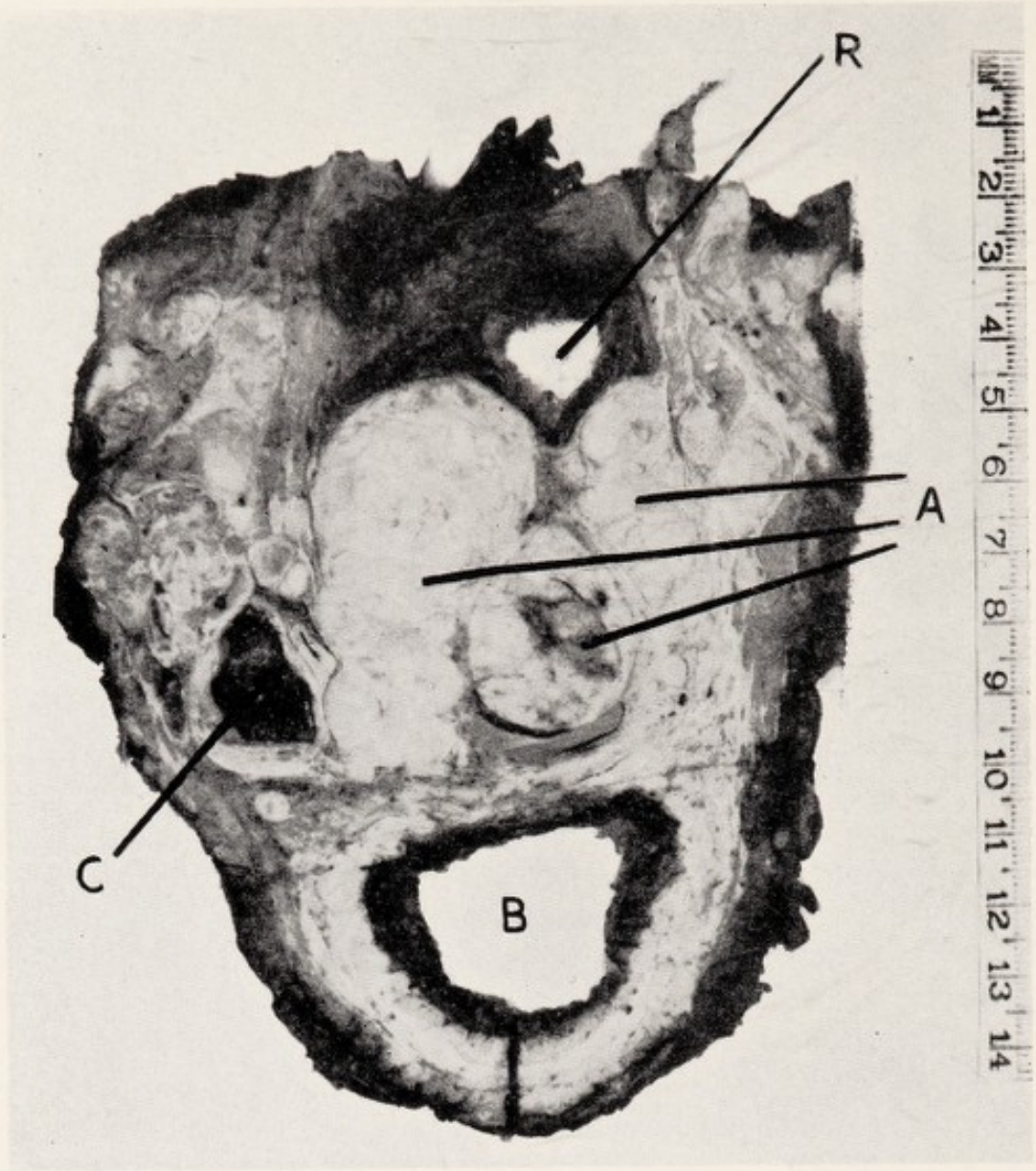


FIG. 6. Pelvic viscera secured at autopsy. (A) stromatous nodules throughout the pelvis; (R) constricted rectum; (B) infiltrated bladder wall; (C) hemorrhagic cavitation.

in the mind of the writer that he was dealing with an intramural fibroid.

Operation. The operation was performed at the Royal Victoria Hospital on April 24, 1929. During the operation for perineorrhaphy the vagina was found congested, and venous bleeding was unusually free. There was also a thickened band which ran up the right wall of the vagina which was thought to be scar tissue, but when its margin was reached in the perineorrhaphy the tissue was very friable, and the bleeding was hard to control from the numerous veins in its vicinity.

When the abdomen was opened there were no adhesions. The uterus was the size of a three-months' pregnancy, symmetrical and drawn somewhat to the right. There was tremendous venous congestion of the uterus, and the veins of both pampiniform plexuses were markedly varicose. The right broad ligament was shortened, thickened, and plastic. This thickness extended into the right iliac fossa. The ovary was somewhat enlarged and bound by adhesions and contained a hematoma, and the edematous, congested, right fallopian tube hung down posteriorly like a wet drape. The left appendages, congested and edematous, did not present any infiltration of the broad ligament. This picture was a new one to the writer. The right broad ligament was then clamped near the pelvic wall, and incised between the clamps. Immediately a gray, brain-like substance oozed out of the cut surfaces. The infiltration of the pelvic brim and the iliac fossa was now recognized as an extension of a malignancy. The left broad ligament was then incised at the uterine end, and as the ligament appeared only edematous, the left appendages were not removed. The broad ligaments were then opened to reach the ascending branches of the uterine arteries to complete the operation as a supravaginal amputation, as any further procedure seemed futile. In approaching the right uterine artery a cavity was opened, filled with the same brain-like substance. When the uterus was amputated the cut surface of the stump oozed this tissue from multiple lymphatic spaces, some large and soft, and on the right side was a cavity now cut across filled with the same gray matter. The operation was completed and the patient went from the operating room in good condition. Her destiny was known.

Pathologic Report. Upon examination of the specimen before leaving the operating room it was found that the growth extended out from the uterus along the lymphatics of the broad ligament; that these stood out like soft ropes; that the ovary, though enlarged and soft, was of normal outline; that the lymphatics, when carefully opened, allowed a roll of tissue like an earthworm to be rolled out, leaving the lymph channel intact; that one of these worms was 1.75 inches long, a pinkish-gray substance about the size of an average earthworm, and to heighten the resemblance there was a larger portion in the center about .25 inch long of a dark red color, evidently a small hemorrhage. The uterus was now

incised longitudinally along its anterior wall, and from a hundred channels there slowly oozed up this gray matter, which made one think of the boiling mud-wells of the South. One could grasp the tissue with a forceps, and with traction it would snap back into its hole again, or allow itself to be drawn out like a worm from its hole, leaving the hole perfect and patent. The uterine stroma was firm and fibrous. It was now found that the growth occupied the anterior wall, and that the uterine cavity lay with a convexity backwards. The posterior uterine wall was about .75 inch in thickness, and free from invasion. The mucosa appeared quite normal. The specimen was so novel that the writer sat down and wrote a page-and-a-half description of the extraordinary condition. The microscopic diagnosis was awaited impatiently. It was as follows:

The gross specimen consists of a uterus the size of a fetal head, showing upon section numerous widely dilated blood channels and lymphatic spaces which contain a soft lymphoid structure in the form of a coagulum. (Fig. 5.) Even below the tube and ovary the vessels are thrombosed. The ovary contains a hemorrhagic body looking like a degenerated corpus luteum. The endometrium is soft and glistening.

Microscopic Examination. Sections of the uterus show isolated and diffuse areas of small round deeply staining polymorphic cells which are lying in and replacing a myomatous growth of the uterus. The blood vessels and lymphatics contain plugs of such growth. The picture is that of a sarcomatous degeneration of a fibromyoma.

Diagnosis. Sarcoma of the uterus.

The subsequent history of the patient is of intense interest. She refused to undergo deep–x-ray exposure, and when her recovery, which was uneventful, was completed she returned to her physician. She was a woman of determination. Exactly two years later she was brought back for metrorrhagia, and on examination it was found that the pelvis was filled with new growth, and that large liver-like polypi protruded from a widely dilated cervix and filled the vaginal vault. These broke down easily under the examining finger, and bled freely. There was an ill-defined mass in the right iliac fossa, which did not cause any symptoms. Her general nutrition and state of health were excellent—quite a contrast to what one might expect. It was decided by the radium specialist to excise the polypi and insert radium. Accordingly this was done on April 2, 1931. The following are the postoperative notes:

The patient was in hospital in April 1929. Felt fairly well on discharge. In 1930 felt tired, and went away for the summer and rested. Lately noticed a swelling on the right side which caused a dragging sensation. For the past ten days had pain in both legs, particularly behind the right knee, with difficulty in walking.

Vagina was filled with downward growing sarcomatous polypi and infiltration of the cervical stump and vault. The growth was continuous with that in the abdomen.

Diagnosis. Extensive sarcomatous lesion.

Operation. The vault and shell of dilated cervix were cleaned out digitally and radium was placed *in situ,* 50 mg. for 30 hours, equaling 1500 milligram-hours.

Pathologic Report. Microscopic sections show a widespread cellular structure composed of small, round, and spindle cells, showing numerous mitotic figures. There are numerous small blood vessels in the tissue. The growth corresponds to that seen in previous sections, taken in 1929, except that there are no large vessels involved.

Corrected Diagnosis. Small round-celled sarcoma; metastatic growth in the vagina.

Again the patient would not submit to deep–x-ray treatment owing to some deep-seated prejudice. No one could fathom her dread of it. She disappeared again and re-appeared in May 1932, that is, 13 months later. Her general nutrition was excellent, and her color good. Her functions were normal, except that she now had a mass in the right lower abdomen the size of a small rugby football, insensitive, hard, and fixed. The right leg was three times the size of the left leg about the thigh, and the ankle was as big as her left thigh. She could barely walk, except by dragging the leg along. She was now suffering a great deal of pain, both in the abdomen and down the leg, and she had lost a great deal of weight but not her cheerful disposition. She finally submitted to our combined pressure for the use of x-rays. Frankly it was not expected that it would accomplish much. She wanted to be operated upon, but accepted assurances that operation could not promise anything but futility and danger.

Dr. Howard Pirie began treatment on May 10, 1932, and ended on June 7, 1932, giving 11 treatments in all, a total number of 2.75 hours. Type of treatment: 5 Ma., 200 K.V., 15 inch dis., time 15 minutes.

The change was almost instantaneous. Within two months the growth was barely palpable as a small induration in the right lower quadrant, the vagina and cervix presented nothing abnormal, and on bimanual examination there was some induration in the right fornix which may connect with the induration in the abdomen, though this cannot be definitely determined. But what impressed the patient and her friends most is that her right leg is now the equal of the unaffected side.

At this date, 7.5 years after the x-ray treatment, she is in radiant health, and there is no evidence of any recurrence or metastasis.

The above was written in 1939. At that time a re-study of the slides of the case showed numerous emboli in the broad ligament, lymphatics,

and venous channels, and the sections of the uterine wall gave unmistakable evidence of the origin of this invasion from the basal stroma cells of the endometrium. After writing the above description I lost observation of the patient until July 1940. I was then called because she had gone to a neighboring doctor complaining of hemorrhoids and painful varices in the left leg. The right had been the one previously involved. The injected substance had infiltrated the perivenous tissues and had caused three deep ulcers with a great deal of induration. The doctor naturally was not aware of the nature of her former pelvic disease. I immediately examined her and found the whole pelvis "frozen" with new growth. The vagina was cyanosed and as stiff and tortuous as an old distorted lead pipe. The rectum was similarly affected. She was given further deep–x-ray treatments at the Royal Victoria Hospital without any appreciable improvement. The growth gradually extended down the vaginal walls and encroached somewhat upon the vulva. Regional x-ray here had no effect.

Later she developed incontinence of urine followed by a fetid cystitis, and one month later rectal incontinence. At no time was there any bleeding from the bladder or bowel. Later there was complete anorexia, followed somewhat later by vomiting. Eventually she sank into a coma and died with all the signs of uremia.

An autopsy was granted. The body was x-rayed from head to foot. Nowhere was there any sign of bone lesions. Doctor Pritchard, pathologist to the Montreal General and St. Mary's Hospitals, performed the autopsy. The lungs were carefully examined macroscopically and were pronounced free from disease. All the organs including the brain were found free from disease, except the following:

The pelvis was a mass of tumors of various sizes intimately bound together and so distorting the structures that occupy the pelvis that they were difficult to detect. (Fig. 6.) These tumors were chiefly of a white color, with whorls of cells on the cut surfaces. There were numerous broken-down areas filled with detritus in the center of the growths. The right kidney, reduced to a thin shell, had shrunk to the size of a plum. There was no cortex remaining. It consisted of a thin-walled sac containing pus and detritus. The right ureter was completely blocked by a growth in its wall in the pelvic portion of the organ. The ureteral lumen was not invaded. The left kidney was reduced to about one-third the normal size, with a cortex not more than one-half inch thick at any spot. Its pelvis was filled with pus. The ureter was completely blocked by a nodule in its wall in the pelvic region. The lumen of the ureter was not invaded. The rectum could be traced with difficulty in the impinging growth in its walls. The mucosa everywhere was intact. The vagina was similarly involved. The left iliac vein was invaded by the new growth

which filled the lumen and was surrounded by a small amount of clot. This is the only instance in which I have found endometriomata perforating the intima of channels and invading the lumen. Usually they invade the walls of vessels and organs and push the mural structure, be it intima or muscularis, before them. The bones of the pelvis were excised where the new growth was intimately attached to them.

Sections, removed *en bloc,* were catalogued from all organs as well as pelvic structures; they were hardened for serial slicing which was carried out later. Plate II shows a cross-section of these pelvic organs and emphasizes their distortion. (See facing p. 64.)

Microscopic Examination. The microscopic study of these many sections from all parts of the body revealed some most interesting and one most startling result. This latter was the detection of small groups made up of 4 to 8 or 10 cells in the intervesicular spaces in the lungs. At first these passed unnoticed, but were later detected by Doctor Pritchard, who pronounced them endometrial metastases. They were fairly abundant and were scattered chiefly in the subpleural area. I could not agree with him that these were foreign to the lung. They were such small clumps that one could not get a clear picture of their cellular composition. But Doctor Pritchard maintained his stand, and showed the slides to Doctor Masson, pathologist to the Notre Dame Hospital, who confirmed Pritchard's findings. Any skepticism on the subject was swept away when the lungs of the next similar case came under study.

The pelvic tumors had all the hallmarks of a sarcoma of stromatous endometrial origin—or shall I call it a benign stromatous endometrioma. There were areas of degeneration side by side with areas of cells well preserved and dividing. Colloidal deposit in the connective-tissue strands and in the dominant cells of the tumor were common. The ureteral and bladder walls were invaded, but their lining was intact. The kidneys were completely disorganized. The sections of the iliac vein showed a direct invasion of the lumen by the endometrial cells, and doubtless the lung metastases were from this source. None of the bone sections showed any invasion of either the periosteum or the bone structure.

Case X. In response to a requisition on February 6, 1931, the writer visited the metabolism ward of the Royal Victoria Hospital to see a Mrs. G., aged 48 years, suffering from diabetes mellitus and pelvic symptoms. She had all the usual symptoms of a glycemia of five months' duration. For some months past she had suffered pain in the lower left quadrant. This was quite similar to the pains during the first three days of her menses, but the pain was bilateral at that time. Six years before she had been told she was diabetic, and she thought this was the cause of her malaise, so she consulted her family physician who sent her to the

hospital. In her past history there were repeated gallstone attacks. Her menstruation was normal and regular every 28 days, lasting for five days; recently she had had dysmenorrhea during the first three days. Menorrhagia and metrorrhagia were absent. Leukorrhea was fairly copious, and recurring vaginitis due to glycosuria. She had not had any miscarriages. The systems, other than the pelvic, presented nothing relevant. The vaginal outlet was large, relaxed, and parous, and the vulva was excoriated by the pruritus and vulvitis of glycosuria. The vagina presented a blue congestion with varicosities quite pronounced. There was a marked cystocele and rectocele. Internally a firm, rope-like band could be felt along the left wall. It could be easily rolled beneath the finger, and felt like a thrombosed and fibrosed vaginal vein. The cervix was at a low level, and was lacerated. The cervix was displaced backward by a mass extending up almost to the umbilicus. This could not be separated from the uterus, and moved with it. Appendages were thickened on both sides.

Preoperative Diagnosis. (1) Fibroid of the uterus. (2) Large cystic ovaries. (3) Diabetes mellitus.

Operation. February 9, 1931; median incision; uterus the size of a four-months' pregnancy. The congestion of the pelvic tissues was very pronounced. Both broad ligaments were shortened and thickened. There was much free bleeding. Both appendages were brought up with difficulty, and removed. There was an amount of peculiar pus-like exudate from the left broad ligament incision. Supravaginal amputation was then performed, and upon sectioning the stump the latter oozed a brain-like substance, as in the former case. The operation was then completed, and the patient—though she had lost considerable blood—stood the ordeal well.

Upon opening the uterus by a longitudinal incision along the anterior wall, the same brain-like tissue exuded from hundreds of lymphatics. The broad ligaments were now carefully examined and both found to be infiltrated in a manner singularly similar to the previous case. There were two distinct differences. In this case, all the walls of the uterus were equally thickened and involved. Both ligaments were apparently equally involved, but there was no palpable extension into the iliac fossae. The diagnosis was at once made, of a diffuse sarcomatosis of the uterus, with extensions into the parametrium and cervical stump.

Pathologic Report. The specimen consisted of a uterus measuring 7 inches by 5 inches, with tubes and ovaries attached. Upon section the mucosa was smooth and yellowish. The wall was uniformly thick and contained small, nodular, whitish growths, looking like a widespread sarcomatosis. The fallopian tubes were normal and the ovaries fibrotic. The broad ligaments were infiltrated by the growth.

Microscopic Examination. Sections taken from the uterine wall

showed larger and small circumscribed and partly plexiform arrangements of immature histoid cells, having numerous mitotic figures. In the broad ligament, below the fallopian tube, the lymphatic spaces were filled with this cellular growth. The picture is that of a small round-celled sarcoma, which was replacing uterine muscle and infiltrating endothelium-lined channels.

Diagnosis. Diffuse sarcoma of uterus and broad ligaments.

The subsequent history is interesting. Under appropriate ante- and post-operative and antidiabetic treatment, the patient made an uninterrupted recovery. She was operated upon on February 10, 1931, and x-ray treatment was begun on February 18 and terminated on June 11, 1931, 23 treatments being given in all, for a total number of 5.75 hours. Type of treatment: 5 Ma., 200 K.V., 16 inch dis., time 15 minutes.

On May 24, 1933—that is, two years and three months after treatment—the writer was called to examine her in a diabetic ward where she was under observation. Her only pain was in the region of the gallbladder. X-rays showed some defective drainage of the bile. Bimanual examination did not show anything abnormal, except some slight fixation of the stump of the cervix, and when she was being prepared for examination the patient asserted that it was unnecessary as she was exceptionally well as regarded her pelvis.

In September 1937 Mrs. G. was back again in the metabolism department for recurrence of her diabetes, owing to her own neglect. She was free from any detectable pelvic disease, nor did she have any abnormal pelvic symptoms—that is, six and a half years after the first diagnosis of sarcoma. This was the end of her case history as reported in the *Journal of Obstetrics and Gynæcology of the British Empire*.

The subsequent history offers points of interest, first in its similarity to the previous case, and in putting the question of lung metastases beyond any doubt. In November 1940 Mrs. G. consulted me again for signs of urinary incontinence and bladder pain. Examination showed a "frozen" pelvis, similar in almost every respect to the previous case. There was a foul-smelling cystitis with incontinence. The urethra was difficult to penetrate owing to its tortuosity between tumors in the urethral area. The vagina also was tortuous, was of almost ligneous hardness, and was deeply congested; the rectum was surrounded by masses of new growth, though the mucosa was smooth. Treatment by x-ray had no effect. We tried to penetrate the tissues not only from without, but also through the vagina, without appreciable effect. Fecal incontinence developed, followed later by vaginal bleeding. She slowly lost strength and was confined to the hospital for a long period. An x-ray of the chest was taken six weeks before death. The plates showed nothing abnormal,

but a plate taken ten days before death showed a diffuse involvement of the lungs by hundreds of small new-growth areas. The relatives, sensing that death would not be long delayed, insisted upon removing her from the hospital so as to avoid any question of autopsy. She developed a wild delirium for several days, and gradually sank into a uremic coma.

CASE REPORTS

The question of malignancy at once presents itself. What is malignancy? I think we all agree that malignancy is an invasive and a destructive disease—destructive of the normal tissues in the region of the invasions, followed by a general cachexia. Perhaps many will cavil over this definition, yet it is acceptable to me and many pathologists with whom I have discussed the matter. Judged by these two standards, the last two cases of stromatous endometriosis are not malignant, except in a very restricted sense. Malignancy and nonmalignancy, from both a clinical and a pathologic point of view, are still very difficult to place in well-defined separate compartments. Many growths are still in the borderline class, in which there is unanimity of opinion among neither clinicians nor pathologists. The terrain plays such an important part in modifying growth characters that pathologists will frequently and cautiously not venture a diagnosis until the clinical antecedents and course of the disease are known to them.

Stromatous endometriosis in the two above-cited cases remained a pelvic disease for a period of 11 years in one case, and for 10 years in the other, and showed no sign of extrapelvic transplants (and then only in the lungs) until the patient was practically moribund from chronic uremia, induced by compression of the ureters by the endometriomata, and consequent destruction of the kidneys. One is justified in these cases, supported by the great infrequency of malignant degeneration in the other forms of endometriosis, in assuming that the endometriosis in these cases remained true to all endometriotic growths in restricting its invasion to the region below the umbilicus.

A DISCUSSION OF THE TWO CASES IX AND X

This new type of endometriosis was found in 1937. The cases are fortunately extremely rare, or if not rare have not been recognized. There are only two in my series. They came under observation in 1929 and 1930, respectively, were recognized as odd and as not conforming to any known type at that time, and it was only in 1937 that their true significance and origin were recognized and only in 1940 and 1941 that their complete courses were known, when both patients died within six months of each other.

In both of these cases the stroma cells of the endometrium were traceable both microscopically and macroscopically from the basal layer of the endometrium through the uterine wall into the lymphatics of the broad ligaments, and in one case into the right iliac fossa. These two cases are so similar in their common characteristics and so dissimilar from any other form of endometriosis as to place them in a category by themselves.

That the disease in each case was discovered by accident in the course of a general examination for "fatigue," that there were no symptoms or signs referable to the pelvis at the time, and that in each case the condition was diagnosed clinically as fibroid of the uterus, are significant facts. It was only when the uteri were removed that their extraordinary characters were detected, and they were variously diagnosed during the next eight years as sarcomata with various prefixes to denote either origin or cell characters. It was not until stromatous endometriosis was discovered, and a re-study made of the numerous sections taken from the tissues of these cases, that their origin was disclosed; and it was not until death and autopsy that their growth characters were completely understood. It was not until these patients' bodies were so saturated with the vitiated products of uremia that all cell distinction was lost. It was then that the life-long metabolic difference between susceptible pelvic and nonsusceptible extrapelvic tissues were obliterated, permitting a pulmonary flooding by emboli from a vein invasion into the lumen of the internal iliac. Whether we can count this as malignancy is a debatable question, but I am recording facts—time will solve the problem.

Two facts, however, are outstanding. The tissues of which this growth was composed were at first very sensitive to both radium and deep x-ray. But after years of quiescence of the disease, the renewed growth, due to repeated treatments, became x-ray–resistant to the degree that finally the effect was practically nil.

Another way in which these cases differed from other forms of stromatous endometriosis is in this—that the extra-uterine growth persisted in a stunned manner, and later renewed itself actively after removal of one ovary and deep x-ray in one case, and after removal of both ovaries and deep x-ray in the other. This differs markedly from all other forms of endometriosis which invariably retrogresses after removal of the ovaries or elimination of ovarian function by nonoperative means. I stated in the opening of the chapter on these cases that this power of multiplying transcended the usual curative influence of ovarian removal, and, though responsive at first to deep x-ray and radium, after years of stunned somnolence they again took on growth activity, became x-ray–fast, and eventually caused death by compression and arrest of normal function in

neighboring organs. These facts place this form of stromatous endometriosis in a class separate from the ordinary, frequent cases of slow-growing stromatous growths. Consequently I have placed them in a separate chapter for further study of any additional cases.

11

Extra-uterine Endometriosis

As stated in the previous section it is a mistake, and misleading, to divide endometriosis into uterine and extra-uterine, because it is now clear—and, I think, beyond all possibility of doubt—that all cases of endometriosis take their origin from some part of the endometrium, and by one route or another, as will be clearly explained later, reach the other pelvic organs. It would be better, and the sequence would be more clearly established, to take each type of endometriosis and trace it to its ultimate limits of invasion. But this would involve a great deal of tiring repetition, so that a regional description into uterine and extra-uterine types of the disease offers a facility which pathologic extensions do not warrant. This subdivision makes a grave break in disease continuity which is apt to be misleading. But, if one can bridge this lack of continuity, there are compensating advantages.

There is a still more potent reason for the subdivision. As pointed out in many of my writings, there is a "silent area" in the pelvis—an area comprising tubes, uterus, and vagina—which is poorly supplied with sensory nerves and in which disease processes can produce widespread destruction without eliciting any symptoms, whereas the areas outside these organs, when invaded, soon develop symptoms of dysfunction of which the patient is quickly aware. Need I mention the symptom-free cervical cancer, the painless cautery of the cervix, and the painlessness of vaginal operations?

For this reason uterine endometriosis is a symptom-free disease usually discovered only by accident, and recognized only by its signs. On the other hand, extra-uterine endometriosis, the first type of the disease described by Russell, is recognized by its symptomatology, disturbance of function, destructiveness, and palpable signs. There is a still more potent reason for the distinction between uterine and extra-uterine endometriosis. Intra-uterine endometriosis (that is, endometrial endometriosis) responds to the hormones of the menstrual cycle, and shares with the endometrium generally the congestion, follicular and luteal changes, and subsequent extravasations and shedding of its surface layers. This form of endometriosis, like the normal menstrual flow, has a free outlet through the cervix for the extravasations.

But parietal endometriosis, derived as it always is from the basal mucosa-muscular layer of the endometrium, does not respond to the hormones of the cycle, and therefore lacks the destructiveness of monthly increasing blood extravasations which would add a destructiveness that is beyond our wildest imaginings. Therefore, it is apparent that uterine endometriosis, whether endometrial or parietal, possesses only the two properties of invasion and degeneration, both of which are slow and insidious, and far from causing obtrusive symptoms. Cases of extra-uterine endometriosis, on the other hand, are overwhelmingly responsive to the cyclic changes, and as it is a burrowing disease there is no outlet for its vascular extravasations unless the pressure finds an outlet by bursting into areas of less pressure resistance—a common means of spread of the disease, especially when a blood collection with its desquamated cells bursts into a portion of the peritoneal cavity.

PERITONEAL CHANGES, INVASIONS, AND CONTAMINATION

The peritoneal epithelium has been incriminated as the offending agent in many diseases, and has not been overlooked in the incidence of endometriosis. Its seeming obtrusiveness in this respect arises out of many factors, chief among which is the knowledge that it is the progenitor of most of the abdominal viscera, and as such must possess a proteanism and a potentiality surpassed only by that of the fertilized ovum. And yet, in my estimation of the peritoneal lining, after critical examination of thousands of sections from all conditions and diseases, I find it one of the most stable structures in the complex human and animal body.

Apart from the changes incidental to infections of the peritoneal cavity or of its immediate vicinity, there are only two types of new growths (if one may dignify them with the term new growth) found with great frequency and remarkable consistency to type. They are the small peritoneomata, and the cystic form of this tumor. (Plate I.) They are found chiefly on the posterior leaf of the broad ligaments, often discrete to the naked eye, usually multiple when present at all, and the tumors (various in size from microscopic dimensions to that of a half pea) are made up of cells that are so individualistic in type as to be unmistakable for any other tissue. They are so obviously benign that one cannot imagine anything more than a very gentle reproduction of their kind, and even that at an uncommonly slow rate. The cysts are lined by the same type of cell and are prone to undergo degeneration of their lining, and an inspissation of the cyst contents which remains inert for long periods of time before absorption is complete.

