

A REVIEW OF THE LITERATURE OF OVARIAN TRANSPLANTATION.

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That the removal of healthy tissue is bad surgery has always been an axiom among operators. Many have reproached the gynecologist for being the most marked offender in this regard, and certainly it would seem that there has been some truth in the charge. His excuse for the destruction of tissue has often been that, while it was without doubt healthy in itself, it could subserve no good purpose because the removal of some other portion of the structures functionally interdependent was rendered imperative on account of disease. It has more or less generally become realized, however, that no structure can be looked upon with certainty as having only a single purpose in the economy, and that to remove a portion, or, worse than that, all of an organ in itself healthy, is to sin against the principles of good surgery. While gynecologists have theoretically been in accord with these surgical principles, they have been hampered in their application by a lack of knowledge as to the function of the sexual organs, aside from the mere process of reproduction. Again, in the early days of operative gynecology, not so many years ago, the removal of diseased structures previously considered as beyond the province of the surgeon was looked upon as leaving but little to be desired. Careful study of the after histories of operative cases soon showed however, that although the patient might recover from the immediate operation, she might still be the victim of symptoms of a subjective nature, which made her life miserable. These symptoms were soon rightly attributed to the castration, and conservative gynecology owes its existence to the attempt to escape the results of the operative menopause. It is often however demanded, by the conditions present, that a complete removal of the ovaries be done, and in such cases it has seemed that there was no way to avoid the unfortunate chain of symptoms referred to above. The various attempts which have been made to at least mitigate the severity of the condition by the use of ovarian and other extracts have given, to say the least, no very encouraging results, so that we are forced to the conclusion that in all operations it is most important to leave any portion of the ovaries that appears healthy. Moved by these considerations, a number of men have attempted the solution of the problem of ovarian grafting in order that cases

in whom conservative ovarian surgery is impossible might still have the ovarian influence maintained by a transplanted organ.

As the following review of the literature upon this subject will show, there has been a decided measure of success attending the attempt in so far as it relates to animal experimentation and, further, that its importance aside from its practical bearings is considerable, in as much as it seems to throw light on the subject of the mechanism of the so-called ovarian influence. Its practical bearing, in so far as it relates to the performance of the operation in the human being for the relief or prevention of climacteric symptoms, is a question which will be considered later in this article.

The most complete paper which has appeared is that by Knauer (*Archiv. f. Gynäkol.*, Bd. 60, H. 2, 1900). The author's work as reported in this paper falls into two classes, the first, comprising a series of experiments in which the ovary after removal was grafted into some other situation in the same animal, while in the second class the attempt was made to transplant it from one animal to another.

The technique of the author is given in full and in general was as follows: All operations were carried out under aseptic conditions, the use of antiseptics except alcohol being avoided because of the susceptibility of animals to these agents. In removing the ovaries any squeezing was avoided and great care was taken not to wound them and particularly to avoid partial removal. After removal they were at once implanted in the mesometrium in pockets of peritoneum, or placed under the skin of the abdominal wall between the muscles and the fascia. The author especially calls attention to the fact that he had no operative assistant and thinks that in that fact he was able to avoid a certain percentage of danger from sepsis.

In the first group the author experimented upon twelve animals and an account of one of these experiments is inserted in the present review for the sake of clearness. Series I, experiment 2, rabbit with well-developed genitalia and breasts. Operation July 16, 1895. One ovary transplanted to right mesometrium and the other to the plane between the muscles and fascia of the abdominal wall. Animal killed and examined January 20, 1896. Ovaries

shown by microscope to be functioning, the uterus well developed and the mucous membrane of the cervix and body in a normal condition. In addition to this case, the eighth in the series is of so much interest from the occurrence of pregnancy after the transplantation that it will also be given in brief: Large white rabbit operated upon September 8, 1896, both ovaries being transplanted to the posterior surface of the corresponding mesometrium. On October 3, 1897, the belly was reopened to see the result. At this time the nipples were as well developed as in any healthy adult animal, the vagina was of normal appearance and its mucous membrane was of a rosy red color; the uterine horns were also found well developed. In the right mesometrium was found the transplanted ovary of nearly normal size and containing follicles. The left ovary was also found but it did not contain follicles. Fimbriated ends of the tubes were not atrophic. Belly was again closed and on January 3, 1898, she was delivered of two well-developed young. Was crossed again in June, 1889, but without result which was very likely the fault of the male. On September 29, 1899, three years and three weeks after the transplantation, the animal died and section was performed. Breasts and external genitalia were well developed. Both ovaries found and uterine horns appeared well developed. On the right ovary were four Graffian follicles but the left although larger than in the previous examination did not contain any. Adhesions had formed between the intestines and the right ovary, and the left was cut in two by an adhesive band. The fimbriae of the tubes were free, while the convolutions were bound by adhesions and the situation of the ovaries in the original state was only represented by a faint scar.