These two types of variation are always just below the surface of the peritoneum, and are very obviously mere inclusions. They never seem to exhibit any other tendency than to be just inclusion masses and cysts.

One rarely finds sections of the broad ligament without these inclusions. This frequent incidence and consistency to type, and the absence of any other varieties, stamp the peritoneal epithelium as a structure of rare stability—in this respect, almost in a class by itself.

PELVIC INVASION AND CONTAMINATION

The distinction between these two, though theoretically sound, is not always possible to determine in certain cases. The distinction lies in their mode of spread. By *invasion* of the peritoneal cavity is understood an approach to the peritoneal surface by infiltration from without. By *contamination* is meant an invasion of the pelvic peritoneal cavity from a tubal "spill" or by the bursting of a subperitoneal or intraperitoneal endometrial cyst, causing contamination of the peritoneal cavity by its dead, bloody, and living endometrial cellular contents. Both processes may operate simultaneously.

It was pointed out at the beginning of this section that all cases of endometriosis, of whatever type or wherever located, trace their ancestry to the uterine endometrium. It was also pointed out that endometriosis, starting from the uterine mucosa lining, may pursue a mode of spread singularly resembling the spread of any of the various types of intrauterine infections. Chronic infections have a strong tendency to remain local. More acute infections tend to burrow through the uterine mucosal and parietal lymphatics to various depths, and may be arrested at any stage of their penetration within the uterine wall; or, they may continue to penetrate, if more persistent, to the peritoneal cavity by a subperitoneal extension to the peri- or parametrium. Still others, with a special predilection on the part of the infective agent and an individual susceptibility on the part of the host, extend, along the venous channels and thence to any part of the lesser circulation, by embolism. And still another type, of subacute but persistent characters, but with weak penetrating powers, tends to spread by continuity of surface from the uterine cavity along the mucosal surfaces to the fimbriated ends of the tubes to "spill" over into the pelvic peritoneal cavity.

The prototype of this mode of spread is found in gonococcal infections, although we know that the gonococcus is described only as a classic of that type of spread, of which there are many other organisms possessed of the same characters. These modes of spread of infections were fully described in my monograph on puerperal infections. I revert to them here merely to show that the cellular elements of new growths possess penetrating properties remarkably similar to those of microbic life. So it is, almost to a degree, with endometrial ectopias. There is this difference, however, as previously stated, that there are two processes at work in many of the intraperitoneal endometriotic implants: (2) Invasive

replacement, and (2) destruction caused by menstrual extravasations.

Endometrial invasions of whatever origin are invasive, but only those which reach the peritoneal surface by permeating the uterine wall are nonresponsive because of their origin from the nonresponsive basal layer of the endometrium. Intraperitoneal implants are responsive only in the acute progressive stage of the disease. In the regressions, not only do bloody extravasations cease, but absorption of the former extravasations takes place slowly, so that the liquid plasma, being slowly taken up, leaves residual masses of variable consistencies from a thickish, black fluid to that of sticky tar.

It was pointed out in a previous chapter, and is here repeated for emphasis, that in our records at St. Mary's Hospital two-thirds of the cases of clinical endometriosis that came to operation were those in a state of regression of the disease. These cases, to those who are conversant with endometrial intraperitoneal pathology, lend themselves easily to diagnosis, by many fine points of distinction: (I) The sites of the adhesions; (II) the types of adhesions; (III) tarry cysts, at specific sites; and (IV) the old blood extravasations and hemic stains. These deserve more specific descriptions.

I. The Sites of Adhesions

The sites of adhesions are characteristic. Endometrial "spills," in order that they may take root, must reach a resting place. When one examines the abdomen, even in the exaggerated Trendelenburg position, and before one disturbs the pelvic contents, one invariably finds the tubes lying on the posterior wall of the broad ligament beside its buttonholed ovary. Under normal conditions this is always the case. Exceptions are found in movable ovarian tumors which drag the tube with them, or in parovarian cysts which stretch the tube over their surface and displace it out of its normal relations. But the incipient stages of tubal "spill" find the pelvic cavity singularly free from disease, with an open tube and free access to the peritoneal cavity. This is a *sine qua non*. So we find that the "spill" will ordinarily contaminate the surfaces posterior to the broad ligaments. This is in accordance with clinical and operative experience. Involvement of the vesico-uterine pouch is in comparison relatively rare, and usually a secondary contamination.

There are sites of predilection for the sedimentation of a primary contamination in the posterior pouch. (Plate II.) These are the base of the pouch of Douglas, which by extension may involve the contiguous surfaces of this pouch—namely, the rectovaginal septum, rectum, peritoneum, and mesorectum; next, the shelf of the utero-ovarian ligament which, with its trough, leads directly to the ovary; and lastly, the undersurface of the ovary as it lies against the posterior wall of the broad

ligament. Once the desquamated menstrual cells have taken root in any of these sedimental sites, progress in extension of the disease is unrestricted. And the pelvic contamination, being an offspring of the cells of the surface layers of the endometrium contained in the menstrual "spill," carries in these transplanted cells the potential susceptibility to reaction to the hormones of the menstrual cycle.

II. The Types of Adhesions

There is something quite characteristic in the adhesions of endometriosis which, when once experienced, one can recognize by the exploring finger. Adhesions due to inflammatory disease seldom completely obliterate the normal cleavages between contiguous though adherent organs. Viewed under the microscope one finds small clefts along the lines where the normally contacted peritoneal surfaces lay. In the interval between these clefts the two organs have become fused by bands of adhesions. The clefts are still lined by the normal or somewhat altered peritoneum, and it is usually very easy by hand dissection to follow these cleavages and separate the adherent structures. There are three diseases to which this does not apply: tuberculosis, malignancy, and endometriosis. These three are destructive and invasive diseases. It is always possible to recognize the characters of tuberculosis, with its common involvement of the endosalpinx—the most susceptible of all the pelvic organs. But from malignancy the differentiation of the type of adhesion is not so easy, because—though it is localized to the susceptible pelvis, and governed by a known cause which, when removed, causes regression of the disease—is not endometriosis a local malignancy? In these three diseases the normal boundaries are completely lost and fusion is complete and destructive.

III. The "Chocolate" or "Tarry" Cysts

These are more or less characteristic of endometriosis. (Fig. 7.) It is true that blood extravasations from other causes can simulate these cysts, but endometrial cysts are usually multiple, and the contents of all such cysts are usually of the same degree of tarriness, by virtue of absorption which affects simultaneously all endometrial blood extravasations. Any differences in consistency are dependent upon local causes, such as vascularity, thickness of the wall of the encapsulated blood, and other circumstances of the terrain.

IV. The Old Blood Extravasations and Hemic Stains

There is another form of extravasated blood which is common, and may occur in ectopic endometriosis or in other causes of free blood in the peritoneal cavity. This is the implanting of old blood from an endo-

metrial cyst upon an otherwise free peritoneal surface. This frequently becomes organized, and is soon covered by peritoneal cells as an encapsulated foreign body. These appear as pigmented areas which may persist for long periods, and, depending upon the size of the burst hemorrhagic cyst, the pigmented enclosures may be dispersed narrowly or widely over the whole pelvic peritoneum; but the vesico-uterine pouch is the site of common election and in active cases of endometriosis is the common means of vesico-uterine endometriosis and of vesical plication over the anterior uterine wall.

PERITONEAL SECONDARY CONTAMINATION

Peritoneal secondary contamination is of common occurrence. This takes place through the spontaneous rupture of blood cysts into the general peritoneal cavity. The spontaneous rupture occurs by reason of one of two factors: first, by sudden increase of intracystic pressure beyond the tension power of the cyst wall; and second, by necrosis of that part of the cyst wall that is most remote from the source of blood supply. The effects of spontaneous evacuation of a chocolate cyst depend upon several factors, chief among which are: (1) the size of the cyst; (2) its relations; and (3) the character of the contents.

It is known that small cysts frequently rupture, and rupture repeatedly at the same spot with each addition of pressure during the menstrual extravasation. This repetition will continue unless adhesions form to cover the rupture aperture. Small cysts undergoing spontaneous rupture doubtless produce symptoms of a local peritonitis which subsides spontaneously without their true nature being suspected. But one judges that such is the case from the symptoms which arise when a large endometrial cyst bursts into the general peritoneal cavity. Under these circumstances the patient has all the symptoms and signs of a generalized acute peritonitis, which is seldom diagnosed correctly until the abdomen is opened. It is not surprising that the contents of such a cyst, composed of old blood and cell detritus, should set up a fairly acute reaction, when one considers the acuteness of peritoneal reaction when fresh blood from an ectopic gestation develops such alarming peritoneal response.

When a ruptured cyst is large the liberated contents may spread throughout the abdomen or be scattered widely by gravity and peristalsis in the smaller evacuations. But wherever the contents spread, their fertile field of transplantation is limited to the areas of the abdomen that are susceptible to decidual change, and that are bounded roughly above by a line through the peritoneal cavity at the level of the umbilicus. Cells which reach a level higher than this find a soil inimical to their type of biological chemistry, and are doomed to dissolution. Peritoneal endometriosis by contamination is always of the mixed variety—that is, com-

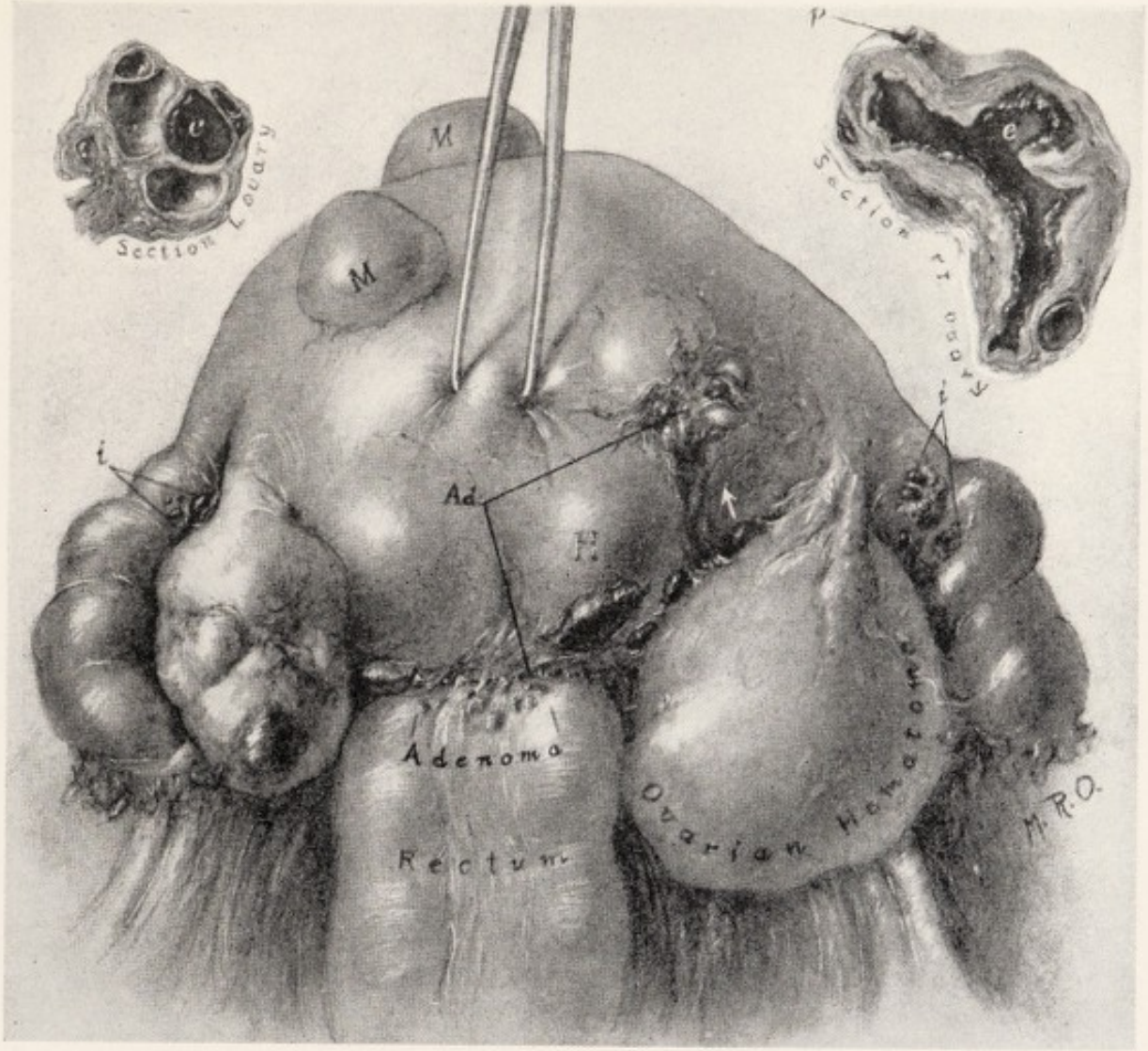


FIG. 7. Implantation adenoma of endometrial type of the rectum, rectovaginal septum, mesentery of the appendix, epiploic appendage of the sigmoid, tubes, posterior layers of both broad ligaments, posterior uterine wall; menatoma of endometrial type of the left ovary (not perforated) and of the right ovary (perforated), multiple leiomyomas. Posterior view of the uterus and appendages as they appeared at operation; × 5/6. The ovaries are also shown in cross-section. On drawing the uterus upward, the rectum is carried with it because it is fused to the posterior wall of the cervix, and to the lower portion of the body of the uterus. The characteristic lesions are shown on the wall of the rectum above its fusion with the uterus. Implantation adenoma of the uterus is shown at *Ad;* at *H* an endometrial hematoma is situated in the uterine wall. The implantations (*i*) are shown on the posterior surface of both broad ligaments. The left ovary was not adherent and a nonperforated hematoma of endometrial type is shown in the cross-section of this ovary at *c*. The right ovary was densely adherent to the posterior surface of the uterus. When it was freed, "chocolate" fluid escaped, because a previous perforation had occurred (indicated by arrow and *p*). The right ovary is shown in cross-section (collapsed).

(Courtesy of John A. Sampson, M.D.: in Arch. Surg., *5*:234, 1922, Chicago, American Medical Association.)

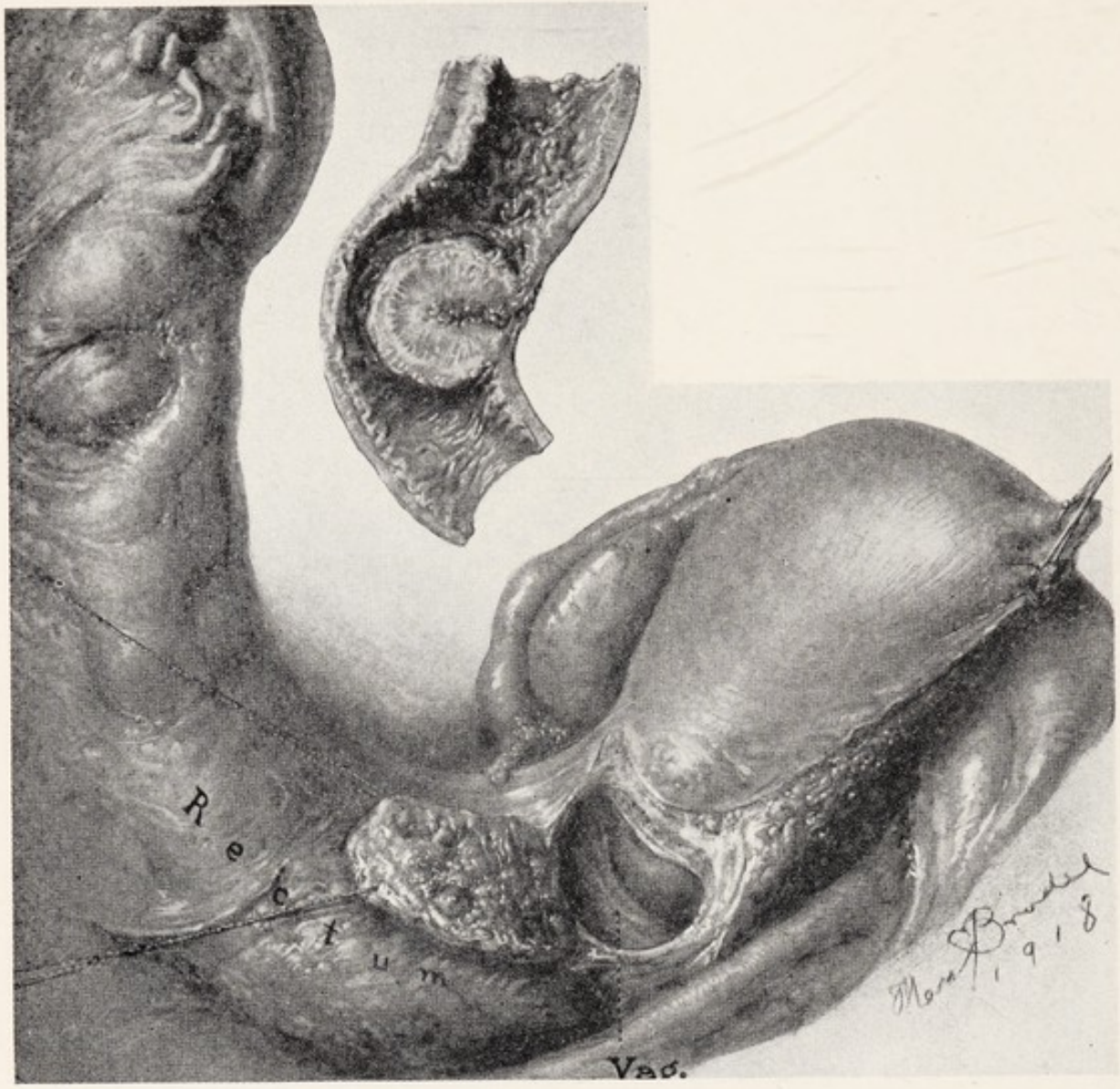


FIG. 8. Adenomyoma of the rectovaginal septum, independent adenomyoma of the sigmoid almost completely blocking the lumen of the bowel. The right appendages have been removed, the right broad ligament opened up, the right uterine artery ligated and cut, and the ureter dissected out. The vagina has been opened, and the adenomyomatous thickening on the posterior vaginal wall cut away from the vagina and left attached to the rectum. We were preparing to push the adenomyomatous area together with the adjacent rectum down so that it would be entirely extraperitoneal and so that it could be removed through the vagina a few days later. At this moment, however, we noticed the puckered area at the pelvic brim. This bore a strong resemblance to carcinoma, but no metastases could be found, so we came to the conclusion that it also might be an adenomyoma. The peritoneum of the sigmoid was then severed on either side to a point well above this second growth, the entire mass was pushed down to the pelvic floor, and the peritoneum so drawn over it that the entire area was practically extraperitoneal. The abdomen was then drained. We expected to remove the entire diseased area from below at a later date. The patient, however, died of infection. At necropsy the sigmoid growth was found, as indicated by the picture, to have blocked almost completely the lumen of the bowel. It was a typical adenomyoma. This accounted for the fact that the bowel symptoms were so marked at the time of the menstrual period.

(Courtesy of Dr. Thomas S. Cullen: in Arch Surg., *1*:269, 1920, Chicago, American Medical Association.)

posed of the glands and stroma cells because the peritoneal disease is derived from emboli scattered from the menstruating endometrium, and composed of all the cellular elements of the endometrium.

PERITONEAL INVASION

By this term is meant the invasion of the peritoneal cavity through the subperitoneal lymphatics by endometrial growth spreading through the lymphatic system. The peritoneal cavity is looked upon as a large lymph space communicating by various ostia with the subperitoneal lymphatics, through which lymph ebbs and flows. It is natural, then, that uterine parietal endometriosis in its progress must reach the peritoneal surface of the uterus, or through the parametrial tissues eventually reach some portion of the parametrium covered by peritoneum. Such peritoneal invasions are possible directly through any part of the pelvic peritoneum, such as in the pouch of Douglas, or from the invaded lymphatics of the mesosalpinx, or from the surfaces of the broad ligament. Such peritoneal invasions, derived primarily from the basal layer of the endometrium, thence through the uterine wall to the peritoneum or parametrial peritoneum, are devoid of menstrual extravasations, and consequently are less destructive than peritoneal contaminations derived from a tubal "spill." The adhesions which they develop are of the same nature as those of tubal origin, and they fuse contiguous surfaces completely.

Clinically, these cases may be confused with cases of healed contamination, but there are some distinctive features. There are no tarry cysts, no patches of subperitoneal blood pigment, and under the microscope the tissues in this type of case present the well-preserved dual tissues of the normal endometrium. In the regression of "spill" cases the first tissues to die and be cast off are the ectopic elements, which disappear completely by necrobiosis. Peritoneal endometrial invasions, as distinguished from "spill" contamination, may be composed of glands and stroma cells, or may be made up solely of endometrial stroma. This will be dealt with more fully in the chapter on degeneration.

OVARIAN ENDOMETRIOSIS

Endometriosis of the ovary is always secondary. It may be of any type of endometriosis, mixed or stromatous, and, depending upon its mode of invasion, either responds or not to the hormones of menstruation. Invasions of the ovarian stroma by endometrial elements which reach the ovary by tubal "spill" far outnumber those which reach the ovary through direct lymphatic extension. Since, however, a more careful study has been made of the broad-ligament lymphatics in the vicinity of the ovary, the cases of broad-ligament lymphatic involvements up to

and into the ovary are becoming increasingly numerous. And cases of ovarian stromatous endometriosis are now unquestionable facts.

From the frequency of incidence and the destructiveness of ovarian endometriosis, one is led to believe that the ovary offers a very favorable soil for the implants and transplants of endometrial tissue, whatever their origin. As stated above, most of the ovarian invasions are of "spill" origin and therefore most ovarian growths suffer the destructive influence of menstrual blood. So that the two destructive factors are at work simultaneously. In major involvements the affected ovary enlarges, due to many factors: (1) chiefly owing to blood cysts and (2) the new invasion by the endometrial growth; but also (3) by hypertrophy of its own specific cellular elements. This last, it is now thought, is a response or a factor in the production of hyperestrinism, similar to the hypertrophy of the uterine elements in cases of parietal endometriosis.

Not only does the normal function of ripening of follicles go on in the immediate neighborhood of the endometriosis, but, from a careful study of active cases of ovarian endometriosis, there seems a decided increase in ovarian function. Whether many of the ripening ova reach maturity is questionable, but some do. This fact is of importance when we come to the question of sterility, which is almost an invariable accompaniment of endometriosis.

When the ovary becomes contaminated by "spill," the endometrial cells may come to rest in its creases and clefts. Here they take root and invade the ovarian capsule. The contamination contains both stroma and glandular cells, and each tries in its new location to assume its normal relation to the other. Consequently glandular cells grow into acini and become clothed with stroma cells. At the next menstrual epoch these cells *in loco novo* go through all the changes of: (1) growth in response to the follicular hormone, (2) succulence in response to the luteal hormone, and (3) blood extravasations both into the newly formed acinus and into its surrounding stroma cells as a sequence to the withdrawal of both hormones. In this manner blood is set free and the first ectopic cyst is formed. During one of the subsequent menstrual extravasations the cyst or cysts now rupture and recontaminate the surface of the ovary, and if the surface of the ovary at this spot has not been fused by the burrowing endometrial cells, the cyst contents, composed of living endometrial desquamated cells and blood detritus, brings about the fusion. From that time on the ovary and its fused neighbor operate as a conjoined soil for the uninvited guest of ectopic endometrial cells, which set up their own ménage to the seemingly great discomfort of the hosts.

As stated above, the surface cysts rupture and agglutinate that contaminated organ with that of a contiguous organ, causing a welding of these two surfaces. This goes on repeatedly so that large surfaces may be-

PLATE I

Small peritoneal cysts on the posterior wall of the broad ligament.

come agglutinated and neighboring organs become invaded, in this manner, over a bridge of adhesions or by secondary implants from the ovary where surfaces are free. If ovarian endometriosis has progressed for a long period in a chronic form, changes of a sclerotic nature occur in both ovaries. Since the two ovaries are seldom afflicted to the same degree they usually differ markedly in size, but (whether large or small) cystic degeneration arising out of unruptured hyperdistended atrophying follicles is the rule, with a progressive sclerosis of the tunica albuginea of the ovary. Viewed from above, when the abdomen is opened, any free surface of the ovary presents a white appearance often stained a soiled white by cells filled with blood pigment.

Blood cysts of the ovary differ markedly in size and in appearances. (Plate III.) The small cysts are best for study, because they are a recent development and are less disfigured by old blood pigment and necrobiotic changes. (Plate IV.) The endometrial invasions respond, not, as one might be led to think, by a free bleeding into a columnar-lined cavity by the rupture of a blood vessel near the cyst lining, but the flow is similar in every respect to that of the uterine mucosa during menstruation. There is a widespread diapedesis into the stromatous tissues for some depth below the surface epithelium. Eventually the blood reaches the lining epithelium, percolates through it into the cyst cavity, and causes a desquamation of large parts of the specific columnar cells. This blood diapedesis mixes with the blood of previous extravasations, while the blood-infiltrated tissues in the subjacent structures undergo slow resolution in the intermenstrual period.

It is noteworthy that a complete reproduction of endometrial architecture in the ovary is a rarity. Usually one finds only a tortuous ovarian cavity lined by a single layer of columnar cells, which may present various forms of imperfect development or of atrophy. Seldom does one find the normal tubular glands and the various layers of the uterine mucosa. This is not true, however, of ovarian endometriosis derived from a uterine parietal invasion and reaching the ovary by the broad-ligament lymphatic chains. In such cases I have seen the ovarian metastases reproduce the uterine architecture down to its minutest detail. There are not, of course, the distorting and destructive influences of menstruation to disrupt the natural and hereditary architectural potentiality of these transposed tissues.

OVARIAN STROMATOUS ENDOMETRIOSIS

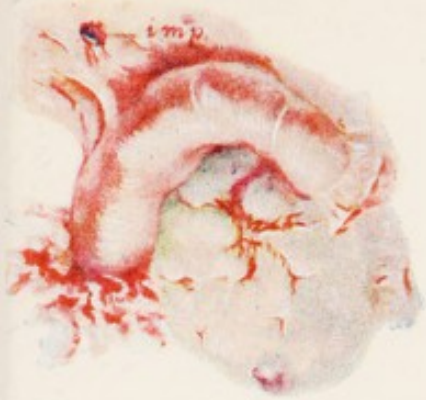
These cases are now a well-recognized though somewhat rare type of ovarian invasion. They are less numerous than the mixed types from the same source. Stromatous ovarian endometriosis has the same origin as uterine parietal stromatous endometriosis. It occurs in the ovary as in

the uterine wall, either in the form of strands or in the form of a definite circumscribed tumor. Some very beautiful specimens of these latter have been discovered lately. They have the same characters as similar tumors in the uterine walls. They are, however, easily confused with tumors derived from the tunica of follicles in the ovary, and their true origin can be determined only by tracing the new growth in the lymphatics of the broad ligament adjacent to the ovary and in the uterine parietes—a condition which is not always possible. A close study of the undoubted cases makes identification of these tumors relatively easy. Not infrequently the cause or causes which incited endometrial tissue to invade the ovary by the lymphatic channels also favored transplant by "spill," so that one may discover stromatous and responsive endometrial implants in the same ovary, or one may find mixed unresponsive and responsive invasions which have reached the ovary by two different paths.

It was pointed out in a previous chapter that in many invasions of the uterine parietes by endometrial elements there was also a concomitant invasion of the ovary by the "spill" approach, which means that the condition which made invasion of the uterine wall possible made also the terrain favorable to other forms of propagation. How like infections it is in this respect also! How frequently one sees in the same patient a perimetritis by "spill" and a parametritis by lymphatic invasion, both originating in common intra-uterine infection! Conditions favorable to endometrial new growth are not only restricted territorially, but also in point of time. In all biologic metabolic upsets, nature, as a rule, manages to restore the *status ante quo*. The time required to complete that restoration varies with each individual. In some it is of short duration; in others it becomes a chronicity. The damage therefore may be slight or very great, depending upon the period of variance between the patient and her environment. In the end, however, restoration must take place because endometriosis *per se* is not a deadly disease even though it may destroy the function of kidney or bowel by obstructing the outflow of the products of those channels. And, though regressive changes may destroy the ectopic endometrial cellular elements, no amount of absorption can destroy the adhesions that have fused organs and neighboring tissues, nor can it eliminate pain which may arise out of the restraint imposed by those adhesions.

INTESTINAL IMPLANTS AND TRANSPLANTS

By implants we mean a primary seeding from the site of origin (Plate V); by transplants we mean secondary imbedding from implants. With the exception of the rectum and mesorectum, intestinal contaminations are all derived primarily from tubal "spill," or secondarily from rupture of endometrial cysts. Every implant or transplant upon a free



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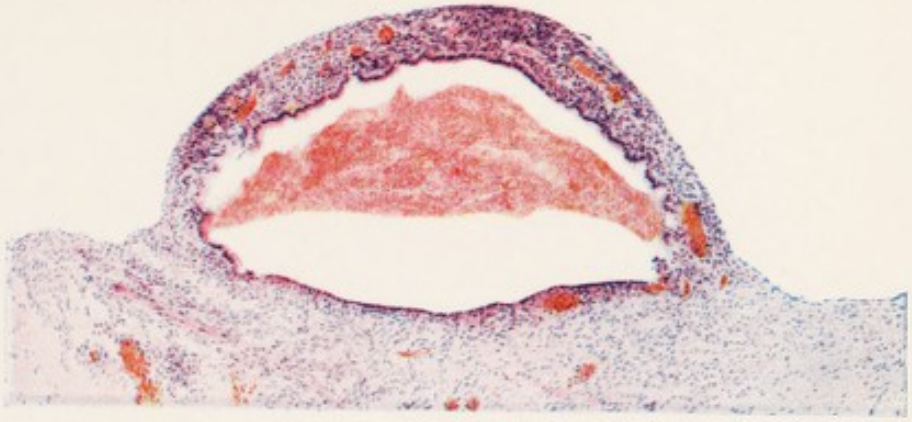

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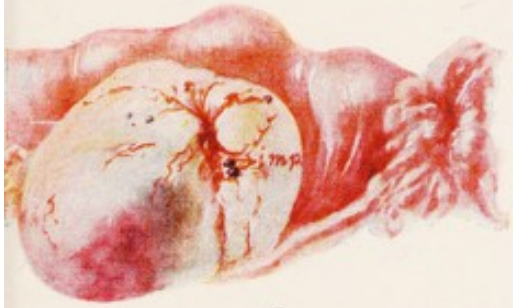

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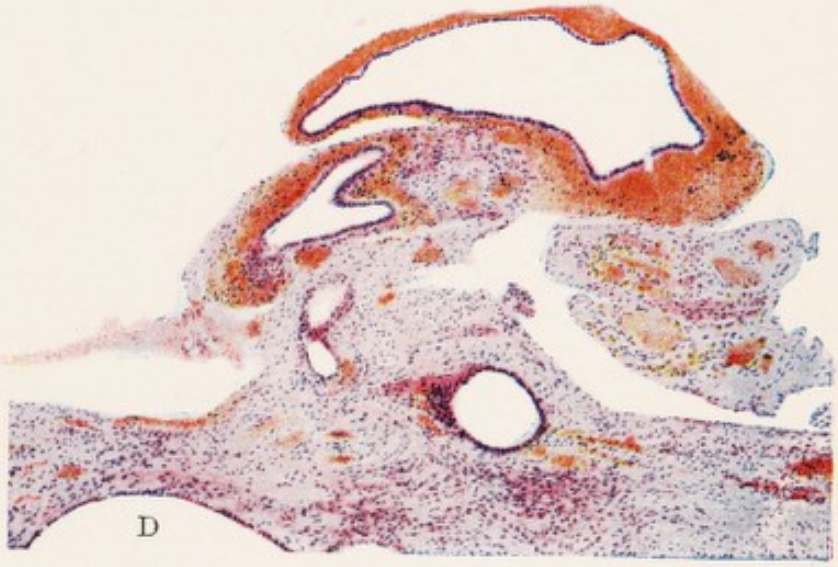

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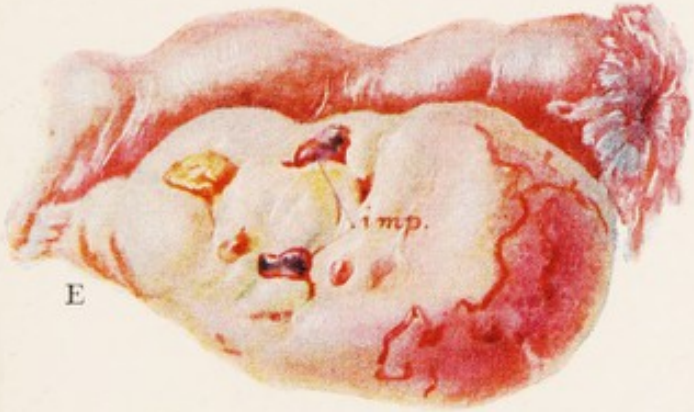


E

Benign Endometrial Implants in the Peritoneal Cavity

A. The left tube and ovary with an implant on the suspensory ligament of the ovary (natural size). The "red-raspberry" appearance is due to a recent hemorrhage.

B. Colored photomicrograph (× 60) of the implant shown in *A*. (hematoxylin and eosin stain). It is similar to a dilated uterine gland with a vascular stroma, resembling that of the endometrium, about it. Hemorrhage has occurred into its lumen.

C. (A. H. No. 88156.) Right tube and ovary, the latter turned upward, showing implants on its lateral surface (natural size). Implants were present on both ovaries, the posterior surface of the uterus, and the sigmoid, including one of its epiploic appendages. The patient was aged 47 years. She had had one child 21 years earlier. The uterus was retroflexed. Operation was on the day after menstruation had ceased. The distribution of these implants suggests a common origin, and could be accounted for by epithelium escaping through the tubes.

D. Colored photomicrograph (× 60) of a section through one of the implants shown in *C*. Hemorrhage is present in tissues about the glands, and the latter have invaded the ovary.

E. Undersurface of right ovary. The implants are larger than those illustrated in *A* and *B*, and have a "purple-raspberry" appearance (natural size). Courtesy of John A. Sampson, M.D.: from *Surg., Gynecol. and Obstet.*, 38:287, Plate I, 1924. Surgical Publishing Co. of Chicago.

peritoneal surface becomes a potential center for further transplants. When a group of endometrial cells settles upon a favorable peritoneal surface, fixation occurs followed by invasion. The small operculum in the peritoneum by which the invasion was made soon closes over and a potential endometrial cavity is thus formed, because these tissues wherever transplanted tend to develop (though somewhat imperfectly) their original architecture. A menstruation diapedesis occurs in this potential cavity at the next menstrual epoch, and rupture at any subsequent menstruation is a possibility. The parts of the alimentary tract susceptible to these transplantations are the appendix, the lower part of the ileum, the sigmoid, and the rectum. It will be seen from this enumeration that soil is favorable to transplantation only when the tissues have been in close contact with the pelvic cavity, and have been bathed in some secretion which is restricted to that vicinity. This applies also to the peritoneum covering these parts of the alimentary tract, and to a similar restricted portion of the parietal peritoneum.

Peritoneal transplants cause neighboring coils first to agglutinate by virtue of the extravasated blood, later to fuse with a fixity that it is impossible to separate without the risk of perforation. Not only may the peritoneum covering the intestinal wall become infiltrated, but the mesentery of that part of the bowel is favorable soil also, though in the case of the ileum, only in the immediate neighborhood of the bowel. As one recedes from the bowel toward the root of the mesentery, transplants grow fewer and finally cease altogether. We are getting too far away from the source of the activating agents as we ascend to the mesenteric roots. In the rupture of cysts of large size, doubtless many endometrial emboli reach the upper abdominal cavity, and doubtless also many emboli reach remote parts of the body through the venous channels, but they are disposed of and we learn nothing of their innocuous absorption. There is a close similarity in the action of syncitial masses which may flood the whole system but are allowed to function only in a restricted area in the pelvis and even then under only very special conditions of pregnancy. In a few cases, however, this restriction is broken down as in the two cases of stromatous endometriosis cited in a previous chapter. So also in a few cases the restrictions ordinarily placed upon syncitial cells are broken down, and so the patient becomes a victim of widespread chorio-epithelioma.

THE RECTUM AND MESORECTUM

A separate heading is allotted to this part of the alimentary canal because, unlike the rest of the large bowel, it is in direct lymphatic connection with the organs of generation and in particularly close relationship with the uterus, the mother of endometriosis. The avenues of

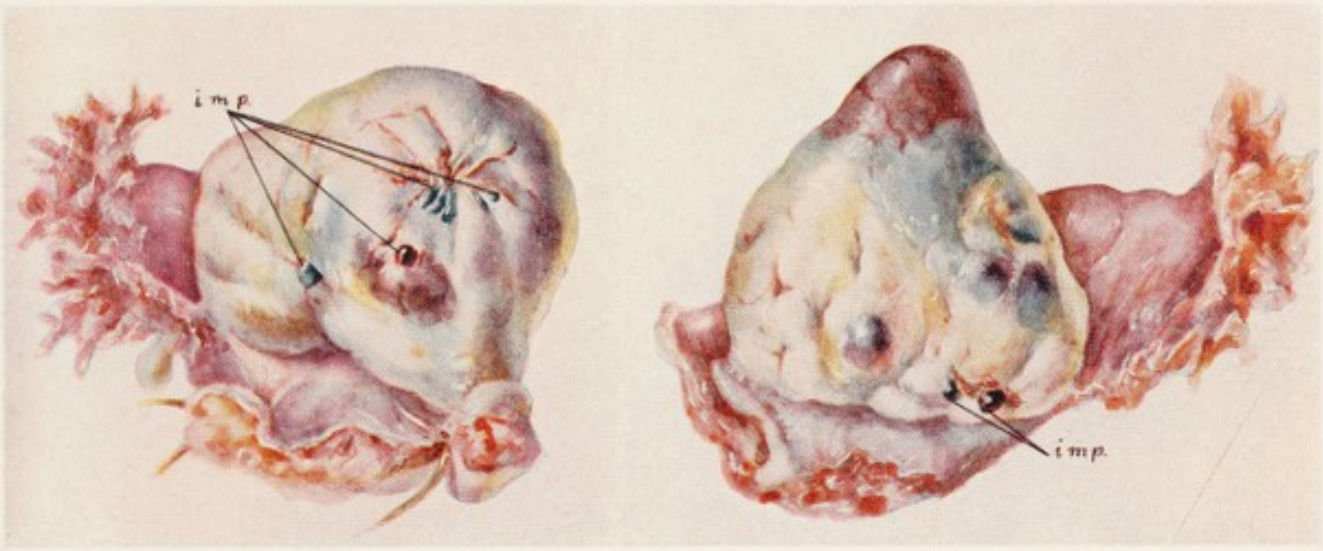
approach to the rectum are: (1)by direct lymphatic extension through the parametrium from the uterine wall, or (2) from the peritoneum of the pelvic cavity into the pararectal tissues. It can easily be seen, therefore, that, depending upon the route of access, rectal and pararectal endometriosis may be either of the chocolate-cyst-forming variety or of the simple infiltrating type. To recognize this distinction of characters is of the utmost clinical importance. It is being recognized today that many of the cases diagnosed as carcinoma of the rectum recover spontaneously because it is now known that they were really cases of non-responsive perirectal endometriosis. In the blood-cyst-forming types the diagnosis is considerably facilitated, but in the purely glandular type of endometriosis without cystic response nothing but a biopsy can remove the doubt. In my own experience there have been many of these cases, and the prompt response of these to deep–x-ray treatment without confirmation of the diagnosis has given to x-ray a curative value in carcinoma that it does not rightly deserve.

The bowel involvement by endometriosis differs essentially whether the ileum or the colon, including the rectum, is affected. In involvement of the small bowel obstruction is the common complication. This may be brought about by the gradual constriction by the endometriosis of adherent loops, causing acute kinks, or it may arise out of a gradually increasing cyst of the mesentery causing the bowel to be stretched over its surface like a fallopian tube over a parovarian cyst. In the large bowel, however, and in particular in the rectal region, obstruction may arise out of two forms of growth.

In the one type a large cyst is found in the mesorectum or rectovaginal septum, which causes slow partial obstruction of the bowel, or in the noncystic types the growth may infiltrate the whole circumference of the bowel and by its slow constriction eventually cause a complete block. It is in this type that the mistaken diagnosis of malignancy is so common. I have seen two cases of the cystic type in the last six months. In one of them the peritoneum was free except for a characteristic adhesion about the left ovary.

In the other case there was a well-defined peritoneal endometriosis. The intraperitoneal condition when recognized gave an easy clue to the rectal disease. In the noncystic annular type the diagnosis may be extremely difficult, except that there is one infallible point of difference. Rectal malignancy is a disease of the mucosa and always presents this palpable or visible break of mucosal continuity. (Fig. 8.) This, in the later stages, is accompanied by discharges. Endometriosis is a disease that attacks the bowel from without and leaves the mucosa smooth and unimpaired. In bowel endometriosis there is never any unnatural rectal

PLATE III



The left tube and ovary (natural size), the latter turned upward, exposing the endometrial implants on its lateral and under-surfaces. The pigmentation is due to hemorrhage (which we infer is menstrual) into the tissues of the implant.

Right tube and ovary (natural size), the latter turned upward, exposing the endometrial implants on its lateral surface.

(Courtesy of John A. Sampson, M.D.; from *Arch. Surg.*, 10: Plate II, 1925, Chicago, American Medical Association.)

discharge. A biopsy seldom leaves the case in doubt. Some interesting cases will lend point to these remarks.

Case I. This was a woman operated upon two years previously for a supposed appendicitis. Sections of this organ showed that it was a periappendiceal endometriosis. I saw her in consultation two years later with symptoms of bowel obstruction. Pelvic examination revealed a "choked" nodular pelvis, and a large mass in the right iliac fossa.

Diagnosis. Diffuse intraperitoneal endometriosis with large cyst formation causing obstruction.

Operation. Operation revealed a large chocolate cyst in the meso-ileum over which the bowel was tightly stretched. Removal by resection of small bowel and removal of both ovaries restored normal bowel function.

Case II. A case of large-bowel obstruction. A pelvic and abdominal examination revealed a smooth rectal mucosa and signs of a nodular growth in the pelvis and left lower quadrant.

Operation. Upon opening the abdomen there was a diffuse endometriosis in all the pelvic organs. This had been of long standing, and the adhesions were extremely diffuse and dense. In the mesorectum there was a large cystic mass, the black contents of which shone through the capsule at one spot. It was at once determined that complete extirpation was impossible, so the contents of the cyst were aspirated, causing the cyst to collapse. The abdomen was closed. The obstruction was relieved. It was determined to await eventualities. In four months the symptoms of obstruction and pain returned, and the patient, a private secretary, was again incapacitated. Treatment by deep x-ray was then begun, and improvement was prompt. Now, 15 months after treatment, the patient is enjoying full working capacity and good health, and except for complete fixation of the pelvic organs there are no subjective symptoms of the pelvic storm.

Case III. A very interesting case of pelvic tumors, diagnosed as ovarian cystoma.

Operation. When the abdomen was opened the peritoneal cavity was found free from any visible or palpable pathologic lesion, except a large mass, extraperitoneal and situated low down in the rectal region. My colleague, whose case this was, was somewhat nonplused by this finding. Carcinoma of the bowel became the tentative diagnosis because of the absence of obvious signs of endometriosis in the pelvis. The abdomen was closed and the case was turned over to the general surgeon. Proctoscopic and digital examinations showed that the rectal mucosa was smooth and movable over the tumor. So, for purposes of biopsy, the

tumor was incised from the rectum. Examination revealed an endometriosis. Some hours after this incision the patient bled profusely from the growth into the rectum, and her condition became precarious. Finally this was controlled by appropriate means and deep x-ray was at once begun with prompt results.

Such cases of mistaken diagnosis are numerous, and will remain all too numerous until the frequency of perirectal endometriosis is fully appreciated and appropriate means adopted to meet this complication. I know of three other endometrial cases of rectal resection for carcinoma, only to have the proper diagnosis established after biopsy.

TUBAL AND BROAD-LIGAMENT ENDOMETRIOSIS AND INCIDENTAL CHANGES

It is doubtful whether there is such a pathologic entity as endometriosis of tubal origin. Theoretically there are grounds for such a development, though, owing to its being a developmental error, it would necessarily be a very rare occurrence. That the normal tube contains islands of endometrium is no longer doubted. In one case loaned to me by Dr. Joseph Pritchard, pathologist to St. Mary's and the Montreal General Hospitals, the whole tube is lined by typical endometrium—a reversion to the lower vertebrate types. Such conditions, however, are rare, and to the best of my knowledge an undoubted case of primary endometriosis of tubal origin does not exist.

Infiltration of the tubes from without, however, is a relatively common complication. This invasion may be from the peritoneal surface as part of a more widespread peritoneal soiling from a primary tubal "spill"; or from a secondary rupture of a hemorrhagic endometrial cyst. This type of invasion requires no further special description. It runs the same course of penetration and subperitoneal growth as happens in other peritoneal transplants.

Invasion of the tubal wall from the broad ligament, however, deserves special mention. In all cases of active broad-ligament invasion from a primary uterine endometriosis or from peritoneal transplants, the trend may be upward to the tubes and outward toward the ovaries. Uterine parietal endometriosis, especially when involving the uterine walls near the cornu, may involve the lymphatics in the uterotubal triangle of the broad ligament and invade the musculature of the tube at this point. Near the ampulla of the tube the wall may be invaded through the musculature into the tubal mucosa.

That the broad ligaments may be widely involved is shown in the description of stromatous endometriosis cases, and, since publication of those studies in 1937, many new cases have demonstrated the frequency of broad-ligament endometrial rests both by lymphatic channels and by

PLATE IV

TOP

Reproduction of a colored photomicrograph (obj. 16 mm.) of a portion of wall of hematoma, showing endothelial leukocytes escaping into the cavity of the hematoma, and the formation of the pigmented lining. To the right, the epithelial lining is still present with an underlying stromal hemorrhage. In the center, endothelial leukocytes have developed and are pouring into the cavity of the hematoma through a breach — probably caused by a previous subepithelial hemorrhage rupturing into the cavity of the hematoma — and carrying the overlying epithelium with it. To the left, the luteal-like pigmented layer is forming, which is composed for the most part of endothelial leukocytes containing blood pigment. The contents of the cavity of the hematoma (above) consist of blood and endothelial leukocytes, epithelium, and stroma cells in various stages of preservation.

MIDDLE

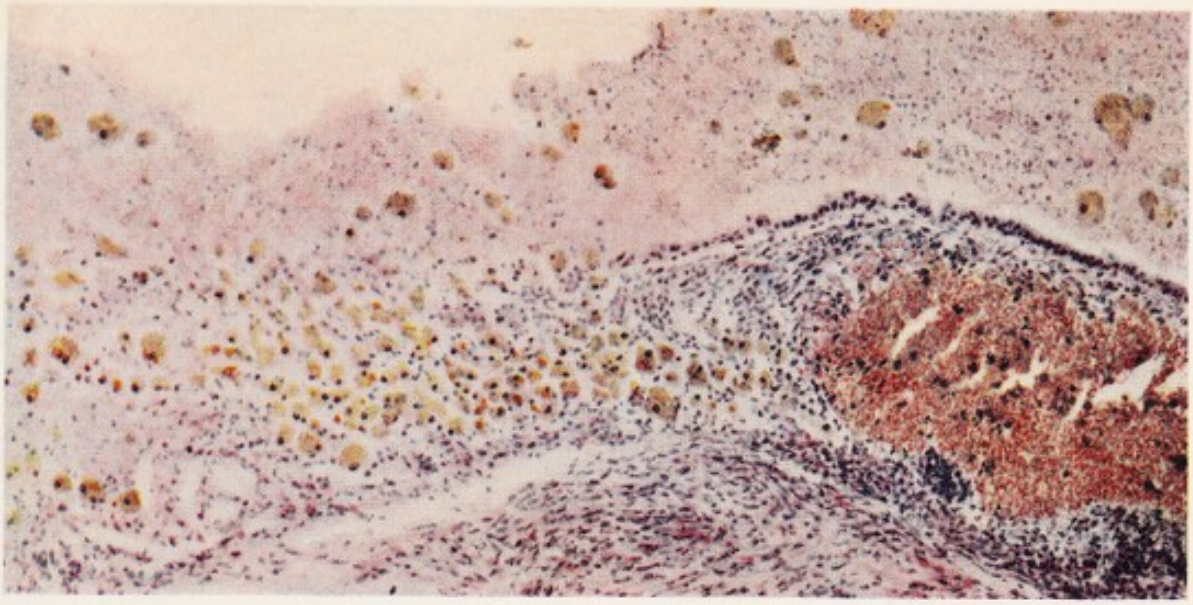
Reproduction of a colored photomicrograph (obj. 16 mm.) of a portion of wall of hematoma, showing the pigmented layer lining of the greater portion of the hematoma. This represents a later stage of the condition shown in the preceding illustration. The endothelial leukocytes are breaking down, and hyaline connective tissue has developed in the stroma of the wall of the hematoma.

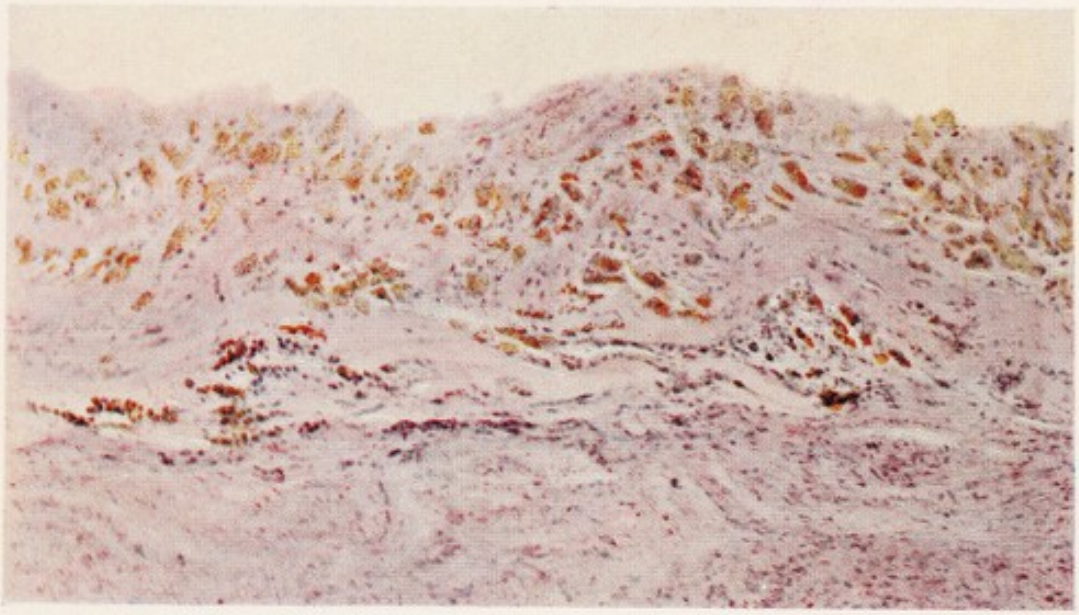
BOTTOM

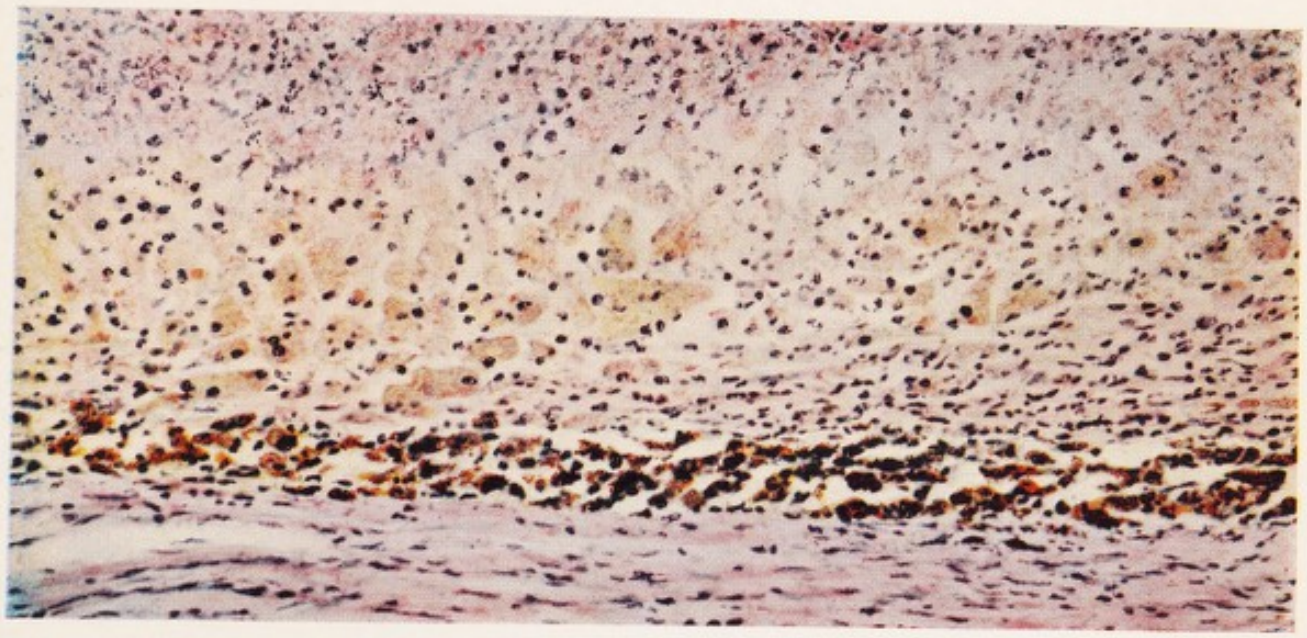
Reproduction of a colored photomicrograph (obj. 16 mm.) of a portion of wall of ovarian hematoma. This demonstrates very well the breaking down of the endothelial leukocytes in the superficial portion of the wall of the hematoma, and the deposit of blood pigment in the deeper tissues.

(Courtesy of John A. Sampson, M.D., from *Amer. Jour. Obstet. and Gynecol.*, 4:486, 1922, Plate VI, St. Louis, C. V. Mosby Co.)

PLATE IV







transperitoneal implantation. Many of these have been shown to be stromatous in type, and the morphologic characters of the endometrial cells vary like those of intramural uterine endometriosis. They vary from large oval cells to streamlined types. Mixed types of endometrial rests are not uncommon.

THE PAROVARIUM IN THE PRESENCE OF PELVIC ENDOMETRIOSIS

At this point it may be opportune to describe the behavior of the parovarium. Ordinarily and normally this structure, being embryonic, does not by its tinctorial properties give one the impression of an active organ. In acute or active endometriosis, however, this organ may change its cellular appearance and so simulate the characters of active endometriosis, both in the lining cells and in the stromatous covering to the latter, that in many cases I have not been able to differentiate between the activated parovarium and mixed endometrial rests. Not only that, but many of the parovarian acini become dilated with secretion giving rise to parovarian cysts, usually of small dimensions, lined by cells which may show all varieties of cell compression from intracystic pressure. But the most striking change is seen in the tinctorial attributes of these cells which, under the influence of the endometriotic agency, give one decidedly the impression of cells no longer quiescent, but actively stimulated. These changes accompany only the active phase of endometriosis.

CERVICAL ENDOMETRIOSIS AND INCIDENTAL CERVICAL CHANGES

Cervical endometriosis is a relatively rare development. However, several undoubted cases have come under observation. In the section on stromatous endometriosis, the common involvement of the cervix in its lymphatic channels as an extension downward from a similar process in the uterine wall was given full description. In one of these cases the penetration of the vault of the vagina and the grape-like protrusions through the external os were described. Several cases of a less active type of growth have been discovered since the publication of the above-cited cases.