Microscopical sections of the ovaries were made and in both the following conditions were found: The free surface was covered with germ epithelium and from it processes of spindle cells ran centrally. The rest of the organ was composed of large cells in a reticulated structure like connective tissue and containing many blood-vessels. The cell bodies were well differentiated and the protoplasm was somewhat granular (fatty). The nearer the edge of the ovary was approached the more follicles were found but they were for the most part the larger ones and no primary follicles were to be found in the organ. The muscle of the uterus was well developed and the mucous membrane was filled with glands. The epithelium was of the cylindrical cell variety.

As the result of Knauer's experimentation the following conclusions may be drawn: (1) That there is no doubt that in the rabbit the ovaries can be

transplanted; (2) that they may be placed on muscle or on the peritoneum; (3) that they will not only be nourished but will functionate (Grigorieff, *Cf. Gynäk.*, 1897, No. 22, S. 663; Rubinstein, *St. Petersburg med. wchenschr.*, 1899, No. 31,) also show that function is not destroyed and the latter author indeed was able to show repeated pregnancy in a case; (4) that pregnancy and parturition are normal and that the young are suckled and are normally developed.

The author considers case eight, the second one reported in this review, to be an exceptional one and says that such a long continuance of function is only to be expected when there has been no great destruction of the organ. A certain portion of the ovary always perishes after transplantation, this, the central part, is for a while deprived of nourishment after the transplantation, as vessels of the adhesions by which the cortex is nourished are not able to reach the internal parts of the organ. The large follicles are as a rule destroyed, the primary follicles and those of middle size being preserved. Ribbert agrees with this statement as he found in the study of the methods of ovarian sustenance after transplantation that as a rule the tunica albuginea, the germinal epithelium and the small follicles were retained while all other parts of the organ involuted. The absorbed ovarian tissue is replaced by connective tissue developed from the peritoneum. Ribbert found new vessels in the ovary only after seven to ten days, while Knauer found them after four days. This difference is probably due to the fact that Ribbert did not surround the transplanted ovaries with peritoneum while Knauer always did. At first after the operation the ovaries become smaller but then again increase in size, the middle sized follicles increasing till they are as large as the largest follicles of the normal ovary. New formation of true ovarian substance may actually occur and depend on the action of the germ epithelium, though this is not proven.

It is to be especially remembered that after transplantation of the ovaries there was not found atrophy of the external or internal genitalia, or breasts. On the other hand castration causes a general atrophy of all the organs just mentioned. These statements are agreed to by Rubinstein, and it is to be borne in mind that the macroscopic appearances are not alone referred to but also the microscopic conditions (the muscles, glands, mucous membrane and gland epithelium were all normal). Knauer discusses the various theories of ovarian influence and inter-relation between the different sexual organs in the light of his experiments and concludes that the idea of Hegar,

(*Die Castration der Frauen*, etc., Leipsic, 1878), that the tubes and uterus were simply the ovarian ducts and that the atrophy occurring after castration was due simply to the interference with the afferent blood, was not tenable. If this, which is also Sutugin's theory (Wratsch, 1885, No. 20), were the true one atrophy would take place after transplantation as well as after castration, as in both the afferent blood paths are severed. The theory of Hofmeier (*Zeitschrift f. Geburt. u. Gynäk.*, Bd. 5) and of Benkiser (*Verhand. d. deutsch. Gesellsch. f. Gynäk.*, Fourth Congress, 1891, S. 286) that castration atrophy results from the ligation of the art. spermat. interna with the resultant diminution in uterine blood supply is also shown to be false as in transplantation it is also tied.

These experiments also show that the opinion held by some that the removal of nervous influences is the cause of the atrophy after castration is false. Among others Buy and Vanderveld held to this opinion believing that the trophic influence was exerted by the help of the nervous system reflexly from the ovaries upon the uterus. This, however, is self-evidently false, as, if true, it would occur as well after transplantation as after castration.

Sokoloff's opinion, that the ovaries contained the nerve centre of uterine nourishment, based upon the occurrence of pregnancy in dogs after section of all spinal and sympathetic nerve paths is for the same reasons impossible, as in transplantation these nerve paths are also severed without consequent atrophy. It is rather interesting to note that Sokoloff remarked the fact that atrophy occurred after castration while if the ovaries were not removed there was no such result.