Mixed endometriosis of the pelvis occasionally finds an extension into the lymphatic spaces of the cervical musculofibrous tissues. In several of these cases the invasion breaks through onto the squamous portion of the portio. But the other interpretation of this development is that the endometriosis is first an implant on the portio with a subsequent burrowing into the underlying cervical tissues.

By far the most interesting development in the cervix is the growth of the cervical glands that frequently accompanies an endometriosis on

other parts of the genital tract. This association was first described in the *Transactions of the American Association of Gynecologists, Obstetricians, and Abdominal Surgeons* in 1937. Since then many other cases have been found to confirm this response of the cervix to the stimulant that brings about endometriosis. The cervical change is a benign overgrowth of the cervical glands which multiply in various degrees from a slight increase over the normal to definite adenomatous proportions. (Fig. 9.) These racemose cervical glands may invade the cervical tissues fairly deeply, or may grow into polypoidal excrescences about the cervical canal and on the portio in the vicinity of the external os. The clinical appearance and the secretions appear to the naked eye as a severe endocervicitis with ectropion. Under the microscope, not only is there a marked increase in the cervical glandular elements, but a great heaping-up of the lining cells and marked hypertrophy of the squamous elements near the cervical glands. The sections strongly suggest a precancerous cervix. (Fig. 10.) That adenomatous hypertrophy is relatively rare, except in association with endometriosis, is shown by the fact that it was found in 30 per cent of the cases of endometriosis reported in the year 1937.

VAGINAL ENDOMETRIOSIS AND VAGINAL CHANGES INCIDENTAL TO PELVIC ENDOMETRIOSIS

Vaginal endometriosis is a fairly common primary development or secondary complication.

Primary endometriosis consists of patches of endometrial tissue of various dimensions scattered over the vaginal mucosa. The great majority of these are found in the upper third of the vaginal wall with increasing frequency near the fornices. They appear as red patches on the pearly white of the normal vaginal mucous membrane. They become congested in the premenstrual period and bleed with menstruation. When large enough to be appreciable to the examining finger the surface gives a soft velvety sensation in marked contrast to the normal cervical mucosa. The largest patch that I have ever seen covered a quarter of the surface of the vaginal circumference in its upper third. Some authors look upon these ectopias as congenital in origin; others consider them implants upon breaches of continuity. The question is still a debatable one. In most of these cases there is usually no appreciable endometriosis in other parts of the pelvis—a finding which is used as an argument for their embryonic origin, similar to ectopic endometrial islands in the tubes as described in a previous chapter.

Secondary vaginal endometriosis is due to an endometrial disease in the pouch of Douglas or in the rectovaginal septum; it burrows through the vaginal sheath to appear as an excrescence upon the posterior vaginal

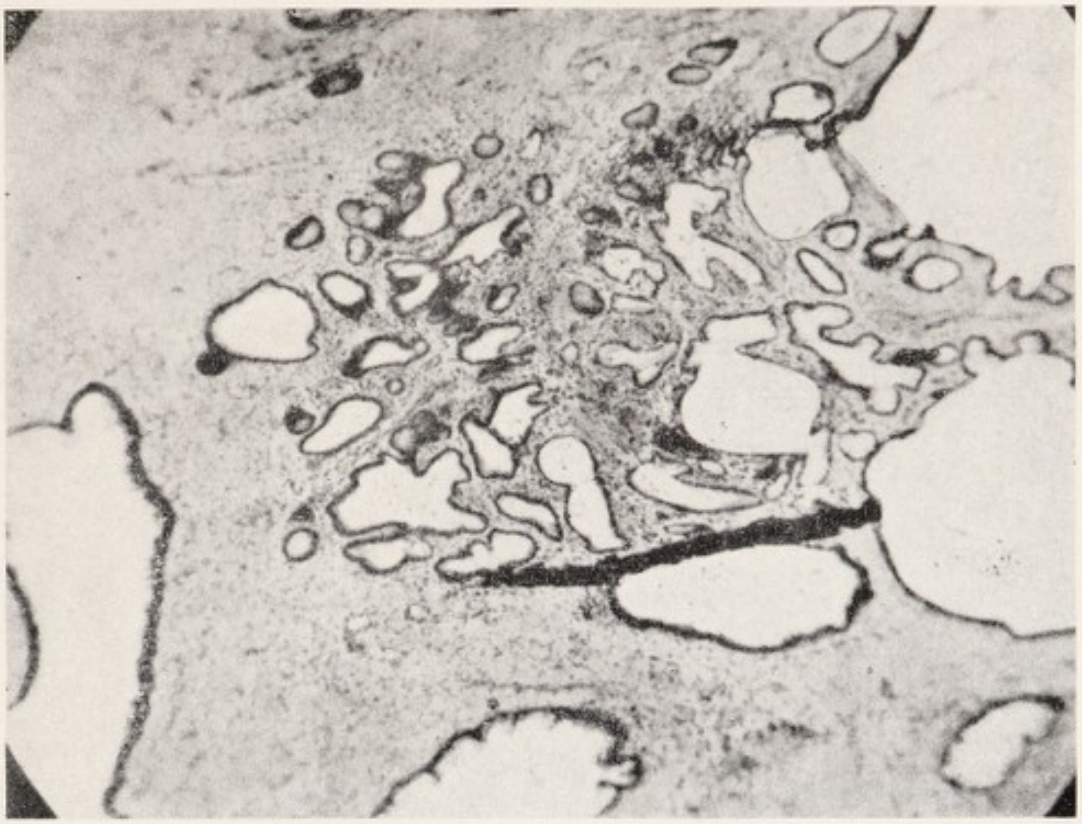


FIG. 9. Adenoma of the cervical glands of the slowly growing type, associated with uterine endometrioma.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricians, and Abdominal Surgeons, *50*:206, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

FIG. 10. Precancerous condition of the cervix in association with endometrioma.

(Courtesy of Trans. Amer. Asso. Gynecologists, Obstetricians, and Abdominal Surgeons, *50*:207, 1937, Minneapolis and St. Paul, Bruce Publishing Co.)

vault. These excrescences are much like polypi—of a blue color, friable, and hemorrhagic. Primary vaginal endometriosis is flat and smooth, whereas the secondary type is a definite, always circumscribed tumor, and is always situated in the posterior fornix or upper posterior vault. There are always evidences of advanced pelvic endometriosis, and of advancement of the disease down the rectovaginal septum beyond the point of perforation.

The involvement of the vaginal wall in the two cases of stromatous endometriosis was described fully in the section dealing with this type of endometriosis. In the early stage of this disease, at the first operation, the extension of the disease down the vaginal wall was seen as a hard band, blue with venous congestion; and the later involvement of the vaginal vault in perforations and the rapid recession of these under radium have been described, together with the complete involvement of the vaginal sheath in a massive infiltration, so that digital examination of the vagina was like passing one's finger into a lead pipe.

VULVAR ENDOMETRIOSIS

Vulvar endometriosis is nearly always of the stromatous nonresponsive-to-hormone type. Previous to the description of uterine stromatous endometriosis, these vulvar growths found in the fibromuscular tissues of the vulva were looked upon as sarcomatous tumors. Closer examination has revealed their true nature, and their amenability to treatment. Dr. P. J. Kearns has reported quite a few of these cases from the Royal Victoria Hospital. He writes, "Endometriomas of the vulva, formerly called sarcomas, appear as hard, raised, bluish areas on the vulva and vaginal outlet. The growth is slow; after excision recurrence is tardy as compared with sarcomas. One of our patients had a growth on the left vaginal wall in 1935, and it was diagnosed as sarcoma. Four years later she returned with another similar node in a parallel line with the first. The tissue was examined and compared with the first, and a corrected diagnosis of endometrioma was made. Endometriomas differ from endometriosis in that the histologic picture shows a cellular unorganized stroma, devoid of glands and differing from sarcoma in not showing necroses or digestion of tissues. The growth seems to creep along the blood vessels and lymphatics in parallel extension."

This description applies to stromatous endometriomas as distinguished from mixed endometriomas of the vulva. The ratio of the former is very high, as compared with mixed endometriosis of the vulva, which is relatively rare.

VESICAL ENDOMETRIOSIS

Vesical endometriosis is always secondary to pelvic endometriosis that has extended into the bladder from affected contiguous organs. It is a

relatively rare complication. Several cases are on record in which blue excrescences upon the pale bladder wall with intermittent attacks of hematuria and the palpable presence of endometriosis in the other pelvic organs make the diagnosis relatively easy.

In the two cases of stromatous endometriosis cited in another chapter, the bladder and urethral walls became involved early in the disease and in one case profuse vesical hemorrhages developed. Later the complete infiltration of the urethra, sphincter, and vesical walls caused in both cases a total incontinence followed by a troublesome cystitis. Still later the involvement of the ureteral walls brought about a progressive hydronephrosis, and later a pyonephrosis; and finally, a complete atrophy of the kidney and progressive uremia developed.

ENDOMETRIOSIS OF THE UMBILICUS AND ANTERIOR ABDOMINAL WALLS

Endometriosis of the umbilicus is a relatively rare occurrence, but its incidence has been known for many years. It is characterized by a tumor growth which is subcutaneous, and which becomes painful and enlarges with each menstruation, receding during the intervals between periods. The method by which the endometrial cells reach the umbilical region is a matter of dispute. There are those who contend that the invasion is along the course of the obliterated hypogastric veins, while others claim that the cells reach the umbilical area by peritoneal implantation in the depression in the peritoneum at that spot. The point is still one of debate. Its solution is of small importance.

Endometrial invasion of the abdominal wall is a much more frequent occurrence, and is always a sequence of operations upon the uterine mucosa or upon endometriosis of any kind. The operations that usually precede these complications are cesareans, myomectomies involving the mucosa, uterine suspensions, and any laparotomies in which endometriosis and its dispersion play a part. Harbitz in 1934 reviewed this subject in all its aspects, and cited all the cases up to that date. However, there is very little new light thrown upon this subject except a complete bibliography.

It is an extraordinary thing how frequently this complication occurs in some regions and how seldom in others. In spite of the very large number of cases of endometriosis that have come to operation, only two cases of abdominal parietal endometriosis came under my observation. The histories showed that one followed a cesarean, and the other complicated an uterine suspension in the presence, I presume, of an already existing but overlooked ovarian endometriosis. The infiltration of the abdominal wall sprang from the remaining ovary that had been approximated to the abdominal walls by the round-ligament suspension. An

interesting feature of these abdominal rests is that the dislocated endometrial cells may remain dormant in the scars for long periods before taking on activity both in multiplication and in menstrual function.

ENDOMETRIOSIS OF THE ROUND LIGAMENTS

This is a well-recognized but infrequent extension of the disease. It is usually a primary extension along the lymphatics from the cornual attachment of the ligament outwardly to the inguinal canal. Depending upon the origin of these invasive cells the ectopic inguinal growths may function synchronously with the uterine menstrual changes. The true nature of the unresponsive type can be determined only by biopsy. The blood collections and the history of recurring pain and swelling, in the responsive type, usually leave no doubt about the true character of the disease.

ENDOMETRIOSIS OF THE PELVIC LYMPH GLANDS

In any of the burrowing processes of endometriosis the glands, in the course of the extension, may become involved by the development of rests in their substance. That the lymphoid tissue of the glands is not a favorable soil for the growth of ectopic endometrial tissue is attested to by (1) the infrequency of adenoid growths, compared with the frequency of endometriosis, and (2) the small size of the intragland growths. These, in the vast majority of cases, are of microscopic dimensions, and discrete palpable glands are extremely seldom met. In my own experience such cases have always been found with the microscope, being more in the nature of emboli than growths *in situ*.

ENDOSALPINGIOSIS

Endosalpingiosis, as the term implies, denotes a transplanting of endosalpingeal cellular elements and reconstruction of these into architecturally glandular forms resembling the parent tissue. It is a common disease usually easily recognized and possessing some properties that are common to it and endometriosis, but differing from endometriosis in many very fundamental characteristics. First of all, endosalpingiosis is a purely local disease of the pelvis; it is local not for the reasons that endometriosis is a local pelvic disease, but because of the common confinement of inflammatory diseases to the pelvis when they are of low virulence and of pelvic origin. This is because endosalpingiosis is not the result of an endocrine imbalance, but of a subacute endosalpingitis of the productive type. Endosalpingiosis implies some other more subtle agency associated with the inflammatory change. Otherwise, endosalpingiosis would be as common as inflammatory disease of the tubes—which is a very common disease as we all know. Endosalpingiosis, how-

ever, seems to be restricted to those catarrhal infections which involve only the endosalpinx, cases that have a hypertrophic tendency upon its lining epithelium and some round-celled infiltration of the subepithelial stroma, and to those cases in which plastic tubal closure of the fimbriated end of the tube does not take place, but in which patency (at least of this end of the tube) remains. Not in one of my many cases was there any tendency to forming cystic disease of the tubal lining by adhesion of the plicae, nor any marked tendency to rigidity of the tubal musculofibrous structures by infiltration of its walls. In short, all my cases have conformed to a type—a distinct, simple, catarrhal salpingitis. Endosalpingiosis occurs in two distinct forms, owing to its mode of spread. The common method is by contamination by "spill"; the less common method is by invasion of the tubal wall and mesosalpinx through the lymphatic chains. In many of the cases both processes combine.

In the spill method the ovary becomes the favorite site for the transplants. The endosalpingitis, by casting off some of its endothelial elements, transmits this same type of inflammation to the surface of the ovary, thereby setting up a definite catarrhal local perioophoritis, in which endosalpingeal elements are caught and become adherent. Later they infiltrate the ovarian substance producing glandular acini lined by typical or atypical tubular epithelium, but nearly always surrounded by a shell of endosalpingeal stroma, which has a shaggy appearance and contains various degrees of round-celled infiltrations and edema. Endosalpingeal implants do not possess anything like the invasive characters of endometriosis. The disease is usually confined to the surface of the ovary, but seldom penetrates beyond the tunica albuginea. The glandular structures are merely acini and have no tendency to reconstruct the architectural plicae of the tube. The surrounding stroma is scant and loose. Regressive changes in many of these ovarian implants are common, from the stage of compression atrophies to complete exfoliation of the lining epithelium. In many others there remains but a thick amorphous homogeneous jelly-like content which stains deeply with hematoxylin. Atrophic and seemingly progressive properties are frequently seen side by side in the same section.

As compared with the peritoneum, the ovary seems to show a decided nonresistance to tubal invasions. The peritoneum, on the other hand, offers a stout resistance to these invasions as it does to all mild infections. The peritoneal surfaces allow but a limited subjection. This is generally found in the region of the broad ligament in the immediate neighborhood of the ovary, though in some cases the whole uterine peritoneum is involved. These infiltrations are usually slight, and are usually confined to the immediate subperitoneal stroma. These have the same characters

PLATE V

A. Left tube and ovary, the ovary turned, exposing its lateral surface (natural size). The pigmentation ("blueberry" coloring) is due to hemorrhage in the endometrial tissue implanted on the surface of the ovary. The position of the fimbriated end of the patent tube, which was adherent to the lateral surface of the ovary, indicates a source for these implants; namely, epithelium escaping through the tube. For the histologic structure of some of these implants see *C*.

B. Endometrial implants on terminal loop of ileum, from sketch, natural size, made at the operation. These were not excised, but were identical in their appearance with those situated on the ovaries, which were examined microscopically.

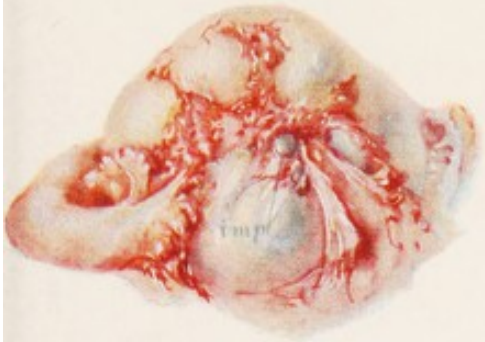
C. Colored photomicrograph (× 25) of a section through the implants on the surface of the ovary shown in *A*. These consist of glands of endometrial type with evidence of old and recent hemorrhage in the tissue about them. The glands have invaded the tissues of the ovary and a small endometrial cyst is present at the left, which, I believe, arose from these glands.

D. (A. H. No. 89902.) A portion of the lateral surface of the right ovary with pigmented elevations on its surface due to hemorrhage into the tissues of an endometrial implant (natural size). The fresh hemorrhage (red) is due to trauma from the manipulations of the operation. The patient was aged 29 years, single; the uterus was greatly enlarged due to multiple leiomyomata. Implants were present on the surface of both ovaries and in the cul-de-sac. The right ovary contained a hematoma of endometrial type about 4 cm. in diameter, which had perforated. Operation was two weeks after the last menstrual flow. For the histologic structure of the implant see the next illustration.

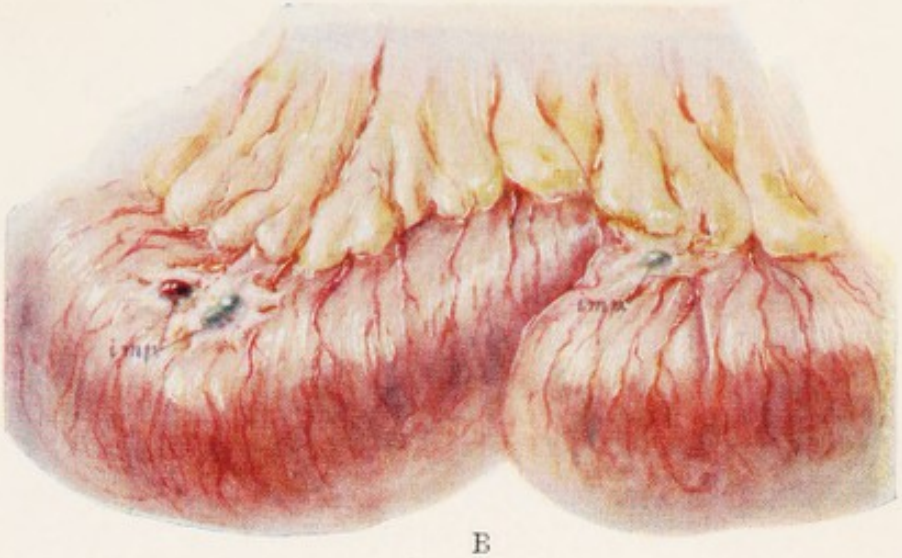
E. Colored photomicrograph (× 25) of a section through the implant, taken from the right ovary, shown in *D*. Endometrial tissue is present with normal-sized and dilated glandular spaces, and old and recent hemorrhage in the tissues about the glands and in the lumina of the same.

(Courtesy of John A. Sampson, M.D.: in *Surg., Gynecol. and Obstet.*, 38: facing p. 290, Plate II, Surgical Publishing Company of Chicago, Chicago, March, 1924.

PLATE V



A



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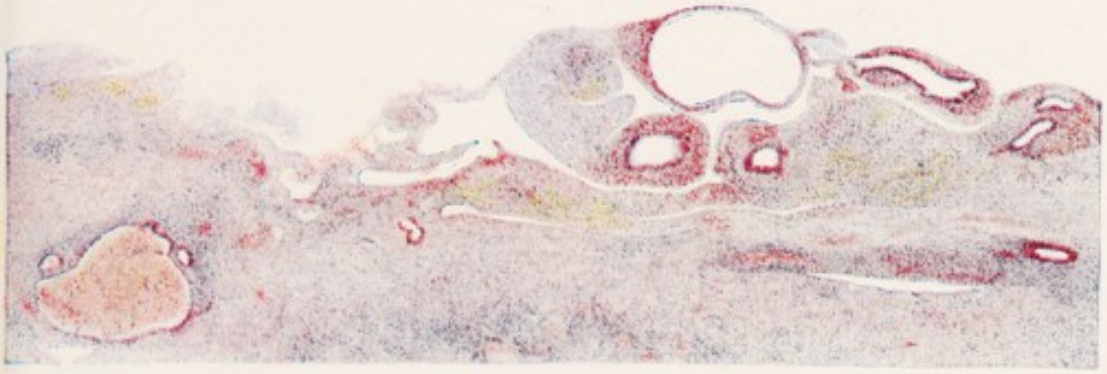
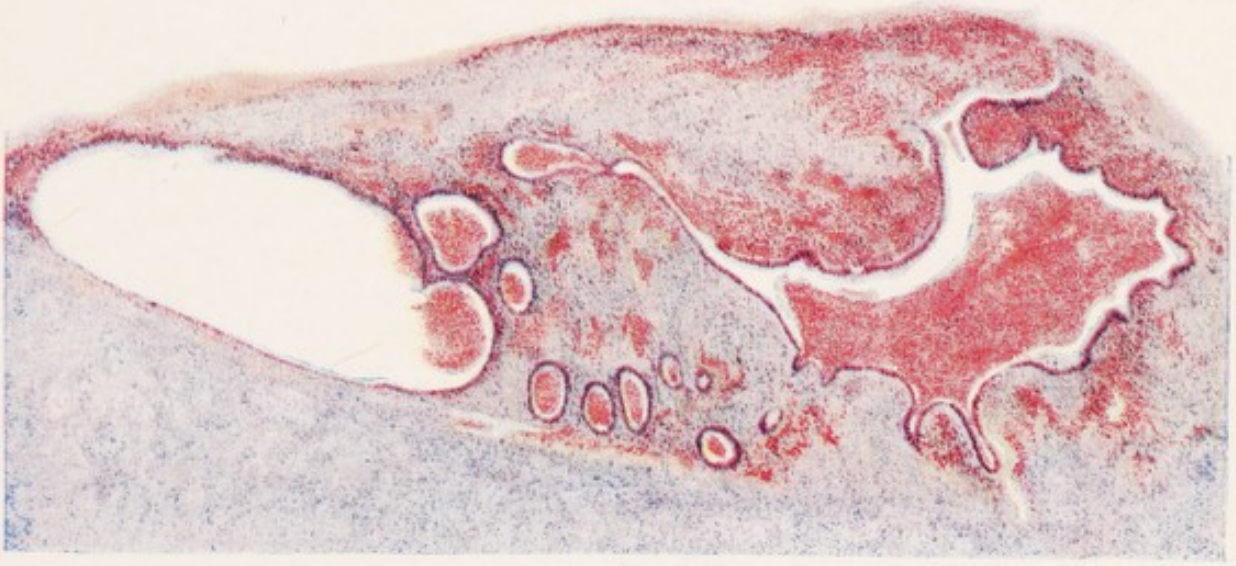


C

D



E

Benign Endometrial Implants in the Peritoneal Cavity

as those of the ovary, and a layer of filmy adhesions usually covers the point of invasion.

Two fairly recent cases clearly show the salient points of this disease.

Case XI. Mrs. M., a nulliparous woman aged 26 years. She became pregnant three years ago, and aborted at the second month. Her doctor undertook to do a curettage, and in so doing perforated the uterus. He then immediately performed a laparotomy, and sewed up the uterine aperture. From that time on she suffered with severe abdominal pain localized in the right lower quadrant. Her brother, who is a surgeon, brought her to me. On examination there was exquisite tenderness in the right abdomen, and a very large keloid of the abdominal wall; on bimanual examination a right ovary the size of an egg, and exquisitely tender, was found.

Operation. At operation both ovaries and tubes were involved in filmy adhesions of a pink prune-juice color, and when liberated these adhesions were short, shaggy, and covered the surface like moss. The right ovary and tube were removed with the appendix. Though affected, the left appendages were left owing to her youth. Both tubes were somewhat thickened, and a turbid fluid could be expressed from the fimbriated ends. She made a smooth recovery except for a mental derangement.

Six months later she had a lighting up of the infection on the left side, and was hospitalized twice for this reason. She recovered under treatment, and the left ovary, each time considerably enlarged, regressed to something like normal dimensions. The patient was sent to the country for six months under tonics and thyroid. One year later, when in excellent health, she became pregnant, threatened twice to abort, and finally went to full term. Cesarean section was performed in order to sterilize, owing to her own previous mental history and her hereditary mental taint. Examination of the left ovary and tube showed the ovary to be free from adhesions to other organs, but covered by dark red moss-like adhesions which could be moved over the surface of the ovary like thick slime stuck to the surface. In the network interstices of these the white albuginea of the ovary could be seen. Recovery was uneventful and the patient has not suffered any relapse since operation.

Microscopic Examination. Microscopic examination of the ovary and tube removed at the first operation showed a widespread endosalpingitis with islands of small round cells and edema in the tubal wall. The ovary was covered with filmy newly formed connective tissue, adherent in parts and free in others. Imbedded in these adhesions were numerous glands, each surrounded by the characteristic stroma showing signs of infection. Where the adhesions were adherent to the ovary these endo-

salpingeal elements had penetrated the substance of the ovary to about one-third of its depth. There were numerous signs of hyperactivity of the ovarian function.

Diagnosis. The case was at once diagnosed as endosalpingiosis, with its characteristic accompanying and causative chronic infection.

Case XII. Mrs. S. had a Rubin test and cautery of the cervix owing to sterility. The left ovary at the time was enlarged, tender, and fixed.

Operation. Owing to severe dysmenorrhea a laparotomy was performed, when it was found that both ovaries were bound by filmy adhesions, which covered the whole ovarian surface. These were broken down and the left, the more affected side, was removed. It was questionable how much good such a partial operation would do. However, her dysmenorrhea was completely relieved, and one year later under the administration of large doses of thyroid she became pregnant. She elected delivery by cesarean. At the time of operation the remaining appendages were examined. The ovary and tube were free from adhesions to other organs. But the ovary and part of the tube were covered by pale red filmy adhesions like a moss over the ovarian surface, and in the interstices the white albuginea shone through, similar in every respect to the previous case. These are the only two cases in which I have been privileged to see the late after-effects of a diffuse endosalpingiosis.

Microscopic Examination. Microscopic examination of the many slides made from this case, now of three years' standing, shows a diffuse involvement of the delicate surface adhesions over the ovary, with numerous salpingeal elements in both the adhesions and the surface stroma of the ovary. Around each of these cellular rests is a rim—now large, now small—of stroma cells showing signs of inflammatory reaction.

In another case in which I did a cesarean section there was a moss-like growth of a dark red color covering the vesico-uterine pouch. I had to cut through this in my low section. A portion was taken for biopsy. Examination of the ovaries revealed the characteristic appearance of endosalpingiosis, and the biopsy confirmed this diagnosis.

Endosalpingiosis has invasive properties somewhat resembling those of endometriosis, but differing from the latter in minor and major attributes. One of the main differences is found in the lessened destructiveness of endosalpingiosis because it does not create blood cysts, owing to its lacking the reaction to the hormones of menstruation. The invasion has all the characters of an adenoma, but much more scattered in its growth and distribution. The ovary involved in endosalpingiosis never reaches the proportions of those afflicted with endometriosis, due to two factors: the lack of chocolate cysts, and the restricted invasion of the ovary. In endometriosis the whole ovary may become pervaded with the new

growth; in endosalpingiosis the invasion is limited to the outer zone of the ovary. The cysts of endosalpingiosis are chiefly of microscopic dimensions, and in all my cases I have never seen an endosalpingiotic ovary exceed the size of a hen's egg. The adhesions of endosalpingiosis are delicate, loose, and filmy, and easily broken down; whereas those of endometriosis are among the three most destructive pelvic diseases. Releasing the ovaries at operation seldom mutilates the ovary in endosalpingiosis; the release of an endometriotic ovary cannot be done without destruction of the organ. As an activating agency in endosalpingiosis there is always a mild, subacute infection of the fallopian tube. In endometriosis there is no such forerunner.

We have seen how the endosalpinx may implant itself by a "spill" of infected cells upon the ovarian terrain. We have seen how the ovary is always the chief organ of invasion. Under other circumstances of more acute infections, brought about by many types of diseases, the endosalpinx, activated by these infections, begins a local invasion of its own walls and the subjoined mesosalpinx. This type of invasion is of small pathologic interest. It is not a disease *sui generis,* but merely a complication of a local infection of greater intensity than those of the previous group. In the present types of invasion the proliferative properties of the endosalpinx may approach a quasi-malignant degree, but the diffuse inflammatory reaction among the clusters of epithelium makes for an easy diagnosis. This type of endosalpingiosis is often qualified by the name of proliferative endosalpingitis, and as such should really not come into the category of the ordinary invasive diseases, such as endometriosis and endocervicosis. Removal of the tubes usually removes the slight excrescences of the tubal endothelium; their clinical interest is slight, and their pathologic interest chiefly academic.

In 1941, in conjunction with Ayre, I published in the *Journal of Obstetrics and Gynæcology of the British Empire,* Vol. 48, No. 1, p. 73, an article entitled "Chronic cornual disease: its symptomatology and pathology." In it we outlined several cases of the disease. In the opening paragraph we wrote, "To the best of our knowledge chronic cornual disease has never been described as a clinical entity. This is a series of four cases, so distinctive in symptomatology and pathology that they constitute a clinical entity." I now consider this an error—a partial error. It is true that this disease is a new clinical entity, but Sampson, we now know, described these invasions of the neighboring tissues by the truncated end of a tubal mucosa. The clinical entity of exquisite pain arising out of the uterine cornu and spreading by being referred to other nerve centers is new.

In all these four cases described below, and in several others of later date, the dominant pathologic finding is the infiltration of the uterine

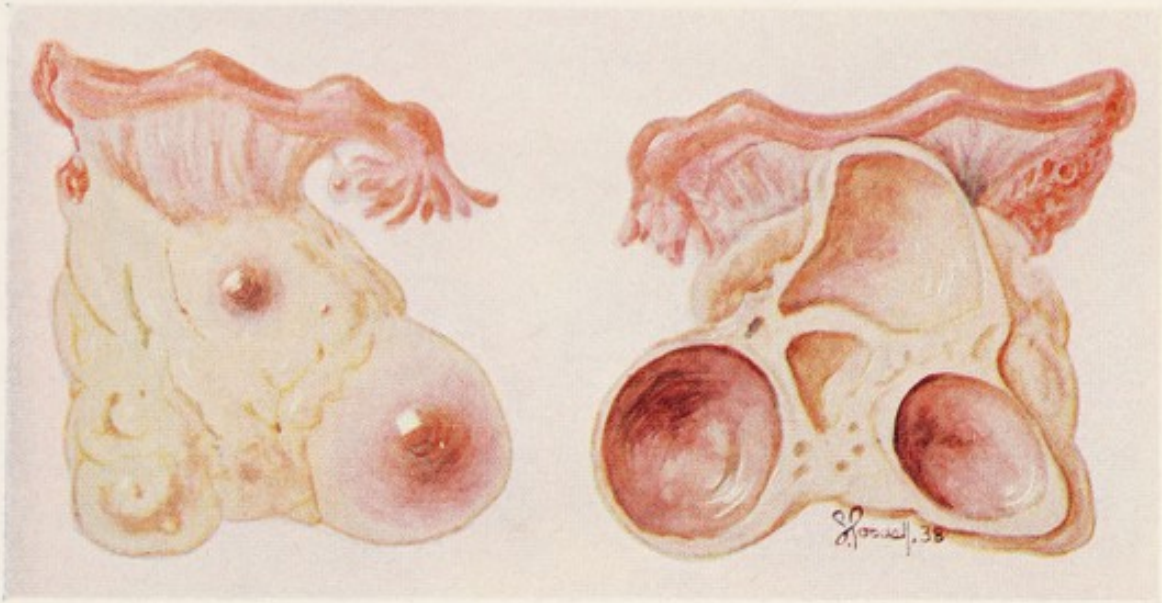
parietes in the immediate neighborhood of the truncated tube by the tubal mucosa, which has been heightened in its invasive power by a low-grade inflammation which is always found about the ectopic epithelium. Sampson described this condition fully, but so far as our knowledge goes he did not associate inflammation as a causative agent whose importance we consider a *sine qua non* in its production. We are strongly of the opinion that it is the primary inflammation and not the tubal invasion which is the cause of the very severe local pain. In all of our cases a salpingectomy had been performed. Doubtless the trauma of crushing and ligation in the presence of an infection started the slow pathologic state.

In the first case the tubal mucosa had been destroyed by the inflammation which was the most virulent of the series. In the others, in which the pain was not of such severe character, the inflammatory process was less prominent, and *per contra* endosalpingiosis was more pronounced. The series of six cases, as a matter of fact, fell serially and chronologically into a gradually lessened inflammatory type, and a gradually increasing endosalpingiotic group. The local pain which is the distinctive symptom of the series was most severe where the inflammatory infiltration was most marked. That is as it should be, for endosalpingiosis, like endometriosis, is a nonsymptomatic disease. The pain of these diseases must be attributed, not to the infiltrating process, but to the complications which naturally befall these infiltrations, such as bloody cysts, adhesions, inflammation and necrosis, etc.

The following renumbered cases are recorded from the above-quoted article with whatever slight modifications were justified by a more intense study of the microscopic specimens.

Case XIII. The first case is that of a Mrs. D. G., who had had two children uneventfully and eight years later was operated upon for a left-sided ectopic gestation by one of my colleagues who is now deceased, so that it is impossible to gain access to the records of his private hospital. Since this operation she developed a pain in the left lower quadrant of the abdomen. The pain came on insidiously, and gradually grew worse over a period of two years. By that time the pain was severe at all times, but became so intense at menstruation that the whole abdomen was painful and sensitive, and morphine hypodermically had had to be used for the past six months at the menstrual periods. It was then that the patient came under Doctor Goodall's attention. Her general health was good, on bimanual examination the uterus was somewhat larger than normal, and asymmetrical, owing to a mass the size of a walnut felt in the region of the left cornu.

PLATE VI



Chronic cystic sclerosis of the ovaries from a woman aged 33 years.

Diagnosis. The diagnosis of fibroid undergoing red degeneration was made, and an operation was recommended.

Operation. Adhesions were not found when the abdomen was opened. The left fallopian tube had been amputated at the cornual margin, and the left ovary had been removed. A mass the size of a walnut was found in the left cornu, but it did not give one the impression of being a fibroid for two reasons: first, because its margins melted into the uterine tissues, and second, because of its diffuse cartilaginous consistency. Total hysterectomy was performed. Upon opening the mass it was found to have a necrotic center forming a small cavity about the size of a pea with infiltrated hard friable walls. It was thought this might be due to an infected silk suture, but no trace of this was found. The rest of the uterine tissues was normal.

Pathologic Report. Sections taken from various parts of the tumor showed it to be a chronic inflammatory process with a broken-down center. There was nothing specific about the inflammation, and there was no trace whatever of tubal mucosa in the growth. Secondary further examination of these specimens reveals the presence of glandular elements that have been so modified by the chronic inflammation as to be barely recognizable.

Case XIV. Mrs. J. B., aged 35 years, was operated upon in 1935 for chronic appendicitis. The right fallopian tube and ovary were involved to a slight degree, and were removed at the same time. The recovery was symptomatically uneventful. Some months after the operation pain and tenderness appeared in the right lower quadrant of the abdomen. This gradually became worse and constant, over a period of about 18 months, and became so severe at menstruation as to require therapeutic alleviation. The pain continued for a further 12 months, when the patient then came under Doctor Goodall's observation.

The patient was a fine physical and mental type, and not suggestive of any neurotic tendency. On bimanual examination the uterus was tender on palpation, but the point of maximal tenderness which was exquisite was over the right cornu. No asymmetry could be made out with any precision, owing to the resistance of her abdominal walls due to the severity of the symptoms. Exploration was recommended.

Operation. At the operation there was but a small omental adhesion to the abdominal scar. The right ovary and right fallopian tube were absent. In the right cornu of the uterus was a fusiform mass about the size of an almond, definitely not a fibroid for the same reasons as those given in the other case. This mass was incised; it cut like inflammatory tissue, and owing to our previous experience and similarity of the mass,

total hysterectomy was performed. The other ovary and fallopian tube were normal. The recovery was uneventful and the patient's symptoms were completely relieved.

Microscopic Examination. Microscopic sections presented an appearance almost identical with those of the prevous case, except in very minor and insignificant details. In this specimen we had evidences of a definite infected endosalpingiosis invading the uterine wall in the immediate neighborhood of the truncated tube.

Case XV. Mrs. G. C., aged 37 years. Her menstrual periods were normal, and she had two children, aged 11 and 8 years. She had an ectopic gestation with removal of the left fallopian tube and ovary in 1935, and cholecystectomy and appendectomy in 1937. She came under observation in 1938, complaining of intense pain in the lower left quadrant of the abdomen. This was constant, and felt definitely over a small area below and to the left of the umbilicus. The pain became much more severe at the menstrual periods, the whole of the left side of the abdomen became rigid and tender, and the pain radiated to the left loin. It was impossible to define anything abnormal on bimanual examination, owing to the tenderness and resistance. She was seen in consultation several times, and her evident distress was so convincing that exploratory operation was advised.

Operation. The abdomen was found free from adhesions, and the uterus was so little affected that the pathologic condition was overlooked until Doctor Goodall came into the operating room and asked to see the organs. The uterus was exposed, and in the left cornu was a mass the size of a filbert nut, fusiform and of cartilaginous hardness. The condition was recognized, and total hysterectomy advised. Recovery was uneventful and the patient has been free from symptoms for two years.

Pathologic Report. This was similar to the two previous cases.

Case XVI. Mrs. S. O., aged 42 years, nulliparous, married four years, was operated upon five years ago for subacute appendicitis, and the left ovary, owing to the presence of a cyst, and left fallopian tube were removed at the same operation. From that time on she began to suffer from abdominal pain which so grew in severity that eventually she was incapacitated most of the time. During the next three years she was admitted to hospital for various periods on four different occasions, owing to abdominal pain, most intense over the lower abdomen, but at times quite generalized. The pain was greatly intensified at the menstrual periods.

Operation. After every form of diagnostic examination had been

made the abdomen was finally opened under the impression that adhesions were present. We are not cognizant of what was found at that time. There was no improvement after the exploration. She came under our observation about four months ago, complaining of severe abdominal pain, worse at menstruation, gastric distress after food, and chronic invalidism. Exploration was eventually decided upon. There were widespread omental adhesions about the appendix scar, and a small adhesion of small bowel near the old median incision. This was freed and the raw surface on the bowel covered. In the left cornu of the uterus was a fusiform mass about 2 cm. long and 1.5 cm. thick, hard and nodular. Total hysterectomy was performed. Recovery was completely uneventful, and the patient (formerly inured to soporifics and narcotics for insomnia and pain) now sleeps without any medication and is a most cheerful character, whereas previously she had been looked upon as a hypochondriac and neurasthenic.

Pathologic Report. The sections of this case differ somewhat from those of the other three cases here reported, chiefly in the degree of destruction. In the earlier cases there were remaining evidences of tubal mucosa, but in this one there was a definite chronic cystic endosalpingitis and a well-marked interstitial inflammation about the cystic lumina. The cavities were filled with large desquamated cells and leukocytes in a turbid, though decidedly not purulent, fluid.

Two subsequent cases leave no doubt as to the tubal disease being the cause of the severe distress, nor is there any doubt of the endosalpingiosis following upon an inflammation.

A DISCUSSION OF CASES XI-XVI

The incidence of these six cases is interesting. They came, chronologically, in perfect cadence. The first case (Case XI) was probably the most symptomatically severe, and the cornual growth was the largest. The others were decidedly less pronounced in asymmetry, but were recognized by the impressions of the first case. The similarity of the symptoms in all cases is striking. The incidence of the ectopic gestation in two cases and of appendicitis in the other two is interesting, showing that in all cases this would appear to be a postoperative complication. In the first three cases (Cases XI, XII, and XIII) there was no other pathology to explain the symptoms. In the last case (Case XVI) there was an intestinal adhesion which was released, but the omental adhesions were not disturbed because they were not under tension. Apart from this last exception the symptomatology was attributable to the cornual disease, and the distressing symptoms were completely relieved by the removal of the uterus.

Another striking feature is the similarity of the pathologic process,

which differs hardly at all except in matters of degree. The first three, though differing in the size of the growth, vary hardly at all in the destruction and infiltration. The fourth case differs chiefly in the lessened destruction of the tubal mucosa, and presents a picture of less intensity and probably of shorter duration. One is impressed by the severity of the symptoms, even when the mass in the cornu is of quite diminutive size—a fact which should keep us on the *qui vive* that even such slight asymmetrical defects can be productive of symptoms of severe intensity.

The two latest cases but confirm the former descriptions.

12

Endocervicosis

Endocervicosis is a new disease, a recent discovery. It is characterized by a nonmalignant invasion of the deep cervical and paracervical tissues by the mucosa of the cervix uteri. Just as the endometrium may penetrate deeply into the uterine myometrium, and even extend into the parametrial tissues, so can the cervical mucosa under abnormal stimulation take on similar invasive properties, causing distortion and fixation of the organs involved.

Only two such cases have come under observation, both in the past year. Doubtless others will be found when surgeons are familiar with the signs. The true nature of the disease was never suspected prior to operation, but at intervention the multiplicity of the cysts, their diminutive size, their opalescent tenacious contents, and their rigid walls led one to suspect their true nature.

SYMPTOMATOLOGY

There are not sufficient cases to permit deductions relating to symptoms. The only symptom which was common to both cases was backache, felt low down over the sacral region. One of the patients complained of rectal symptoms giving her the impression of pressure in this region. There was no disturbance of the menstrual cycle in point of either time or quantity, nor any increase in dysmenorrhea. The ages of the patients were 38 and 42 years. They were parous women, without offspring for eight and ten years respectively. The disease, however, may be diagnosed, or at least suspected preoperatively, by its physical signs. The cervix is large, hard, and nodular owing to nabothian cysts on its surface. It is fixed, its degree of fixation depending upon the degree of infiltration of the paracervical tissues. In the more advanced case the posterior vault of the vagina was of ligneous hardness, and cysts and nodules similar to those of the cervix were palpable and visible, shining through the vaginal mucosa in this region and through the upper third of the posterior vaginal wall. By rectovaginal combined examination the same hardness and nodular characters were felt through the rectum, but the rectal mucosa was not involved, and moved freely over the underlying infiltration in the anterior pararectal tissues. The uterus in each case was

symmetrically enlarged, and owing to the fixation of the cervix the fundus was restricted in its movement.

OPERATION

In one case, the peritoneal cavity was free from adhesions. In the other there were signs of an old inactive endometriosis of the appendages. Upon reaching the extraperitoneal paracervical tissues, the adhesions were of the densest nature. Tissues could be separated only with cutting instruments, and at each incision tenacious gluey contents exuded from small cysts. These were never larger than the usual cervical cyst, and the pericystic tissues were so fibrotic that the cyst walls remained rigid and uncollapsed after evacuation of their contents. The separation of the rectum from the cervix and vaginal vault was extremely difficult, in that all normal cleavages were lost. I think it was fortunate that, in the first case, the ovarian endometriosis necessitated the removal of the appendages; and that, in the second case, the true nature of the case was recognized during operation, and total ablation of the sex organs was performed in the hope that removal of the ovaries would put an arrest upon the disease processes, as occurs in cases of endometriosis. Recovery in both cases was uneventful. Examination, six and nine months after operation, revealed a hardness of the tissues in the vault of the vagina, and some regression of the cysts, both in the vault and in the pararectal tissues. Backache has continued, seemingly unchanged, at this date.

PATHOLOGY

The pathology of endocervicosis is very simple, and the microscopic diagnosis extremely easy. Cervical glands in general are so characteristic in their construction and functional activity that they are unmistakable when seen. Macroscopically the hard, enlarged, cystic cervix, which, on section, presents numerous small cysts similar in every respect to nabothian cysts and their contents, offers an easily recognizable condition. The process extends into the tissues contiguous to the cervix. But just here arises a problem. There are many cases, and I have seen a great number of them, in which the cervical glands have penetrated very deeply and widely throughout the cervical tissues, especially in the region of the internal os, and yet have not extended beyond the confines of the cervix into the paracervical tissues. These are analogous to uterine endometriosis which has not passed beyond the confines of the uterine wall. That there are cases of endocervicosis, similar in degree to an endometrial uterine myometrial invasion, cannot be doubted. But who will hazard an opinion upon the normal depth of cervical and uterine glands? And until this problem can be answered accurately, there will be many borderline cases that cannot be defined.

The incidence of ovarian endometriosis as a complication of one of these cases of endocervicosis, and a considerable penetration of the uterine musculature in its inner third in the other, show that this coincidence is not merely fortuitous. In my previous chapter on stromatous endometriosis it was shown that in this form of uterine endometriosis the cervix was involved in a well-marked adenomatous overgrowth of its own glands in over 30 per cent of the cases. This, in the same sense as a uterine endometriosis, is a true endocervicosis, yet, like the uterus, the disease has not gone beyond the confines of the organ of its origin.

I think it best for purposes of delineation that the term endocervicosis be restricted to such cases as the two described above, where the disease has become extracervical, and has invaded the deeper paracervical areas.

Microscopically, uterine-wall endometrial invasions differ characteristically from endocervicosis. The endometrium is made up of two specific cell tissues—the gland cells, and the stromatous cells. Wherever invasion takes place, one or both of these cells are found. Commonly, they bear the same relationship to each other in their ectopic invasions as they do in their normal situ. This, however, is not true of endocervicosis. The endocervix has no matrix of specific stroma cells as found in the endometrium. The cervical glands are set in juxtaposition upon the fibromuscular tissues of the cervix, without intervening structures. As a consequence of this embryology, the ectopic cervical glands are found embedded in a matrix of fibrous tissue. It would seem that this fibrotic element is adventitious, and is a reactionary product to a foreign new growth. In different portions of the same case, and more especially in different cases, the relative amounts of glandular and fibrous tissues vary within wide limits, as does also the density of the fibrous element itself. In this respect, endocervicosis in promoting defensive reaction resembles the great majority of other types of invasive ectopic new growths.

Needless to add, the endocervical tissues and their ectopic growths do not respond to the hormones of the menstrual cycle.

ETIOLOGY

Of course, the subject of causation is still shrouded in mystery. But certain associations and coincidences lend weight to certain deductions which, though hypothetical, are interesting.

I think we are all of the opinion that endometriosis of whatever form is an expression of a vitiated endocrine function and consequent imperfect metabolism. It was pointed out in my work on endometriosis, quoted above, that cervical adenoma (a rare disease by itself) was found in association with stromatous endometriosis in 30 per cent of the quoted cases; and now, in these two cases of endocervicosis, there was found a co-existing ovarian endometriosis in the one case, and mild invasive uterine

endometriosis in the other. From these associations we may infer that there is more than coincidence, rather that they are simultaneous products of an abnormal influence which causes normal structures to transgress their normal bounds. In endometriosis, the almost positive cure for these tissue transgressions is found in the ablation of ovarian function.

Two cases are too small a number from which to draw inferences as to treatment, but the foregoing argument and the good results obtained in both the cited cases would indicate, until something better is determined, that surgical removal of the ovaries, or the destruction or reduction of their functions either by radium or deep x-rays, offers the only rational solution for the time being.

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Conditions Closely Allied to Endometriosis

Under this heading are included certain pathologic conditions so frequently found in association with endometriosis that there is much to warrant a belief in a common agency. If two diseases are found frequently associated—more frequently than could be accounted for by mere coincidence—then these two diseases must arise from a common cause, or they must stand in the relation of cause and effect.

Two diseases now described for the first time in this category are commonly found in association with endometriosis, but found also in cases in which endometriosis is absent: chronic peritoneal sclerosis, and chronic ovarian sclerosis.

CHRONIC PERITONEAL SCLEROSIS

Peritoneal sclerosis is a very common disease. The anterior parietal peritoneum differs so markedly in thickness and consistency in different patients that it has been a subject of close study for many years. It was impossible to explain why in some cases, particularly in women with a great deal of extraperitoneal fat, the peritoneum is usually so thin as to be composed of a single layer of transparent cells, while in others the same tissue is thick, whitish, tough, and opaque. To aid in finding a solution to this problem a very large number of specimens of peritoneum were excised for biopsy. The pathologic picture proved to be monotonously similar in all the specimens, differing only in degree of colloid deposit in the subperitoneal tissues. But it was later found that the probable cause of the disease could be detected by a more careful examination of the abdominal cavities during operations. It was found that sclerosis varies in degree in different patients, and in different regions of the peritoneal cavity in the same patient. These differences range from the barely unrecognizable degrees of sclerosis to types where the peritoneum is leathery, white, opaque, and cuts like cartilage. (Figs. 11 and 12.)

The distribution in the patient also varies quite as much as in different patients. Observation has shown that, when present, peritoneal

sclerosis is always most intense in the deepest parts of the pelvic pouches, usually most marked in the pouch of Douglas, in a slightly less degree in the vesico-uterine pouch, and in gradually diminishing degrees as one rises out of the pelvic region, until above the umbilicus the sclerosis is imperceptible. These are the uniform, constant changes when sclerosis is present. In dozens of instances where pelvic endometriosis had not been suspected and had not been considered in the preoperative diagnosis, endometriosis was diagnosed as a strong possibility when the parietal peritoneum was found thickened upon incision. In the majority of such cases the pelvic cavity was found to be the seat of a chronic endometriosis. But not all cases of peritoneal sclerosis are associated with palpable or obvious intraperitoneal endometriosis. Nor are all cases of intraperitoneal endometriosis associated with peritoneal sclerosis. But many—yes, most—cases of peritoneal sclerosis are found in association with cystic sclerosis of the ovaries—an association which will be dealt with more minutely later.

Chronic peritoneal sclerosis is, therefore, commonly found in association with discrete intraperitoneal endometriosis, or with chronic sclerosing cystic oophoritis. But in a goodly percentage of cases it was found in an advanced state without either of these two diseases. What is the explanation? That was the problem set for solution. It at once became evident that intraperitoneal endometriosis is only one form of endometriosis. Consequently it behooved us to ascertain whether in cases of this peritoneal disease we might not have a chronic uterine parietal endometriosis, or an endometrial endometriosis, and sure enough, the association was again sustained. But still there remains a group of cases of peritoneal sclerosis without discoverable endometriosis. How account for these? Let us first describe peritoneal sclerosis.

In nearly all of the cases of advanced peritoneal sclerotic disease there is a good deal of free fluid in the peritoneal cavity. It is either straw-colored fluid, or slightly turbid from admixture with blood and cellular detritus. Microscopically this fluid contains many forms of cellular elements which cannot be classified because they are often in stages of disintegration. In the turbid fluids blood elements predominate. The peritoneal sclerosis, if uncomplicated by other disease, never produces adhesions. The uncomplicated peritoneal sclerosis is always free. Biopsy specimens show an intact endothelial lining to the peritoneum, but the sclerosis is due to a deposit of colloid material in the subperitoneal spaces. It seems to be more abundant the deeper one sinks into the pelvic pouches. The same deposit in the major types of the disease is found about the smaller blood vessels, causing a slight clinically inappreciable vascular sclerosis. What are the clinical deductions?

Peritoneal sclerosis is essentially a very chronic manifestation of a

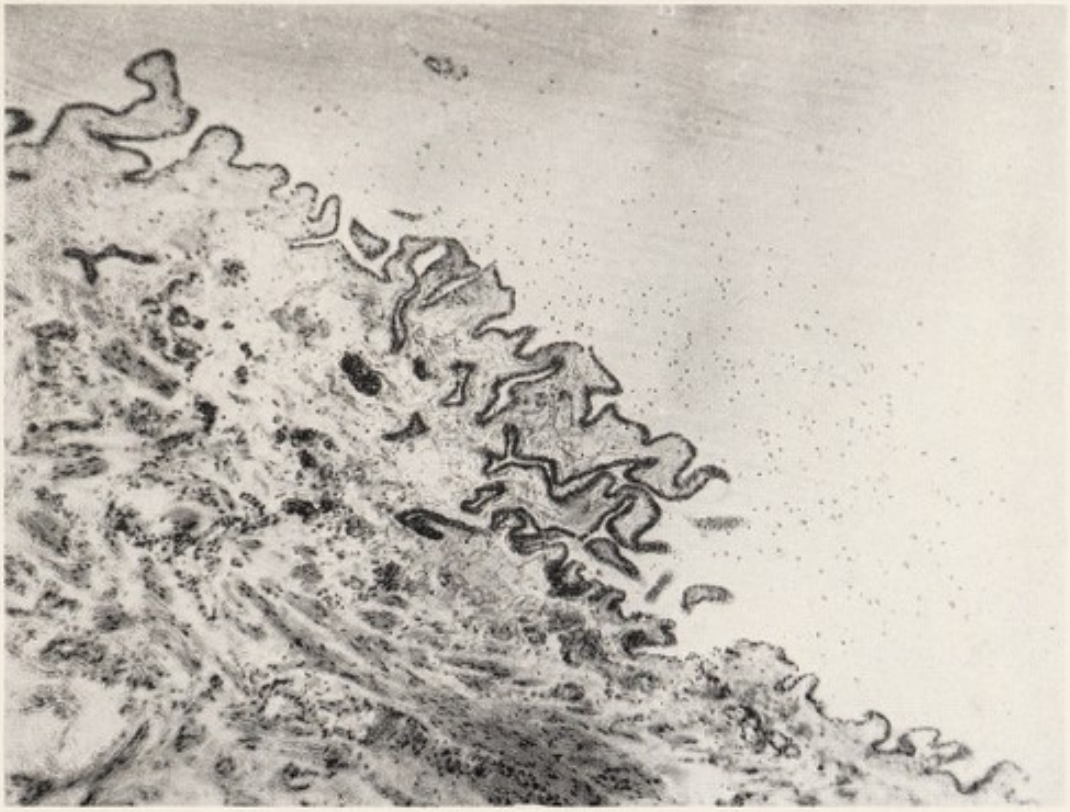

FIG. 11. Normal peritoneum.

FIG. 12. Sclerosed peritoneum showing deposit of colloid material in the subperitoneal tissues.

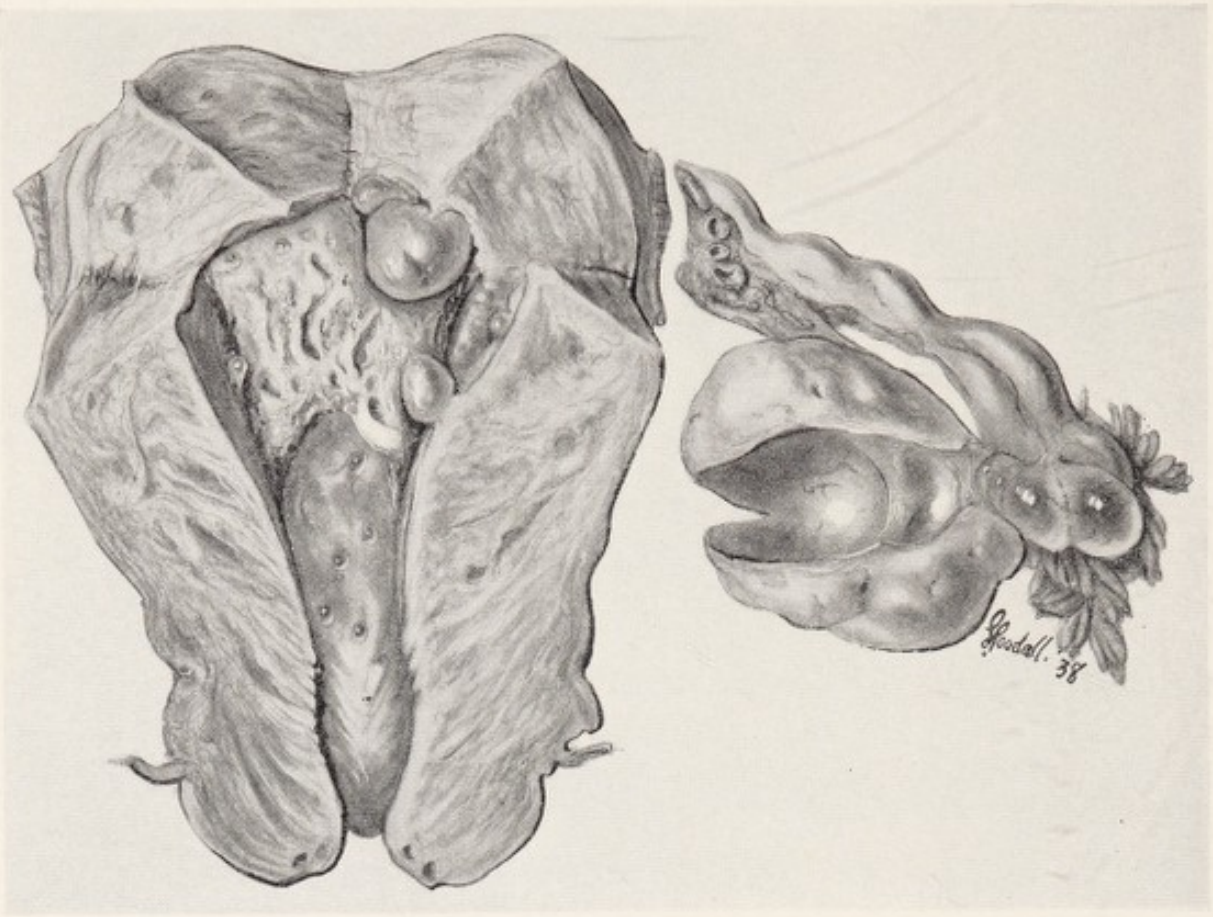

FIG. 13. Drawing showing sclerosis of ovaries with cystic disease, hypertrophy of the uterine walls, and mixed endometrial (intra-uterine) endometriosis of the polypoidal type.

chronic cause. Its chief hallmarks, both clinically and pathologically, are those of chronicity. Therefore its causative agent must be of a chronic nature, operating slowly over a long period. Consequently we should not expect to find peritoneal sclerosis associated with acute endometriosis, but rather with the chronic forms; that is, if there is any common causative factor in these two diseases. Now that is exactly what we do find clinically: an association of these two diseases in the more chronic forms of endometriosis. Still a percentage of cases remain where there is not detectable endometriosis, but where other factors are found of great importance. In several cases of fibroids of the uterus with retroversion and retroflexion we have found a peritoneal sclerosis affecting the pouches and only the posterior wall of the uterus, which, of course, lay submerged in the pouch's fluid. The peritoneum of the anterior uterine wall was not appreciably affected either as seen by the naked eye or through the microscopic eye. And in two other cases of fibroids the sclerosis of the broadened posterior wall was partial, and spread out fanwise from the insertions of the utero-ovarian ligaments.

These following additional facts lend a great deal of weight to the hypothesis to be advanced for the explanation of these associations in pathologic states. The free fluid collected from cases of peritoneal disease has been found very rich in estrin, and the common association of fibroids and endometriosis with peritoneal sclerosis argues a common cause behind these three lesions. This will be discussed more fully under the heading of causation that follows in the next paragraph.

CHRONIC CYSTIC OVARIAN SCLEROSIS

The common association of the diseased condition of the ovaries with peritoneal sclerosis was emphasized in the previous section. It is not claimed that the cause which brings about this association is the only causative agent in the development of this ovarian pathologic state, but it is contended that this is a frequent factor and its operation is now fairly well understood. An ovary afflicted with this disease has been known under various names, such as sclerotic oophoritis, small cystic ovaries, cystic degeneration of the ovaries, etc. (Plate VI.) The disease is always bilateral, though both ovaries are not necessarily equally affected. Closer study of the ovaries from any one case demonstrates very clearly that, though the two ovaries may differ in size, and therefore to the casual observer are different in degree of primary pathology, yet the differences are not in the degree of sclerosis, but in the number of cystic follicles. The disease is essentially a combination of sclerosis and cystic degeneration of follicles. (Fig. 13.) Whether the latter is the result of the former, or vice versa, cannot be determined at the present state of our knowledge. On superficial thought it would seem that the

persistent follicles are essential to the development of the sclerosis. But that is leaving out of account the influence of the pituitary, with its powerful prolan A. I have introduced this statement here only to state that this subject will be discussed more fully in the chapter on causation.

There are all degrees of ovarian cystic sclerosis, from the macroscopically imperceptible to ovaries filled with cysts and with tissues as hard as cartilage. In many of these latter types the cyst walls are often so sclerosed that they remain rigid when evacuated, and in the very chronic cases the lining is often white and almost egg-shell in consistency.

The albuginea of the ovary is very thick and fibrous, and the whole ovary retains its shape even when sliced, as if it had been hardened in formalin. Microscopically the albuginea is seen loaded with colloid substance similar to that of the subperitoneum in peritoneal sclerosis. In the early stages of the disease only patches of the surface are affected, and as the disease advances the process extends.

The cysts are undoubtedly persistent graafian follicles that have never ruptured. Whether this lack of completion of the ovarian cycle is primarily due to the sclerosis prohibiting the follicle from reaching the surface, or whether the condition is due primarily to pituitary asynchronism cannot be stated, though arguments for the latter contention will be advanced in the next chapter. The lining of the cyst is made up of granulosa cells in all stages of pressure atrophy; other cystic cavities are devoid of specific lining, but are made up of sclerosed fibrous tissue filled with vitreous substance. Corpora atretica are numerous, but there are few corpora of normal menstruation.

THE HYPERTROPHIES

In the foregoing chapters frequent mention was made of the hypertrophies which accompany pelvic endometriosis. These are so varied, and some of them so unrecognized by surgeons, that it is thought advisable to bring all of them under one heading.

It must be clearly pointed out that in my opinion endometriosis of whatever kind or region is an expression of a vitiated endocrinology, but it is only one of the expressions of that vitiation. The same endocrinologic dysfunction may manifest itself in many forms of pathologic changes without any gross or microscopic evidence of endometriosis. This was fully explained in the chapters on causation and allied conditions. So we may find hypertrophies with such pathologic states as fibroids, the various manifestations of pelvic endometriosis, chronic symmetrical uterine enlargements, etc.

For purposes of description it will be advantageous to divide these hypertrophies regionally, but in so doing it must be understood that the division is a purely arbitrary one, and that one or more organs may be,

and usually are, coincidentally affected. The chief regions for the endocrine manifestations of growth are the uterus, cervix, parametrium, ovary, and appendix.

Uterine Hypertrophy

Emphasis has, from time to time, been laid upon the frequency of this sign in association with uterine endometrial and parietal endometriosis. Its association with fibroids and myomata is tolerably well known. This is an expression, not of irritation as has been commonly maintained, but of an associated lesion arising from a cause common with that of the chief or most striking lesion. If the hypertrophy were of a local irritative reactionary character it would naturally be centered solely about the growth. But that is not at all the rule. The uterine hypertrophy affects the whole uterus without discrimination, though occasionally the hypertrophy may be more marked in one wall than in the other.

The endocrine disturbance, especially when acute, may cause, on occasions, such a rapid growth of the uterus that pregnancy, on bimanual examination, may be simulated in the smallest detail. The hypertrophic uterus may be enlarged to the size of a three months' pregnancy. Hegar's sign may be present, the uterus soft and boggy, and the enlargement symmetrical. The breasts may be affected so as to simulate more closely a pregnant state. In short, nothing but an Aschheim-Zondek test will differentiate this from a true pregnancy. I have had the good fortune to encounter several of these cases where, in the absence of a positive pregnancy test, the diagnosis of myoma uteri was made. At operation the pelvic contents so closely resembled a 2.5 to 3 months' pregnancy that I hesitated to do a hysterectomy, and was even so uncertain after the uterus was removed that I interrupted my operation to incise the uterus to determine whether the biologic test had failed me. There was no pregnancy macroscopically, and microscopically there was not the faintest trace of it.

There are all degrees of acuteness and chronicity of this dysfunction. Consequently there are all degrees of softness or hardness of the uterine parietes, which in turn depend upon rapidity or slowness of development. Naturally in the acute endocrine dyscrasias the dysfunction may simulate the endocrine imbalance of pregnancy, and produce enlargement closely resembling that of a pregnant state. In the slowly developing dyscrasias that produce growth-stimulation the stimulus will spend itself chiefly upon the connective-tissue elements rather than upon the more specialized muscle, and other such highly organized tissues. The tendency then is enlargement with fibrosis. This state of fibrotic enlargement can be brought about in another way. After an acute enlargement has taken place in which all the component elements of the uterus have undergone

hypertrophy, resolution of the endocrine imbalance may occur slowly, but incompletely, and leave the uterus permanently enlarged with a redundancy of connective and elastic tissues in its walls. The more highly specialized muscle fibers will have degenerated out of proportion to that of the more resistant, lowly fibrous elements. It will readily be seen that the hypertrophy of the organs that accompanies active or chronic endometriosis and fibroids, etc., is not a reaction to local irritation of these foreign structures, but is a concomitant product arising out of a common cause.

Cervical Hypertrophy

The uterine cervix may undergo the same enlargement as that of the uterus described above. If the condition is uncomplicated, the cervix in the acute cases presents a softness and an enlargement strongly suggestive of an early pregnancy. When normal balance is re-established quickly the involution of the affected cervix may be complete, similar to that which would occur after an uncomplicated early abortion. Many of the cases, however, are associated with an incidental chronic endocervicitis which may complicate the picture, giving one on palpation the velvety feel of an inflamed surface, and upon visualization an inflamed os and probably a granular area of ectropion surrounding it. In cases of chronic enlargement of the cervix associated with the uterine hypertrophy, the cervix is enlarged to various degrees, from that slightly above the normal to a condition where it may fill the vault of the vagina. It is almost cartilaginous in its hardness and filled with nabothian cysts which shine through the portio in its whole contour. Microscopically in the uncomplicated cases the fibromuscular elements are increased, and the glands (lying juxtaposed upon the connective tissue) are devoid of any surrounding cervical specific stroma cells. The acini are dilated, due to contraction of the adult tissue about the evacuating ducts. In many of these cases the cervical glandular structures take on the growth-stimulation and become markedly papillomatous or adenomatous.

Parametrial Hypertrophy

In all these cases of myometrial hypertrophy, whether acute or chronic, the musculofibrous elements of the parametrium are affected by the growth stimulus. This is, of course, not so distinctive as that of such specific organs as the uterus and cervix. It is impossible to recognize the hypertrophy when it is soft and succulent, any more than one can recognize this hypertrophy in an early pregnancy. But in the chronic state, whether it be that of incomplete resolution after the acute state, or that of a slow progressive fibrosis, the vaults of the vagina feel indurated and there is a corresponding loss of mobility of the uterus. When hysterec-

tomizing these cases of so-called chronic metritis the structures about the cervix are thickened and fibrotic, and the vaginal vault itself often has taken on a leathery consistency, owing to the chronic fibrotic changes. Ovarian sclerosis and hypertrophy were described separately in a previous chapter.

Tropho-appendicopathy

This term implies an involvement of the appendix in the hypertrophic pelvic changes. The participation of the appendix in certain cases in the decidual change of pregnancy and its frequent involvement in endometriosis has been described in previous chapters. Tropho-appendicopathy is a new pathologic entity which will explain to the surgeon why, when in his estimation a visually diseased appendix has been removed, the pathologic report states that it is a normal structure. Stress has been laid upon the fact that the more deeply an appendix invades the true pelvis, the more is it susceptible to physiologic and abnormal pelvic influences. We can see this commonly in pelvic inflammatory disease. But the same holds true for pelvic endocrine abnormalities. The appendix, when it assumes a pelvic lie, may become involved in the same hypertrophic change as that which may affect the other specific pelvic organs as described above.

In uncomplicated cases of tropho-appendicopathy there are no adhesions. The characteristic change in the appendix is a hypertrophy of all its coats, so that the organ becomes quite rigid and indurated. The pathologic process may involve all, or only a portion, of the length of the appendix. The induration is always most marked at the apex. It may involve only the distal portion and gradually disappear as one approaches the proximal end. In other cases the whole appendix may stand up rigid and inflexible, and when the cecum also has become pelvic the hypertrophy may involve part of the cecum and ilium. This accounts for the marked differences in density of these tissues when the pursestring suture is being inserted. In the most marked cases the cecum and ilium may become pearly white and apparently reduced in their caliber. The surface vessels of the appendix are very discrete, tortuous, and apparently engorged. The mesoappendix is not appreciably affected.

When the appendix is opened longitudinally one sees that the structure is under great tension in its deeper mucosal layers. This is similar to the hypertension of the deeper layers of the uterine wall at cesarean section, whereby the surface layers retract as soon as the tension is relieved by incision. So it is with the appendix. When cut open it curves longitudinally so that its mucosal surface becomes convex, owing to contraction of its longitudinal fibers. It curves laterally so that its mucosal surface becomes outermost and its peritoneal surface is now the inside of a

tube, owing to contraction of its circular fibers. If the appendix is cut transversely after removal the mucosal and submucosal layers will protrude beyond the cut surface. The mucosa also participates somewhat in the hypertrophy, though not necessarily to the same degree as the fibromuscular coats. There are usually no other signs of pathology, and if there are these are nearly always accidental associations.

Microscopically all the structures appear normal except that the musculofibrous increase is striking. All other changes are purely incidental. Heretofore, these changes have been interpreted either as chronic inflammatory in origin, or as individual differences in consistency arising out of hereditary tendencies of development.

It is not known whether such hypertrophies can resolve spontaneously when the pelvic cause is removed. Such cases that have exhibited the hypertrophy have had the appendix removed, and that was the end of that case as far as retrogressive changes are concerned. The recent discovery of this type of appendiceal disease is of too short duration to permit a study of the changes which would ensue in the afflicted appendix when the primary cause of the disease is removed by ovarian ablation. That would imply removal of the ovaries, leaving the appendix *in situ*, and reopening the abdomen for study after the lapse of a specified time. This, of course, has not been possible.

The history and clinical and surgical findings of one of my most recent cases will best illustrate the characters of this disease. The patient was a Jewess, aged 36 years, married 11 years without conceiving. She had been complaining for the past five months of pain in the lower abdomen, dull at times, but acutely severe after intercourse. There was pain of a sharp stabbing character when the bowels moved, or when straining at stool. Menstruation was regular, lasted three days, and was less in quantity than normal. She had excruciating dysmenorrhea for three days before menstruation, and for the duration of the flow. The premenstrual pain was abdominal and boring in character; the menstrual was of the usual uterine cramp type.

On physical examination the uterus was retroverted, and, it was thought, fixed. Its posterior wall bulged and felt hard, and gave the impression of intramural fibroid of the size of a tangerine. Owing to the malposition of the uterus, the appendages could not be defined. There was exquisite pain when movement was imparted to the uterus.

Operation. When the pelvic organs were exposed the two ovaries, each the size of a pullet's egg, came into view. They were free, as were the tubes, and filled with small follicular cysts. When an attempt to raise the uterus was made it was found bound down posteriorly by old filmy adhesions, decidedly not of the endometriotic type. When brought into view the uterus bulged more on the posterior wall than on the anterior.

The organ was the size of a 2.5 months' pregnancy, but of a much firmer consistency. Double salpingo-oophorectomy and total hysterectomy were performed. There was a mild degree of peritoneal sclerosis in the utero-vesical and Douglas' pouches. The paracervical tissues and vaginal vault were thickened and indurated. The appendix, as is the custom in all cases, was then examined, and it presented itself readily for inspection. It was rigid, curved away from its mesentery, small vessels coursed over its surface, and it was free from adhesions. The part of the cecum proximal to the appendix was more opaque than normal, and the cecum was long and freely movable, and would have had a deep pelvic lie when the patient was in the erect posture. Appendectomy followed, during which the cautery went through a thick muscular wall with a small mucosal lumen in its center. The gallbladder had shrunk to clothe a lobulated stone quite closely.

Examination of the Removed Organs. The uterus, when incised along its posterior wall, had a bulging wall 2.25 inches thick. The deeper tissues were under great tension. Small sago bodies of endometriotic origin could be detected in the wall. The anterior wall was slightly less hypertrophied. There was not a sign of a fibroid or of a circumscribed myoma. The process was a diffuse muscular hypertrophy. The mucosa was not appreciably altered. The fallopian tubes exhibited a similar hypertrophy of their muscular coats. The ovaries were sclerotic and were filled with small follicular cysts and atretic corpora. The appendix presented all the characters described above.

Microscopic Diagnosis. The biopsy diagnosis was uterine parietal endometriosis, both mixed and stromatous; sclerotic cystic ovaries, a clinically unrecognized microscopic epithelioma of the cervix, and musculofibrous hypertrophy of the appendix. This organ, on closer study, presented no sign whatever of inflammatory reaction, but merely tremendously hypertrophied musculofibrous walls and a normal mucosa. At the present time it is impossible to form any estimate of the frequency of tropho-appendicopathy, though one may judge of its incidence by the fact that three pronounced cases have come under observation in the past two weeks.

So far as is known, the afflicted appendix does not produce any symptoms. Any symptoms that might be attributed to the appendix might readily arise out of the pelvic state. It must be pointed out, however, that the presence of a tropho-appendicopathy does not necessarily imply a discrete intraperitoneal endometriosis. The rules which govern peritoneal sclerosis as described elsewhere apply also to this form of appendicular disease. Just as endometriosis (and fibroids) are but one of the forms of an endocrine dyscrasia, so the trophic changes involving the appendix are but another manifestation of the disease, and may be unac-

companied by any gross pelvic pathology except hypertrophy of the specific pelvic structures, or sclerosis of the pelvic peritoneum. In these cases of trophic changes in the appendix there is not uncommonly an excessive amount of free fluid in the pelvic cavity.

In all cases of appendicular sclerosis in which there is no appreciable extra-appendiceal evidence of inflammatory disease, the pelvis should be explored for evidences of other manifestations of hyperovarianism. There are definitely appendiceal scleroses of inflammatory origin which can so closely simulate a true tropho-appendicopathy that, it is thought, only the microscope could differentiate the true nature of the disease.

DISCUSSION OF ENDOMETRIOSIS AND ALLIED DISEASES

General

We have seen in the foregoing pages an accumulation of facts bearing upon endometriosis. These are the result of close observation and study. They have stood the test of time and criticism. But in the past our conception of endometriosis was too restricted. We are only too prone to think that any new disease is in a separate compartment by itself, and we close our eyes to the fundamental fact that diseases are allied and the study of any one is an aid and often an open sesame to the obscurities of another.

Endometriosis has a wide range of manifestations, and its expression must in a certain degree conform, as do all diseases, to the milieu in which it operates. For example, endometriosis may grow outwardly into the endometrium, just as cancer may be a surface papillary growth; or endometriosis may burrow deep into the uterine and parametrial tissues from its primary site of origin, just as carcinoma does; or endometriosis may "spill" out of the tubes from a surface endometrial desquamation and implant itself upon susceptible tissues that become soiled with the "spill," just as adenocarcinoma of the endometrium spills its cells out of the fallopian tubes to soil the peritoneal cavity.

Cancer, however, is not so discriminating as endometriosis. Cancer enjoys a very wide distribution in its transplants. Endometriosis restricts itself, except in very rare instances, to a limited area of the body. It has another point in common with cancer, that its adhesions are so fusing that organs lose their normal boundaries and melt inseparably into a common mass.

In common with cancer and sarcoma, endometriosis may be of mixed glands and stroma, or may be made up entirely of stroma cells. So the resemblances might be multiplied, and the more we know of the one disease the easier it is to understand the vagaries of the other.

The objects of this chapter are twofold: (1) to get a clear perspective

of endometriosis and its allied diseases, and (2) to study and speculate upon the general underlying cause or causes.

PERSPECTIVE

The study of endometriosis in the past, like all early phases of knowledge, has been restricted almost exclusively to the pathology of the most obvious lesion of the disease; namely, ovarian endometriosis. Our knowledge has now broadened out to a wide concept of the disease, whose ramifications are extensive and deep; and the part of the disease that strikes the eye is the most obtrusive, and therefore, has captivated our attention to the complete exclusion of its wider ranges and minute morphologic pathology.

We now know that endometriosis takes its primary origin from the endometrium, and always from the endometrium. Wherever it may implant or transplant itself, its progenitor cells emanated and emigrated from the endometrium. That must be our first broad concept. That metaplasia of peritoneal cells might be the cause of intraperitoneal endometriosis has been fully refuted in the previous pages, and may well be discarded into the limbo of oblivion.

The endometrium is not biochemically alike in all its areas, and therefore reacts differently to environment in the ovarian areas. Only the surface layers are strongly responsive to the hormones of the ovary which cause the menstrual cycle. The deeper layer is not responsive except under the major stimulus of pregnancy. We have, therefore, two kinds of endometriosis: that which arises from responsive and that which arises out of the deeper nonresponsive tissues. Daughter cells from these two sources of origin carry over the responsiveness, or lack of it, to any new ectopias of invasion.

The responsive invasions, when active, possess not only the common property of invasion of alien tissues, but add to this the destructiveness of periodic menstrual-blood extravasations. The nonresponsive types are equally invasive but lack this added extravasatory factor of distortion and dislocation. Since responsiveness or nonresponsiveness is a fixed property acquired over years of feminine evolution, and since these properties are carried over by the implanted cells into the ectopic soil, we can foretell that endometrial endometriosis and intraperitoneal endometriosis derived by the "spill" method must respond to the menstrual hormones, because they are derived from the surface cells of the endometrium. So also are implants upon the vaginal wall. The same applies to implants in abdominal wounds following any operative interference which involved the endometrium, and to any transplants from these above-mentioned areas to other contiguous or continuous surfaces. On the other hand, any endometrioses which are derived from the basal layer

of the uterine mucosa and which penetrate the uterine wall into the ramifications of the parametrium are unresponsive, not only in their normal relations, but also in any of their ectopic extensions.

I repeat, that from careful study carried on for many years, responsiveness or nonresponsiveness is a fixed property. It will be shown later that this fixed specificity is applicable to other tissues in the pelvis, so that uterine parietal mixed endometriosis, if it were responsive, would cause the uterine wall to be as completely destroyed as is the ovary when infiltrated with functioning endometriosis. But, as shown in previous case reports, uterine parietal endometriotic hemorrhages are a rarity, and when found are due not to the operation of the ovarian hormones but to a general hemorrhagic state brought about by some toxic agent. In this category of nonresponsive ectopias are uterine parietal infiltration, parametrial extensions into all the connective-tissue elements of the pelvis, and occasionally into the peritoneal cavity directly through the peritoneal surfaces of the uterus or indirectly from the lymphatics of the parametrium.

So this first broad generalization is to the effect that endometriosis originating from the basal layer, wherever it may penetrate or implant itself, is not visibly responsive to the ovarian hormones of the cycle. These ectopias travel chiefly by the lymphatics and blood vessels of the uterine wall and parametrium. These extensions may contaminate the peritoneal cavity from either of these two sources, but the cells would still be devoid of the cyclic changes.

On the other hand, in the contamination of the peritoneal cavity by the "spill" method, the ectopic implants are from desquamated surface cells of the endometrium, and, being responsive, carry over that property to their new environment and into their secondary transplants.

TISSUE SUSCEPTIBILITY

Our second generalization is that only tissues that are within a close radius to the primary sex organs are susceptible to endometrial invasions. The boundaries to this restricted radius are ill-defined. Let it be supposed, for the time being, that the center of production of whatever is necessary to make tissues susceptible to endometrial implants lies in the ovary. The point of maximum concentration of that product will then be within the ovary, and in the vicinity of the ovaries. This concentration will grow diluted as one recedes from the point of production—implying, of course, that the product of the ovary escapes, at least in part, by diffusion or by rupture and not by the blood stream.

This seems to be exactly what occurs. Susceptibility is at its highest peak in the vicinity of the ovary, and the incidence of implants gradually diminishes as one recedes from these sex organs. This emanation, let us

call it for the moment, permeates all the animal's normal pelvic tissues, and by that permeation makes them vulnerable to the endometrial cells. Woman, however, by her erect posture, has caused other abdominal organs to assume a permanent or quasi-permanent pelvic lie, and in so doing has made these vulnerable also, by being closely immersed in the pelvic fluid. These organs are the sigmoid, the ileum and part of its mesentery, and occasionally the appendix with its preternaturally mobile pendulous cecum. These organs, by virtue of woman's stance, coupled with unusually long ligaments and mesenteric attachments and gravity, become pelvic organs during most of a woman's adult life, and as such share the weaknesses of her pelvic organs in a common submergence. The omentum, on the other hand, though frequently a pelvic invader, recedes into the upper abdomen in its migratory travels and thus escapes also an invasion except when it becomes fixed in the pelvis in the mass of endometrial adhesions.

One of my colleagues, a pathologist of international reputation, once stated that he could diagnose pregnancy by the study of a section of the appendix from any pregnancy case, by noting the decidual change in its peritoneal surface. That statement is only partially true. It has been noted by many writers that decidual change in pregnancy has much the same potential distribution as has endometriosis. This is also not quite true, though the two zones of influence—namely, those of decidual change and of endometriotic susceptibility—are very similar. But for an appendix to be the seat of decidual change in pregnancy it must have had a deep pelvic lie for a long period of time. Appendices which are held high by a short cecal mesentery do not show decidual change. That fact we have been able to prove sufficiently frequently to place the question beyond any doubt. And the same applies to involvement of the appendix in endometriosis. A good example of the influence of propinquity to the sex organs is seen in the mesentery of the ileum. It is susceptible in the vicinity of the loops that are capable of a pelvic lie, but the more remote parts of this same mesentery lose that vulnerability proportionately to the distance from the pelvic loop, that is, as one ascends in the direction of the mesenteric root.

The third generalization is that the agent which brings about any type of endometriosis acts in a general way upon all the tissues of the pelvis, in a manner that is characteristic of the susceptibility of that tissue.

Endometriosis finds in this factor its greatest difference from malignancy. Malignancy starts in one cell, and every part of that malignant growth is a descendant of that cell and all tissues of the body may be invaded. Few if any are invulnerable, though they may differ in their reaction to the invading malignancy. In endometriosis the pelvic tissues are prepared beforehand in a manner that makes them susceptible to

implants. That statement, perhaps, requires some further explanation. If one carefully opens the abdomen during menstruation, one finds that in about 50 per cent of cases where the tubes are patulous there is a "spill" of blood from the tubes into the pouch of Douglas. That "spill" necessarily contains the cellular elements capable of implantation. If all these cases were susceptible to implants few women would escape endometriosis. But normally these escaped cells are destroyed, except where they find a new field of nutrition in the peritoneal cavity.

This preparation of the field seems essential for ectopic endometrial growth, though different tissues show a different degree of acceptance of the implants. The ovaries are notably susceptible in these cases, and as a consequence ovarian endometriosis has been the most striking manifestation of the disease. Consequently it occupied the sole attention of observers for many years. But in 1937 I pointed out that endometriosis and its activating agents have many forms of manifestation. By close study of all the tissues of the pelvis in cases of endometriosis, we have shown that the agents of endometriosis cause endometrial, parietal, cervical, vulvar, vaginal, ovarian, peritoneal, intestinal, and many other changes that will be dealt with more fully later. A combination of many of these usually occurs, or all of them in a few instances may occur in the one case. Now this can be brought about only by an agent that has made all these tissues (normally nonsusceptible) vulnerable to endometriotic implants, or susceptible to other changes of an allied nature. These pathologic changes are regional, and are characteristic of both the region or the implant in that region.

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The Cause or Causes of Endometriosis

In the previous chapters we were dealing with facts gleaned by observation of a large number of cases. In this chapter we step into the realm of speculation. It is well known that any disease has not one causal agent, but a succession of active dyscrasias of which the disease is the last expression. The immediate cause is usually easily found, but behind this is another cause of which the immediate cause is but an effect, and if we trace these successive causes and effects we finally reach an impasse. When we bring this knowledge to bear upon endometriosis to ascertain the cause or causes of so many varied manifestations, we finally reach the constant impasse. But before reaching this point it is possible to determine the probable primary factor in the production of this disease. Any advance in scientific knowledge is built upon a hypothesis deduced from observations, and then we look to see if all the facts fit into the hypothesis; if it explains the facts better than any other hypothesis, it is retained as a working hypothesis. The line of reasoning is as follows:

The ovary is a constant necessity for the *initiation* of endometriosis. The ovary is almost a constant necessity for a *continuation* of the endometriotic activity. The exceptions to this last statement are so few as to confirm the rule. Therefore it is logical to assume that the immediate and activating cause lies in the ovary. Whether the ovary is the only organ that is involved in the initiation and continuance of the disease is quite another and a more difficult question to answer. Myer contends that there is an infective agent in all cases of endometriosis, but I have never been able to prove this to my entire satisfaction. But let us suppose that the pituitary—and, to be more specific—prolan A, is the next or mediate causative agent, then the ovary becomes an essential intermediary between the pituitary and the endometriosis. The ovary is the essential intermediary because cessation of the ovarian function, either by surgical ablation or by destruction of function by x-ray or radium, brings about a prompt regression in the endometrial pathology. If, therefore, the ovary is an essential organ, then vitiated products of function of the ovary must be the underlying cause of endometriosis. The functions of the ovary are

both oogenetic and endocrinologic to complete the function of that egg. It is thought that the ovum, though it may have a great governing power over function, has no recognized secretion of its own. Authors have never incriminated the ovum in endometriotic disease. The development of ova seems to go on in the ovary in close proximityy to endometriotic invasions. It is even thought that ovarian endometriosis and other manifestations of the disease seem to stimulate the ripening of ova in larger than normal numbers. But whether these ova reach maturity is very debatable, as will be pointed out later.

We are reduced to considering the endocrine functions of the ovary as the immediate cause of endometriosis and its allied diseases. One cannot assume that a normal function can produce a diseased condition. That would be contrary to all our ideas of normalcy. The mind revolts at such a concept. We are reduced, therefore, to considering as a causative agent an abnormal state of ovarian secretion, capable of taking on one of three possible forms. Vitiated function may be due to (1) a change in the chemistry of the secretion, (2) hypersecretion, or (3) diminished secretion.

The first hypothesis can be eliminated more or less completely by analogy. In studies of other gland secretions it has been found that the common defects are not qualitative, but rather quantitative. We have but to mention the pituitary, thyroid, pancreatic, and other such glands to support that statement. So we are reduced to the view that the ovarian vitiation is quantitative rather than qualitative. If so, then let us look into this matter more closely. As previously observed, the secretions of the ovary are two: (1) estrin, and (2) progesterone.

Estrin is the follicular secretion; progesterone is the product of the corpus luteum. They succeed each other in the rhythm of the menses. When the follicular hormone has reached its height of production, it falls quantitatively as the rise in progesterone production takes place. Estrin is the growth hormone, causing the hypertrophies of all the organs of generation preparatory to pregnancy. Progesterone is the secretory hormone, producing a succulence of susceptible tissues in order to facilitate nidation and placentation. Both of these increase their hormone intensity when conception has taken place, a function which is taken over later, in part at least, by the placenta itself. It is believed now that quantitative vitiation in the nature of an excess of production of estrin is the factor in the genesis of endometriosis. There are many facts to support this belief. Let us place the facts against this hypothesis and see how it stands the usual scientific test.

Most of the manifestations accompanying endometriosis are of the nature of hypertrophies and activation of tissues. In all cases of *acute* endometriosis there is an accompanying increase in the normal tissues of the uterine wall, simulating early pregnancy changes. If the stimulus

continues over a long period this soft hypertrophy turns to a hardness of the tissues due to cell fixation. The adenomatous enlargement of the cervical mucosa and the cystic hypertrophy of a chronic mixed endometrial endometriosis all bespeak a chronic vitiation of estrin production of a quantitative and prolonged nature. The sclerosis of the peritoneum and ovary, a new discovery frequently accompanying endometriosis but sometimes quite independent of it, is an expression of a chronic quantitative abnormal production of estrin. I have found that, in the majority of cases of peritoneal sclerosis, there is also a sclerosis of the ovaries, and the so-called small cystic degeneration of the ovary is an expression of that hyperestrinism in which the follicular cysts of the ovaries become so sclerosed in their walls that they often do not collapse when incised, but have walls that are cartilaginous in consistency.

I believe that the peritoneal sclerosis, restricted as it always is to the pelvic pouches and the peritoneal surfaces as high as the umbilicus, shows in its distribution whence comes the source of the sclerosing agent. If we examine these cases carefully, especially cases of advanced sclerosis without other gross lesions in the pelvis, we find some most enlightening conditions. The points of greatest intensity are the deepest parts of the pelvic cavity; namely, the pouch of Douglas and the vesico-uterine. From these points, as one ascends out of the pelvis, the sclerosis grows less and less pronounced. Obviously, therefore, either the source of the production of the sclerosing agent is in the depth of the pelvis, or gravitation concentrates the agent in the pelvic area. When the sclerosing agent is in operation, the uterus when retroverted and retroflexed will show the peritoneal sclerosis on the posterior wall only, or to a greater degree always on that wall, if both peritoneal surfaces are affected. But two determining factors point to the follicular hormone as the incriminating agent. In two cases of large fibromyoma of the uterus, with the posterior wall of the uterus lying in the pouch of Douglas, the sclerosing process was seen to spread out like fans from the utero-ovarian ligaments over the broad posterior uterine wall.

I have consulted textbooks on veterinary medicine, and nowhere have I found mention of endometriosis or peritoneal sclerosis in animals. That is as one would expect, for animals do not menstruate, and therefore could not contaminate the peritoneal cavity by a "spill" of menstrual blood. But I found, in consultation with Doctor Conklin, professor of animal pathology at McDonald College, that cows do have commonly a cystic disease of the uterine wall, in which the cysts are lined by columnar epithelium, which might well be an endometriosis though it had never been interpreted as such owing to lack of knowledge of that type of endometriosis which is but a recent development of human pathology. The lack of peritoneal sclerosis in animals I attribute to the posture on

all fours in which the pouch of Douglas becomes the highest part of the celomic cavity. Drainage is therefore toward the diaphragm, which presents a large absorption surface and a freer elimination into the circulation of any abnormal secretions into the peritoneal cavity. And conversely, women, by having assumed the erect posture, concentrate the ovarian secretions which accumulate by excretion and by rupture of the follicles in the most dependent parts of the peritoneal cavity. Even when a patient is lying supine the pelvis is the most dependent part. Even when she comes to operation and is placed in the Trendelenburg position the pouch of Douglas still does not drain its contents into the upper abdominal cavity.

In cases of advanced sclerosis absorption from the pelvic region must be further inhibited, and concentration must therefore be greatly increased—so, a vicious circle would be established. In cases of discrete sclerosis there is nearly always free fluid in the peritoneal cavity. In many it is large in quantity, amounting, even in the Trendelenburg, to as much as 50 cc. It is chiefly clear straw-colored in uncomplicated cases, but may be smoky owing to admixture with blood when there is an associated intraperitoneal endometriosis. In cases of uncomplicated sclerosis the ovaries are free from adhesions, but are deeply grooved, hard, and filled with the cysts of persistent unruptured follicles.

Let us continue to see how this concept of hyperestrinism fits the cases. Our concept of endometriosis in the past has been a very narrow one. We must now realize a fact heretofore ignored, that endometriosis in all its types is but one of the facets of a very-many-faceted disease. We cannot recognize the many manifestations of a disease until we accept a causative agent. Then, and then only, do widely different manifestations take on a new and common significance. We have then reduced different factors to a common denominator. We must recognize that hyperestrinism may express itself in many forms of pathology, depending upon susceptibility of tissues, intensity of the dyscrasia, type of onset of the dyscrasia, duration of the dysfunction, age of the patient and her personal and familial background.

In a series of cases one will find only peritoneal sclerosis, varying in degrees of intensity as well as extension. In another series there will be hypertrophy of the normal constituents of the uterine wall, in which local accentuation of the growth hormone may produce fibroids, or myomata, or—associated with these—there may be an infiltration of these tumors by endometrial elements of the basal layer of the endometrium. In still others "spills" may occur, and implants and transplants occur intraperitoneally or elsewhere in the lower genital tract. In still others cervical hypertrophy occurs, usually in conjunction with uterine hypertrophy, and the cervical mucosa takes on adenomatous overgrowth. The

changes in the vaginal mucosa in hyperestrinism are now under study. And in a last group we may find combinations of any or all of these expressions of aberrant stimulation and local response.

Hyperestrinism has another interesting clinical feature. If a patient is injected with a large dose of estrin, it has been discovered that very little of this can be recovered in the urine. But as soon as a dose of progesterone is added the estrin is set free in the circulation and is rapidly excreted. There are many inferences which can be drawn from the above-mentioned experiment. The first is that the estrin is held intracellularly in the specific pelvic cells until liberated by the progesterone. The second is that estrin acts specifically and forcefully during its *secretion* and is *excreted* rapidly by its successor when estrin production ceases and its work has been done. Persistence of estrinism and hyperestrinism, therefore, may arise either (1) out of overproduction, or (2) out of a relative lack of progesterone, thereby causing a constant estrinism, though not necessarily a hyperestrinism. Both processes would seem to operate in the cases that have come under close observation. This is assumed from the persistence of the unruptured follicles, and from the small amount of lutein cells which are formed in the periphery of these persistent follicles by luteal changes in the tunica cells which normally are much smaller and less active than are the normal lutein cells developed from the normal granulosa.

So the pathologic expressions of faulty ovarian secretion are very protean, and endometriosis is but one of its many manifestations.

The association of the various manifestations of this disease is a very interesting study. This association depends upon personal and familial factors. Endometriotic invasions are common in all the years of woman's sexual age. They are inactivated by the menopause, but may be initiated or reactivated by postmenopause relighting of ovarian function. Peritoneal sclerosis may also occur at any time during the years of the sexual life, and is most commonly associated with intraperitoneal endometriosis, though association of this sclerotic lesion with the other manifestations of endometrial pathology is not uncommon. The association of fibroids and myomata with endometriosis is most common between the ages of 30 and 40, though a goodly percentage occur also in the late twenties.

The association of endometriosis with the characteristic cervical pathology is most common in the fourth decade, probably owing to the traumatization of antecedent childbirths, though the association is also met with in the nulliparous, and in the virgin.

THE PATHOLOGY OF OVARIAN FUNCTION AND STERILITY

It is commonly known that sterility follows the development of any of the above manifestations of pelvic disease. In my group of stromatous

endometriosis there had been an average of 14 years of sterility prior to operation. In my experience of hundreds of cases, I have not seen pregnancy in combination with endometriosis, though I have had particulars of three such cases. One was an ectopic, a second aborted, and a third was pregnant in association with large ovarian masses, though the diagnosis was purely clinical and not made certain by operative exposure. The absence of such cases in my own large experience only goes to show the infrequency of conception when this type of pathology is present.

The question at once presents itself—why should pregnancy not supervene when it is known that in the vast majority of cases the tubes are patulous, and the ovaries as pointed out above are unusually fertile in this type of disease? There is, therefore, no physical reason why a sperm and an ovum should not meet. Yet pregnancy does not occur, and neither does it follow even after the disease has become quiescent for long periods. The inference is that it is the underlying cause of the pathology which is inimical to conception. This is very different from the concept generally taught, that the sterility associated with fibroids is due to the presence of the fibroids. As endometriosis and fibroids have so much in common, the belief soon developed that the sterility associated with endometriosis is due to the presence of the endometriosis. Now, for various reasons to be given later, we know that the sterility is due to the same causes as brought these diseases into being. It was stated above that there is no physical impediment to conception in endometriosis or fibroids.

It is also commonly taught that fibroids atrophy after pregnancy. That is too frequently seen to require argument. But there are certain factors in connection with fibroids that have recently come to light in our research laboratory. Emge pointed out some years ago by a painstaking study that fibroids do not grow during pregnancy. That statement threw a bomb into our preconceived ideas. Now comes the statement that in every case where a pregnancy, even in its first weeks, was complicated by fibroids and hysterectomy was performed, the fibroids were found in an advanced state of degeneration and cavitation. The inference is forced upon us from this study that the degeneration of the fibroids began long before the pregnancy supervened, and that the degeneration is an expression of restoration of a normal endocrine balance, and that this restoration made conception possible. Whether the pregnancy, intervening as it frequently does during tumor degeneration, arrests degeneration temporarily, it is impossible to state. But this, however, can be stated with assurance—that when the ovary ceases to function at the fourth or fifth month of pregnancy, degeneration of the fibroids goes on again, and with increasing speed, as complete ovarian quiescence is reached after the seventh month of pregnancy, and especially during the puerperium, when even the placental endocrine store is withdrawn. It would seem that fibroids and

the associated uterine hypertrophy, as outlined in my work "A Clinical and Pathological Study of the Permanently Enlarged Uterus," are evoked by a much milder form of ovarian dysfunction than that required to bring about an endometriotic manifestation. But here again there are varieties of intensity, in both these manifestations. There is the soft, rapidly growing fibromyoma with the enlarged, soft uterus simulating pregnancy; this is an expression of a rather intense, active dysfunction, which, like all acute processes, is more likely to revert to the normal and allow complete absorption than would the case of the slowly growing hard fibrous tumors and the chronically enlarged hard uterus, the result of a slow extended growth consequent upon a protracted, less acute dyscrasia. We see these types in other gland dyscrasias with their tendency to reversion.

The reasons for these deductions are more clearly brought out in the study of endometriosis. It was pointed out that if tissues removed at operation in undoubted ovarian endometriotic cases are sent to the pathologist without a clinical diagnosis, in only one-third of the cases will the pathologist find evidences of endometriosis. Yet from the various findings quoted in a previous chapter, the cases are undoubtedly endometriosis. Why this discrepancy? It is due to nature's power to restore an endocrine balance by her own recuperative power, but that restoration seldom seems complete enough to permit full normal function sufficient to permit conception. Of course, it is impossible to estimate how frequently conception may follow upon the milder forms of endometriosis, because only the graver forms of the disease with extensive pathology usually come to operative corroboration.

The delicate endocrine balance that is necessary to permit conception to take place is not frequently appreciated. But it is clearly seen in the promptness with which sterility is replaced by fertility by the exhibition of only a quarter of a grain of thyroid three times a day (Burroughs Wellcome), which is only one-fifth the strength of the dried preparation. This is a common experience in clinical gynecology, and the prompt result is startling to both physician and patient. Not only is this slight thyroid imbalance operative in sterility, but it is the commonest cause of faulty placentation or embryonic development, and therefore the commonest cause of not only early abortion, but habitual abortion. *Per contra* it would seem to require a much greater departure from the normal balance to initiate endometriosis and the allied diseases, so that when the disease has begun to regress by nature's spontaneous recovery the endocrine balance must proceed a great deal farther than this state to permit conception. The foregoing concept is both logical and according to experience, because endometriosis and its allied manifestations are expressions of a diseased state, whereas conception is a physiologic development which

requires not a diseased medium but a normal or quasi-normal environment.

That the sterility that accompanies fibroids is not the result of the presence of fibroids is clearly shown in the fact that it matters little where the fibroids lie in the uterine wall when the body is ripe for conception. The belief that the lie of the fibroid exercises a profound influence upon sterility must be abandoned. The concept that fibroids that are subperitoneal are not a barrier to pregnancy; that pregnancy is more common in intramural fibroids; and that the submucous fibroids are almost an inseparable barrier to conception, are tenets that have been stoutly held because the fibroids are so obtrusive to the ordinary inspection. I admit that fibroids wherever located are an expression of diseased endocrinology. I admit that the frequency of abortion under these circumstances is striking, but I do not think for one moment that both these eventualities are the result of the fibroids, but instead are an expression of a preventing imbalance in cases of sterility, or of insufficient restoration to continued embryonic development, just as in thyroid dystrophies which offer a complete parallel. In my experience pregnancy is just as common in cases with submucous fibroids as in intramural and experitoneal fibromyomata.

Some of these cases are striking examples. I have removed fibrous polypi with long pedicles (which are practically always corporeal as distinguished from mucous polypi of cervical origin), in no less than 11 pregnant women. In four cases there were large submucous fibroids with retained placentas at full term, and in one case, which was sent to Montreal after delivery owing to a retained placenta, the placenta lay above and was incarcerated by a large submucous fibroid filling the whole area of the uterine cavity below the site of implantation. The frequency of pregnancy and submucous fibroids is revealed in the two great fears of fibroid complicated by pregnancy; namely, torsion or degeneration with infection or intra-uterine evulsion. Some of the most serious cases in my experience have been cases of large submucous fibroids which have degenerated after delivery and have been expelled after weeks or months of foul-smelling discharge and high fever.

It would appear that the location of the fibroids plays a very minor part in the incidence of pregnancy, or in the sterility which so frequently accompanies fibroids. It therefore becomes rather conclusive that the cause lies, not in the tumors themselves, but in the cause behind the tumors. So, it would seem, is the case also with endometriosis, of whatever type it may be. If this be so, and since it has been proved that endometriosis in the majority of cases is a self-limited disease, and that most of the cases at the time of operation are in a regressive state, it would be natural to assume that pregnancy would frequently follow that regression. One might argue that that regression means a restoration of endocrine

balance. But it would seem that a great endocrine defect is necessary to initiate endometriosis. Its regression does not mean a balance sufficiently equable to permit conception, for it has been proved that minor endocrine disturbances insufficient to provoke detectable clinical symptoms may be sufficient to prevent conception or continuous fetal development. In a large number of cases of endometriosis in which the diagnosis had been confirmed by operation, and in which only partial removal did not interfere with conception, it was found that there was a fairly consistent low thyroid output. Yet in spite of the correction of this defect by thyroid substance, pregnancy did not occur, even though some of these patients have been under treatment for many years.

THE INVASIVE PROPERTIES OF ENDOMETRIOSIS

Endometriosis, of whatever type, is an invasive disease caused either by an overstimulation of the endometrial cells or by the withdrawal of a normal growth-restraint. Whatever the cause, the endometrial cells invariably invade the lymph spaces, and push along their channels. If we count the peritoneum merely an extended lymph space, then the predilection of ectopic endometrial cells for lymph spaces is complete. In this ectopic invasion the endometrial tissues are not destructive. They merely push the normal tissues aside as they multiply in the lymph channels. In most instances not even the delicate lining of the lymph spaces is destroyed, but may suffer from compression. Blood vessels may be invaded as to their lymphatics, but in only one instance, Case IX, was there evidence that the growth had actually invaded the vein lumen. Even this had not occurred during the ten years of the course of the disease, except a few weeks before death when all tissue individuality was probably lost in the toxemia of uremia.

Endometrioses, unlike malignant invasions, do not destroy and digest the tissues in their immediate vicinity. And cachexia is an unknown quantity in endometriotic disease, except when the functions of essential organs are obstructed by compression. Undoubtedly, from the frequency of lymph and various polypi and emboli, many endometrial cells must reach remote parts of the body, but these, like syncytial cells in pregnancy, find the terrain outside the pelvis unsuitable for their growth and are rapidly disposed of by the new inimical milieu.

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Major and Minor Forms of Endometriosis

There are all grades of growth-incentive and of tissue susceptibility, and combinations of these two factors produce all grades of intensity and wide ranges of extension of the pelvic disease.

One is apt to assume that any disease that has overstepped the bounds of normal restraint and of normal demarcation must then, *ipso facto,* run the whole gamut of pathologic destruction. Nothing could be farther from the truth. As pointed out in a previous chapter, two-thirds of the cases that come to operation are in a state of quiescence. The ranges of extension of the disease may vary widely. In any form of endometriosis the visual, and therefore appreciable, departure from the normal may be so slight as to escape the observation of all but the most experienced, and even these connoisseurs may differ as to the borderline between normalcy and the abnormal. Endometrial endometriosis may vary in overgrowth within wide limits, and uterine parietal endometriosis, whether mixed or stromatous, may be so slight as to leave one in doubt whether the condition is pathologic or not.

No such doubt exists, however, when we encounter the intraperitoneal type of responsive endometriosis. Here the characters of the disease are unmistakable. They may differ, however, from a few black "beads" and the characteristic puckering about these—either on the ovarian surface, or in the pouch of Douglas or on any susceptible peritoneal surface—to the major types of the disease in which all the pelvic organs are a conglomerate mass, stained with old and new blood, and blood-stained peritoneum, blood cysts, and tissue scleroses. The disease processes may be arrested at any stage of their development, but slight ectopias, denoting minor endocrine dyscrasias, are naturally more readily restored by nature's power to establish a balance between the internal and external milieus.

ACUTE AND CHRONIC FORMS OF ENDOMETRIOSIS

These two forms of the disease differ so fundamentally, not only in the morphology of the endometriotic invading cells, but also in the effect of

the growth incentive upon surrounding tissues, that they must be described minutely to effect a complete understanding.

Let us turn our attention first to the endometriotic invasions, and then describe the concomitant changes which accompany these two types of invasions. Of course, it must be understood that the terms acute and chronic are purely relative terms. They signify, usually, the extremes of activity or chronicity, but between these two extremes are all gradations which pass insensibly from the one to the other.

The acute types bespeak an active, powerful agency, stimulating specific cells to overgrowth and to a capacity to break through the bounds of normal environment. In these cases all cell division is on the ascendant, and the component endometriotic cells have the normal characters of normal endometrial cells in the height of the sexual age—a clear oval cell, with a clear oval nucleus, turbid cytoplasm, clearly defined nuclear chromatin, and skein-like arrangement. The host's tissues which normally respond to the hormones of pregnancy in the form of hypertrophies now respond to this stimulating agent proportionately to the degree of stimulation. Especially does this apply to the fibromuscular structures of the uterus. In these cases the hypertrophy and softening may be so marked as to be confused with a pregnancy of two or three months. Acute processes may continue in their acuity until (1) the process comes rapidly or spontaneously to a complete end, thereby bringing about restoration by regression; (2) the disease may deteriorate into a chronic state; or (3) complications may necessitate surgical intervention with cure or betterment of the state.

In the chronic forms, which are by far the most common, the clinical and the biopsy pictures are very different. Just as the cells of the normal endometrium differ markedly in the different sexual ages, so do the endometriotic cells differ morphologically. The more chronic the disease the more do the cells lose their oval forms to a streamlined type, approaching in the extreme case the characters of connective tissue. The nucleus also becomes streamlined, proportionately with the cell cytoplasm. That these signs of chronicity are due in part to the compression of the tissues of the organ invaded is seen in the fact that all types of changes from the oval to the extreme streamlined may be encountered in the same section. These are due purely to local conditions which do not change the prevailing characters of cell chronicity and cell fixation. Cell division in these cases is considerably reduced from that encountered in the acute cases. Many of these cases were chronic from their inception—others deteriorated from an acute phase of the disease. The host tissues, whether the disease was a chronic one from the beginning or whether it was a late stage of an acute process, develop a hypertrophic state in keeping with the characters of the invading disease.

It would seem that the acute diseases of a major form of dyscrasia produce a large soft uterus which later, in the chronic states, becomes symmetrical, hard, and tender—conditions which are commonly known as chronic metritis. The cellular endometriotic invasions become squeezed and have to accommodate themselves as best they can to the changed circumstances of chronicity. On the other hand, cases of endometriosis that are chronic *ab initio* do not give rise to as large a uterus, but the penetration is usually universally streamlined, and the muscular fibrous structures present adult and fixed types. It would seem, as in all other forms of disease that do not destroy the host, acute diseases are more prone to restoration than are chronic forms of the same disease. So I think the same rule applies in endometriosis. Acute forms of disease bespeak a rapid change in an external milieu, whereas chronic diseases bespeak a slow change in the environment which is more likely to possess an obstinate permanency.

Chronicity in intraperitoneal forms of the disease is manifested in various ways, chiefly in the production of sclerotic changes in the peritoneum of the nature of a deposit of colloid substances in the subperitoneal tissues, and a similar sclerosis, first of the tunica albuginea, and later of the deeper tissues of the ovarian stroma. It manifests itself in causing denser organized fibrotic and specific adhesions and consequently a more intimate fusion of the affected contiguous organs, ending in a conglomerate mass of all the pelvic organs firmly adherent to the fasciae of the pelvic walls.

INCIDENCE OF ENDOMETRIOSIS

It is almost impossible to form any accurate estimate of the frequency of endometriosis. The factors which militate against accuracy are many, but chief among these are three: (1) the inability of most gynecologists to recognize the disease in any but its major manifestations, (2) the inability of the pathologist to identify the disease owing to the disappearance of the endometrial cellular elements in cases of spontaneous cure, and (3) the inability to diagnose with accuracy cases that do not come to operation.

In the year 1939 the incidence of endometriosis in all major operations was within a small fraction of 30 per cent. If we included those cases of minor uterine invasion, the percentage would have been much higher. In 1940 the incidence fell to 21 per cent in my private major operations. These percentages include those cases which are quiescent, but which, by the sites and type of adhesions, leave no doubt as to their original nature. In some estimates the incidence falls to 5 per cent of all operative cases, but I feel sure that this low rate is due to lack of recognition. I have had as guests many surgeons with a wide gynecologic experience who have

been astounded at the frequency of endometriosis in our clinics, and have been equally astounded at their previous inability to recognize the less obvious signs. It is impossible to form any idea of the incidence of the disease in all its manifold manifestations, especially in those cases of uterine infiltration by the endometrium, because we don't know where to draw the line accurately between physiology and pathology. These borderline cases are numerous, but they have little clinical significance except as an expression of something wrong in the interior economy of the nature of an instability with a temporary or permanent deviation from the normal.

PERSONAL AND FAMILIAL SUSCEPTIBILITIES

This ground is almost virginal, so one treads warily and with some awe. However, there are facts which taken singly have no weight, but when taken collectively deserve some recognition.

The problem of causation was discussed speculatively in a previous chapter, and it was pointed out there that hyperestrinism was thought to be the likely culprit, as garnered from the evidence. It was also pointed out (a philosophical generalization) that any given disease is not the product of any one cause, but of a succession of causes and effects. So I believe that endometriosis is no exception, and that behind the apparent cause are other causes more obscure, more intimate, which make for susceptibility to the immediate agent. What these deeper chemical susceptibilities are would be folly to conjecture with our present state of knowledge. But that there is a deeper personal susceptibility cannot be denied. It is this factor, or the lack of it, which makes experimental endometriosis so difficult. That many women may have hyperestrinism and show no ill effects is tantamount to stating the well-known truth that many persons may be hyperglycemic without showing any recognizable clinical or pathologic changes. Reactions to abnormal endocrinology are chiefly in the nature of allergy, and not all persons are allergic in the same degree. The various forms of endometriotic manifestations described in the foregoing pages show not only a personal susceptibility to the abnormal agency, but an organ susceptibility. In one case it is the uterus which shows the chief manifestation of the reaction. In another it is the ovary; in still another it is the peritoneal change that is dominant; and in still others there may be combinations of any or of all of these.

Familial tendencies seem to play a part. In my experience there have been decided family incidences. In one such case the mother at 45 was operated upon for a rather severe type of ovarian endometriosis. Three of her daughters, at various times, have had to have total ablations for most virulent types of intraperitoneal endometriosis. Two of these were among my four cases of spontaneous intraperitoneal rupture of large chocolate

cysts and were operated upon for an acute abdomen. All of the daughters were operated upon between the ages of 24 and 30 years, and all of them were complicated by multiple fibroids. In another family there were three daughters who were operated upon for diffuse endometriosis, and in each of three other families there were two sisters who were affected. It may be contended that these cases would fall within the law of chance. That is admitted, but it is worthy of study. Sampson and others have contended that the virulence of endometriotic implants is heightened by successive implantations, and that the ovary is the best hothouse soil. Perhaps it is because it is nearer the center of production of the suspected causative agent.

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Symptoms and Signs of Endometriosis

There are no symptoms that are characteristic of endometriosis in general. The site and the type of the disease determine the symptomatology. Vulvar endometriosis is generally of the stromatous type. It therefore does not take part in the menstrual cycle, and therefore does not become painful owing to blood extravasations. Vulvar endometriosis is first recognized as a progressive growth the true nature of which cannot be determined except by biopsy. It is, however, important to keep endometriosis in mind as a possibility in all solid tumor growths of the vulva. Its nodules, when multiple, have a tendency to grow in parallel lines. In the vagina endometriosis is found usually by accident. As an implant or as a transplant it menstruates with menstruation, but this is indistinguishable as of vaginal origin. When a large patch is involved it is generally recognized by the experienced finger as an unusually smooth velvety surface in marked contrast to the rest of the vaginal wall. Large involvements are very rare, however. I have seen but two which involved more than two square inches of the vaginal vault. Usually the area affected is not larger than a pea and they are frequently multiple. When not menstruating these appear as strawberry areas. When menstruation is on they are very red, and ooze blood. The disease is always much more extensive than the surface appearance, due to burrowing.

Vaginal endometriosis may be either an implant or a perforating endometriosis. In the former type there may or may not be an appreciable pelvic endometriosis, because the mere fact that endometrial cells have been able to implant themselves upon a breach of continuity in the vaginal wall shows that the susceptibility for endometriosis is present. In the perforating type, the local vaginal nodule usually in the posterior vault is an extension from the rectovaginal tissues. The rectovaginal disease may be an extension from a lymphatic parietal endometriosis or from an intraperitoneal "spill" endometriosis. In the former case of perforation the vaginal nodule will not respond to the menstrual cyclic changes. In the latter case, however, being derived from the surface cells of the endometrium, the vaginal invasion will respond.

Cervical and uterine endometrioses, owing to the absence of characteristic symptoms, are also usually found only when examination is undertaken. Cervical endometriosis is, of course, secondary to uterine endometriosis by extension into the fibromuscular tissues of the cervix. There are no symptoms arising out of this extension, but the cervical dimensions may be increased, though this is due rarely to the invasion but rather to the concomitant enlargement of the cervix under the stimulus that engenders the endometriosis. Leukorrhea, cervical mucous polypi, endocervicitis with ectropion, and precancerous overgrowths are common results of endometriotic stimulation, and symptoms may arise as results of these pathologic changes.

Uterine parietal endometriosis is a very insidious disease for two reasons: (1) because the uterus is insensitive, and (2) because this infiltration of its wall by basal endometrium does not respond to the hormones of the menstrual cycle. The disease is seldom diagnosed before operation, and can be confirmed only by biopsy. There are all grades of infiltration. In the major types there is enlargement of the uterus either symmetrically or asymmetrically, but enlargement, of itself, is insufficient evidence to diagnose endometriosis, because so many other causes may produce a like condition. Mobility of the uterus is not interfered with except in the advanced cases where the disease has spread beyond the confines of the uterus into the parametrium. Endometrial endometriosis may reach large dimensions, on palpation simulating an early pregnancy.

Recently I operated upon a case of single fibroid with old endometriosis of both ovaries, and an endometrial intra-uterine polyp measuring two inches long, one-half inch thick and one and one-half inches broad. The uterine wall was, in places, two inches thick, vascular and soft, closely simulating a complicated pregnancy. The polyp was composed almost exclusively of active stroma cells. Hemorrhage was the dominant symptom. Usually the menstrual flow is more abundant than normal, but any derangement of the rhythm is due, not to the endometriosis, but to the endocrine imbalance.

In ovarian endometriosis we come upon grounds of frequent involvement with more definite diagnostic signs. The symptoms of ovarian endometriosis are circumscribed. As a rule there is no disturbance of either the rhythm or the duration of the menstrual flow. When these occur it has been almost invariably possible to trace them to complications or to extrapelvic causes. The outstanding symptom of this type of disease is pain. This is of two types: premenstrual and menstrual. They require some elucidation.

Premenstrual pain, as the term implies, is pain before the onset of the flow. It may antedate menstruation for a week and is nearly always

the result of congestion upon sclerosed organs, or due to tension upon adhesions. It may be present in active or quiescent endometriosis. Pain during the flow is, however, due to the tension caused in the blood cysts owing to the renewed extravasation of blood into them. It may continue throughout the menstruation in a diminuendo toward the end of the period. Premenstrual pain persists after cure of the disease by x-ray or radium.

Given the case of a woman aged between 25 and 40 years who has menstruated without pain for years, and who then develops progressive distress with her periods, one thinks of endometriosis, red degeneration of fibroids, and inflammatory mischief. In endometriosis the menstrual rhythm and the quantity and duration of the flow are not consistently altered. When menorrhagia occurs it is generally due to complications within or without the pelvis, and not to the endometriosis. Some of these are thrombosed polypi, submucous fibroids, and degenerating fibroids. In several of my cases of stromatous uterine endometriomata, there was a copious vaginal discharge of a plasma-like fluid that coagulated in the vault of the vagina and came away as a mold. Perforation of the vaginal vault by rectovaginal involvement from the pouch of Douglas is not uncommon. The recognition of this would clinch the diagnosis.

In ovarian endometriosis the disease may range from a few small blood cysts in the ovary without adhesions, to a choked pelvis. In the former types, of course, palpation may reveal nothing. In the moderate cases the ovary is somewhat enlarged, fixed and tender, particularly in the period of menstruation. In the advanced cases the pelvis is filled with masses, and nodules are usually distinctly felt in Douglas' pouch, either by bimanual or by rectovaginal examination. Sterility of years' standing is the rule in married women. But, unfortunately, this does not help the diagnosis in any conclusive way because infections may produce the same result.

Symptoms referable to other organs of the pelvis depend upon extension of the disease to these organs or to their attachments. Symptoms suggesting appendicitis are not uncommon, and those of bowel obstruction are well known. The point of obstruction may be any part of the alimentary tract which normally occupies the pelvis or falls into the pelvis owing to the erect posture of woman. These are the ileum, cecum, and sigmoid flexure.

Rupture of small endometrial cysts into the peritoneal cavity probably occurs in a large number of cases during every menstruation. Rupture of large cysts may present a picture of a general peritonitis. Naturally such cases, being of the major types of the disease, always present the signs of a "choked" pelvis on bimanual examination.

When peritoneal endometriosis has undergone spontaneous cure, pain

of a constant boring character may persist due to the dense adhesions of endometriosis, and may frequently be so severe as to require surgical intervention. However, it must be pointed out that endometriosis, in the vast majority of cases, is a chronic disease, and that chronicity usually allows adhesions to form slowly without tension, so that intraperitoneal endometriosis of the most extensive types, with extensive synechias, may be singularly free from premenstrual pain.

And, on the other hand, many of the more moderate cases may have undergone spontaneous cure of the disease and have ceased to respond to the hormones of menstruation, under which circumstances the menstrual pain would have disappeared. From combinations of the foregoing, one may find active cases with both pre- and menstrual pain, others with only menstrual pain. In the spontaneously cured cases, menstrual pain disappears but the pain of adhesions may be always present and may be seriously incapacitating in the premenstrual phase. In the infiltrating lymphatic type of the disease the parametrial tissues may be widely involved with a marked absence of symptoms. Singularly, endometriosis, even of the most extensive character, rarely produces cachexia, or even any appreciable depreciation of normal health.

In advanced cases the outpouring of blood frequently produces a plastic reactionary peritonitis and closure of the fimbriated ends of the tubes, leading to hematosalpinx, a condition found in 3 per cent of our cases. The condition is usually bilateral. It is rare that puerperal infection complicates endometriosis, owing to the coincident sterility. Other types of infection, such as gonorrhea and tuberculosis, are rarely found in association with endometriosis. These diseases usually cause closure of the tubes, and they would have to follow a "spill" endometriosis.

DIFFERENTIAL DIAGNOSIS

Uterine symmetrical growth, so common in parietal endometriosis, is most frequently confounded with chronic metritis—the large, symmetrical, hard uterus—the so-called fibrosis uteri.

Intraperitoneal endometriosis is difficult to differentiate from the pelvis of chronic inflammation, except that in endometriosis there is usually more definition of pelvic organs on pelvic examination, less leukocytosis, and no increase in the sedimentation rate. In cases of bowel obstruction carcinoma, inflammation and diverticulitis may be readily mistaken for endometriosis.

Stromatous endometrial endometriosis and uterine stromatous endometrioma may be readily diagnosed as sarcomatous growth. The vast majority of cases of intraperitoneal endometriosis are still recognized only at operation. The reasons for this are many: (1) the lack of characteristic symptoms, (2) the numerous slight types of cases, and (3) the

absence of any biologic diagnostic test. Until this last is available I see no prospect of our correct diagnostic percentage increasing, except that the now-recognized frequency of the disease makes the tentative diagnosis of endometriosis one that always presents itself to the surgeon as a common possibility.

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Treatment

A period of conservatism has succeeded the radical treatment of ovarian endometriosis. However, our present knowledge of the different forms of the disease and a better understanding of its various types and vagaries of extension encourage the hope that we will soon be able to attack this disease with more assurance of success in treatment.

PREVENTION

First of all, we know that endometriosis of every kind is a disease which occurs between the ages of 23 and the menopause. I am firmly convinced that it is a disease arising out of neglected function of reproduction. Fibroids are called spinsters' children. They occur chiefly between the age of 25 years and the menopause, and predominantly in the later sexual years. In this they differ from endometriosis, which is more prevalent in the earlier half of the sexual age. Neither of these diseases occurs in the multiparous women who have not had too long an interval between children. But they do occur in multiparae who have long intervals of sterility. I consider endometriosis a product of our civilization, in that late marriages and still later conceptions are the rule, owing chiefly to economic stresses. Ovaries afflicted with endometriosis are, in my opinion, unusually prolific ovaries, filled with ova and with the products of developing, matured, and defective follicles. It would seem that prevention in the susceptible lies in earlier marriages and earlier reproductions. When the conditions which breed the disease arise, sterility has already gone before, and a vicious circle is then put into operation.

So much for an opinion on prevention.

THE CURE OF ENDOMETRIOSIS

When the disease has been diagnosed it is no longer a problem of prevention. It is one of how to cause the least amount of mutilation, not only physical but also functional. For the inception of all types of endometriosis, the ovaries are essential organs, and the ovaries keep up the activity of the disease. Their removal, or the arrest of their function by natural or artificial means, usually causes an abrupt ending to the disease. I write "usually" advisedly, for occasionally removal of the

ovaries does not arrest the disease. In my series there were two cases in whom, though stunned by x-ray, after removal of the ovaries the disease relighted from time to time after a period of seeming quiescence of nearly ten years. Others have reported such occasional cases as if the tendency to infiltrate had gone beyond, and become independent of, the primary agency that sent them upon their abnormal reproduction. Fortunately such cases are relatively rare.

Arrest of ovarian function seems the logical solution of the disease, and that seems to be the only, and generally accepted, solution unless one studies a large number of cases and differentiates between the various types and the degrees of their extension.

In studying treatment, we must keep in mind that all cases of endometriosis take their origin from the endometrium.

ENDOMETRIAL ENDOMETRIOSIS

As noted in previous chapters, this disease may involve only the endometrium, or it may burrow into the uterine musculature, or the primary manifestation may be in the peritoneal cavity by "spill." Extensions into the parametrium may be secondary to uterine parietal endometriosis or secondary to intraperitoneal disease. In each of these cases the approach is different. In some cases we remove the disease without removing the cause. In others we remove the activating agent and leave the disease to regress, owing to lack of continued stimulation.

It is well to recognize that in endometrial endometriosis biopsy may confirm the diagnosis, but in removing the hypertrophic endometrium, which often is very prolific and filled with polypi, we must realize that we have not cured the disease but have merely removed an accessible portion of its effects. From a curettage one cannot demonstrate whether the uterine parietes or the various other susceptible structures have become involved, nor how deeply they have been affected, nor can we determine whether the cause of the endometriosis has ceased to operate. If it has not, the chances are that the endometrium will reproduce its hypertrophic state after curettage, as it has done in a large percentage of my cases.

In cases of endometrial endometriosis the microscopic examination of the curettings shows the true nature of the disease, and further treatment will be indicated by the extent of the disease, as shown by both quantity of tissue taken away by the curette, and by the size or fixation of the uterus.

PARIETAL ENDOMETRIOSIS

In all cases of parietal endometriosis in which the disease is confined to the uterine wall, one has the option of either leaving it alone, or remov-

ing the uterus, or putting the ovarian function out of action by either surgery or rays. However, the matter is not so easy, because in most of these cases the real diagnosis may be known only at biopsy. Most of my cases of uterine parietal endometriosis were operated upon for enlarged uterus, or fibroids, and operation was performed for the relief of these conditions and the complicating endometriosis was not known until biopsy revealed the disease several days after operation. When operating upon a case of uterine parietal endometriosis, the extent and character of the operation must be determined by the spread of the disease. If the uterus alone is involved, its removal without removal of the ovaries will prove sufficient.

Should the disease, however, have spread beyond the uterine wall into the parametrial tissues, then the removal of the uterus is of little service, for the ovarian function may continue to activate the parametrial invasions, and therefore would produce no good effect. Removal of the ovaries, under these circumstances, would of necessity bring about a cessation of the impulse to infiltrate. Parametrial extensions are usually easily recognized during abdominal operations, and therefore one's line of conduct is clearly indicated. Either one does a partial operation, hoping for spontaneous arrest, or one becomes radical. The age of the patient and the character of the disease must determine the issue.

In endometrial endometriosis and in the parietal invasive types one has no means of determining whether the disease is still active or not. There is but one sign that is conclusive. This is found in parietal endometriomata, in which cavitation and other forms of degeneration exist. In the vast majority of cases, however, one cannot determine activity, and therefore one must assume that in the absence of degenerations one is facing active endometriosis. In contrast to this, intraperitoneal endometriosis offers much more evidence upon which to determine activity or nonactivity. These points will be emphasized later. Transparietal extensions, however, are relatively rare, as compared with the incipient intraperitoneal extensions. The uterine musculature, just as in infections, is not a very favorable medium, and therefore offers a relatively effective barrier, except in the very acute or very prolonged duration of the disease. The disease, when confined to the uterine wall, is rarely diagnosed even at operation. The enlargement of the uterus is generally ascribed to chronic metritis, or to the frequently associated fibroids.

VULVAR ENDOMETRIOSIS

In vulvar endometriosis or endometrioma, excision for biopsy is indicated, followed by more extensive surgery or local x-ray treatment. Vaginal endometriosis is very persistent and may be treated by destruc-

tion with the electric cautery, by x-ray of the ovaries, or by the local use of radium.

INTRAPERITONEAL AND PARAMETRIAL ENDOMETRIOSIS

In intraperitoneal and extra-uterine endometriosis, the majority of cases will have come to operation before the character of the disease has been fully ascertained. It then becomes a problem how best to deal with the situation which confronts us.

The main factors which must determine our line of conduct are as follows: (I) The age of the patient, and (II) the extent and character of the disease.

I. The Age of the Patient

Very little hesitation enters into our conduct when we are dealing with patients in the late thirties or early forties. In most cases in these years of their life, if bilaterally affected, there should be no hesitation in recommending total ablation of the ovaries, or abrogation of their function by whatever means we may choose. The two deterrents to this line of conduct are: (1) the effect upon the morale of the patient, by the induction of the symptoms of artificial menopause, and (2) the effect upon sex relations. It has been my experience, and I state this with conviction, that patients, even young ones, who have had widespread intraperitoneal active endometriosis suffer surprisingly little menopausal discomfort from the removal of the ovaries. I have been struck with this phenomenon. I have purposely not given any medication in anticipation, and have been very surprised that symptoms often did not make an appearance. There is no explanation that I can advance. Frequently the symptoms make themselves felt quite a long time after the operation.

As to the effect upon libido, the rule is pretty clear. In virgins the libido may be completely suppressed. In women, on the other hand, who have been married for some years, the removal of the ovaries has, or has not, any effect, depending upon the mental impressions that are formed before or immediately after the operation. It is a generally accepted belief among the laity that libido is an outcome of ovarian function, and that the removal of the organ as a consequence removes sexual desire. This matter has been under study for a long time, and in a review of some 1400 cases of total ablation, there was no appreciable change in 60 per cent, an increase in about 15 per cent, and diminished or total absence in 25 per cent. I have noticed that in this latter group of my patients there were those skeptically inclined, who were not forewarned of the possible degree of surgical mutilation, and who believed that my statements as to the effect were insincere and dictated by a wish to assuage mental distress, but without foundation in facts.

As to the question of sterility, one may be more emphatic. The history of sterility which precedes practically every case of endometriosis, and the very rare association of pregnancy with even the mildest form of endometriosis, give us adequate conviction that this question of sterility has already solved itself by the plans of nature.

II. The Extent and Character of the Disease

The problem of extensive endometriosis in the third decade of life is a serious one. The decision whether to operate—and, having opened the abdomen, how much to do—is one in which lack of experience cannot be compensated for by any other attribute. There are all degrees of acuteness, and chronicity of the disease, and all degrees of extension, both intraperitoneally and parametrially, from a few small peritoneal or ovarian black bead-like cysts without adhesions, to a massive conglomerate disease, or from slight shortening of one broad ligament in parametrial disease to complete infiltration of all the cellular tissues. Inasmuch as (so far) there has been no specific cure discovered for endometriosis, then must we use our best judgment in each individual case. We must weigh each patient's resistance against the disease.

In the mild forms of the disease, consisting of a few cysts, it is my policy to close the abdomen and treat the patient as if for some chronic disease. Rest, nutritious food, climatic treatment are all adjuvants that help to overcome the tendency to development or recurrence. It must be emphasized that endometriotic disease is an expression of endocrine imbalance, and, like all imbalances, there may be mild and virulent types—some of short duration with tendency to recurrences; others essentially chronic and therefore very destructive. We have established in our work that two-thirds of the cases that come to operation are spontaneous cures, that is, cures of the active disease, but not of the symptoms arising out of the impediment to, or destruction of, function in the affected tissues or organs.

It is of the highest importance to determine at operation, or before if possible, whether the disease is active or inactive. Have we any means at our disposal to ascertain in any given case?

1. It was stated elsewhere that when the disease becomes quiescent, retrograde changes occur. The first tissues to be absorbed are the specific cellular elements of endometriosis. The fibrous adhesions remain. These become more organized, more adult and tough. The friability of active endometriosis is therefore lost. The estimation of these ovarian changes requires considerable experience in the surgery of these cases.

2. A much more reliable evidence and one more easily appreciated is the character of the contents of the blood cysts (if any remain). In active cases the contents of the cysts is a black, broken-down blood. As

resolution goes on, and no more menstrual blood is thrown into the cyst contents, the liquid portion of this black fluid is absorbed and the less-liquid—and therefore less easily absorbed—portions remain and become increasingly tarry in consistence. Large cystic contents may remain as tarry remnants for a long period of time. How long, I would not care to venture a guess. But tarriness is an infallible evidence of absorption.

In cases of considerable involvement of both ovaries in young persons, it has been our policy again to be conservative. In many cases, even under misgivings, only the more diseased ovary has been removed. In two such cases the abdomens had to be opened for causes other than endometriosis, and all that remained were a few adhesions and conditions which bespoke a quiescent disease. In no case treated conservatively in this way has it been necessary to reopen owing to the effects of the endometriosis. Some gynecologists consider that retro-displacements of the uterus are the cause of endometriosis by favoring "spill," and think that by correcting the displacement by suspension they will produce a cure of the disease. This is a gross surgical error in judgment, and under no circumstances should suspension be resorted to in the presence of any form of endometriosis.

In elderly women, bordering on the forties, it would seem better to be more radical, because of the near approach of the menopause and the almost negligible chance of a pregnancy.

In very advanced acute endometriosis there is very little left to our option. Radical removal of the ovaries is the only logical solution of a deplorable situation. The youth of the patient should not deflect us from this logical course.

In cases where enucleation of the ovaries presents a major hazard, one can have recourse to deep–x-ray treatment and expect excellent results. In two of my cases of obstruction, the large cyst that lay in the mesentery with bowel stretched over it, and which would have necessitated a resection, responded very promptly to deep x-ray after the cyst had been emptied by suction so as to relieve the obstruction until the treatment by x-ray had its effect.

In major extensions of a parietal endometriosis, whether mixed or stromatous, one has to stop the ovarian function in order to bring about resolution, for it is impossible to remove all traces of the disease by surgical means. But the removal of the sex organs does not always produce relief from symptoms. As stated above, symptoms may arise out of blood tension in cysts, peritonitis due to rupture, and pain due to infiltration of nerve trunks and nerve endings, and tension upon tissues. Removal of the sex organs will relieve the first two, but not necessarily the pain due to nerve involvement, or that due to fibrous tension. The

commonest symptoms arising out of this complication and persisting after cure of the primary disease are backache, and pain radiating down the legs. Fortunately these are generally gradually relieved, because the fibrous-tissue development which accompanies endometriosis is not the result of a local tissue resentment to the invading guest, but is a response to a growth-stimulus, just as are the characteristic cellular elements of endometriosis. And, as in the puerperium the uterine fibrous-tissue hypertrophy of pregnancy may completely disappear—or it may not, but leave a large uterus with a great or small redundancy of fibrous elements—so it is, more or less, in endometriosis.

There are all grades of acuteness and chronicity in endometriotic invasions, and in some the endometriotic elements predominate, while in others the supporting tissues are in the ascendant. We see the same in fibroids and myofibromata. Some are soft, succulent, cellular, and indistinguishable on palpation from pregnancy. Others are hard, fibrous, and avascular. Naturally, spontaneous restitution is easy in the first, but difficult and probably never complete in the latter category. In similar cases of endometriosis the adhesions may be very friable, while in others they are as dense as adult fibrous tissue. These differences of the invading elements and the response of local tissue are beautifully illustrated in certain sections of the afflicted ovaries. In some the ovary is pervaded and practically overwhelmed by the invader, while in others there are both action and reaction, activity and regression, cells in active mitosis and cells throwing out a colloidal environment and presenting all the appearances of preparation for absorption.

It is my conviction that, just as there is a rhythm in nearly all functions, so there is a rhythm in endometriosis, irregular though it may be. By careful history taking one finds a great variability, not only in the endometriotic pains of menstruation, but also in the symptoms of endometriosis when they are permanent. And this question of rhythm brings us to the problem of spontaneous cures. This was described somewhat cursorily in the foregoing pages. I wish to deal with it more fully here.

It was brought forcefully to our attention in the laboratory that only about one-third of the cases of undoubted clinical endometriosis were diagnosable as such with the microscope. This question also arose spontaneously and simultaneously in the mind of my colleague, Dr. A. D. Campbell, gynecologist to the Montreal General Hospital. When discussing endometriosis we found to our mutual astonishment that we had both been vaguely entertaining the same opinions. Since then, more careful attention to these spontaneous cures has firmly convinced me that these cases outnumber those of active endometriosis.

The question at once arises—how do you know that such cases are endometriosis? These points were emphasized in the previous pages, but

they center upon specific characters of endometriosis, which, if recognized, cannot be gainsaid. These are: (1) the characters of the adhesions, (2) the sites of the adhesions, (3) the prolonged persistent subperitoneal stains of blood pigment, and (4) the common accompaniment—peritoneal sclerosis. I consider any combination of these tantamount to an indisputable diagnosis. They have been given in the order of their importance. The type of adhesions is considered the most important differential diagnostic sign in these cases; it was stated that in endometriosis the adhesions are not an agglutination but a fusion of contiguous tissues, and all lines of cleavage are lost, leaving a raw, granular surface which if once experienced is not likely to be forgotten. No other diseases approach the fusion of endometriosis except those of cancer and tuberculosis, and with these endometriosis is not readily confused.

The choice of deep x-ray or radium is not one that can be lightly undertaken. There is a possible, though restricted, field for each, but the choice is not always easy. First of all, in dealing with these destructive agents we are using them in a blind way, that is, without being able to see and estimate the effects. We must keep in mind that we are dealing with two variables: the dosage, and the individual susceptibility. Owing to these factors, there is no great accuracy, much as we might desire it. But there are specific differences between radium and deep x-ray as applied to endometriosis.

Let us deal with the first group of cases—those diagnosed without surgical intervention. It is in just such cases that the use of radium is fraught with a great deal of danger. I have emphasized the difficulty of diagnosis in endometriosis. It is so easy to confuse it with chronic pelvic inflammatory disease, and in such an error of diagnosis the use of radium would be very dangerous, and might lead to great exacerbation of the inflammation and eventuation in pelvic abscess and long convalescence. We have unfortunately seen such cases, not where there was an error in differentiating between endometriosis and inflammation, but in cases where radium was used to arrest hemorrhage in an unrecognized or clinically unrecognizable inflammatory appendage disease. Since endometriosis and inflammatory disease cannot be clinically differentiated with certainty, the danger is always present. In this respect deep x-ray enjoys an advantage. The treatment is longer, the effect can be watched, and treatment can be stopped as soon as untoward signs develop. The x-ray apparatus should be strong enough to produce arrest of function. Too small doses may be stimulating, and so defeat their purpose.

In the types of cases where the abdomen has been opened and, for various reasons, surgical cure cannot be carried out, the use of deep x-ray or radium becomes a matter of less importance, because usually either treatment can be carried out with impunity. My own choice in-

clines to deep x-ray, because of its easy applicability, its freedom from anesthesia, and because, when the patient is given the choice, she will almost invariably choose it in preference to radium. Perhaps her choice is influenced largely by the knowledge among the laity that radium carries with it a suspicion of cancer.

In short, treatment by deep x-ray and radium is effective in all cases of undoubted endometriosis. In any mistaken diagnosis, x-ray offers less chances of danger to the patient, and being given in repeated doses, is more amenable to control.

In conclusion, let me state that unfortunately much the most important issues in life are controversial, and offer a wide field for speculation. This applies with special force to medicine, in which fixed values and dogmatism have little scope. Our judgment of what is right is rooted not only in facts, but largely in opinion, in belief. In this monograph I have tried to bring out clearly what is based upon facts, what upon observation, and that which is largely opinion with a directing influence of anticipatory facts. It is by such speculative forecasts that our knowledge is finally confirmed. It is the bridgework, the scaffolding, which anticipates more solid construction. For example, the opinion that prevention of endometriosis lies in early marriage and early conception, with periodic pregnancies not too frequent but sufficiently frequent to maintain woman's youth and health—this opinion, I repeat, cannot be confirmed except by statistical studies, or by a study of the incidence of endometriosis in nations whose mode of life has not made early marriage and early conception a rarity, and where contraception has not added its quota to intervention. For, let it be well understood that the development of endometriosis, like that of fibroids, is not restricted to the spinster, nor to the nulliparous married woman, but is also the common affliction of women who have had one or more children followed by a long period of sterility, either physical or self-imposed.

My own opinion is that the incidence of late marriage is the result of young men's fear of the future, or the aversion to give up some of the perquisites and prerogatives of single life. Young girls as a whole are eager for matrimony, and are more ready to undertake the sacrifices and compromises that are necessary for mutual adjustment and happiness. It does not seem logical that the preparatory functions of reproduction, which are set in order at 12 or 14 years of age, should continue to repeat themselves monthly purposely in the hope that at some remote time they may be called into production. Confinements are becoming increasingly difficult with the delayed reproduction, and stand in marked contrast to the usually easy labors of the 18- and 20-year-old mothers.

In a study which has been in progress for a considerable period of time to determine the correlated functions of ovaries, uterus, and pla-

centa in the late months of pregnancy, and the correlation of the ovaries and puerperal uterus in the puerperium, our results are far from completion, but, nevertheless, they are sufficiently advanced to draw one very striking conclusion. The ovaries are practically devoid of function from the sixth month of pregnancy. From that time on till the establishment of the first ovulation and first menstruation they appear quiescent. At the onset of the renewal of ovarian function, from eight to twelve ova may ripen spontaneously and synchronously. These large numbers cause a burst of pelvic activity, the uterus becomes larger and softer, and the endometrium takes on new growth.

But the most striking feature of this renewed function is the burst of vitality in the reproductive organs, the uterus and ovaries. The tissues stain with a clearness of definition seldom seen. The cell outlines are as a mosaic in the sharpness of their outline and intercellular spaces; the nuclear chromatin takes on a new hue and sharpness under the influence of hematoxylin; the skein of the nuclear filaments is strikingly outlined, and the whole picture is one of burgeoning vitality. The microscopic fields are as clear and clean as visibility after rain. Nature's rhythm and function have been fulfilled and

"It is spring in Arcady."

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