Knauer concludes therefore, in view of the experiments of others and also of his own work, that it may be accepted as a fact that the influence of the ovary is the necessary factor in the prevention of atrophy, and that it can exert its influence from any part of the body provided only that it be maintained in a condition of health. How this influence is exerted is not as yet known. It must however depend on cell activity and the future may show whether it be a product of cells of the ovule or of the germinal epithelium, or whether the stroma cells have a part in its production. Knauer inclines to the belief in an internal secretion of the ovary and says that the investigations of Goltz (*Pflugers Archiv*, Bd. 9, S. 552), have demonstrated that the relationship between the genitalia and other organs is much more dependent on the blood than on the nerves, since after severing the spinal cord at the level of the first lumbar

vertebra a dog became pregnant and was normally delivered. The breasts were well developed and lactation and suckling followed normally. Goltz himself explained the occurrence of the pregnancy on the supposition that there was a peculiar substance introduced from the ovaries into the blood during heat which occasioned, by its action on the brain, certain reflex influences which later caused the anatomical changes incident to the condition. This is, in essentials, the theory of internal secretion. Goodman as long ago as 1878, advocated this theory (*American Journal of Obstetrics*, Vol. II, 1878). The work of Reinl (*Volkmanns Vortrag*, 243, 1884), and of Von Ott (*Central. f. Gynäk.*, 1890), also gives it support. The good results of ovarian therapy in some cases which have been reported also tend to strengthen the belief that ovarian tissue exerts an influence over the economy distinct from the functions of ovulation. In this connection the researches of Von Loewy and Richter (*Archiv f. Anat. u. Physiologie; Supplem. Bd. Physiol. Abeil.*, S. 174, and also *Berlin klin. wchnschr.*, 1899, No. 50, S. 1895), upon the general body changes incident to removal of the ovaries merit attention. The conclusions arrived at by the authors are as follows: (1) That after castration in the course of time a marked increase of gas interchange occurs, the consumption of oxygen decreasing 20 per cent in ten to fifteen weeks after operation, while the body weight increases; (2) by the use of oophorin after operation this diminution in gas interchange is prevented and the consumption of gas is actually increased beyond the original limits. After withdrawal of this oophorin there is a gradual decline of this increase after a considerable time; (3) in normal not castrated animals the oophorin has no influence on gas interchange; (4) use of the male sexual glands has no effect on the castrated female as regards the interchange of gas. The second series of experiments undertaken by Knauer were as has been said; to see whether ovaries could be transplanted from one animal to another. There were thirteen experiments made on sixteen animals. Remembering the almost uniform success which attended the first series, it is remarkable to note that in spite of the most careful methods and the covering of the ovary with peritoneum all but two cases of this class were unsuccessful. These two successful cases can not be looked upon as being of much value, as in the first, while there was found to be ovarian substance in an active condition at the examination, the time, three weeks, was too short an interval to allow any conclusions to be drawn, though, as Knauer remarked, his experience in the former series led him to believe

that if degeneration and absorption were to take place it would have occurred even before this time. In the second of the two in which ovarian tissue was found at the examination while the period between operation and examination was of sufficient length, one and one-half years, still on microscopic examination no follicles could be found. In this latter case also the breasts and external genitalia were markedly atrophic. Knauer, however, believes from the results in these two cases that the transplantation from one animal to another is possible.

In the paper of Knauer, just discussed, the question of the possibility of ovarian transplantation was considered and the question of the influence exerted on the adult genital organs regarding the prevention of atrophy was taken up. In a paper published by Halban in the *Monatschrift f. Geburt. u. Gynaekol.*, October, 1900, another step is made in the study of the influence of the ovaries by the setting out to prove that these organs are necessary for the development of the uterus and other genitalia in the young. It is well known that after castration of new-born animals there will be no development of the organs of generation. This has been previously proved by Hegar, Kehrer and others, their investigations showing that the uterus either simply remains in an undeveloped state or actually atrophies. With these facts in mind Halban attempts to ascertain whether after transplantation of the ovaries there will be a development of the other reproductive organs. If this be the case there are certainly good grounds for the belief that the trophic centre is not only situated in the ovary but also that the ovarian influence is active through some action of the gland other than a purely nervous one or, in other words, that a secretion of some form or another is the actual means whereby this influence is produced.

In his investigations Halban made a series of experiments but lost several of his animals too soon after to enable him to base any conclusions upon the conditions found. Two animals lived, however, for a period of a year and a half and were then killed, and the results seem to show that a definite and necessary influence for the development of the other organs of reproduction is exerted by the ovary. Of the animals which lived there was one in which castration alone was performed. In this case the post-mortem findings were similar to those reported by various other observers as Glavecke, Kehrer, Benkiser, Eckhardt, Sokoloff and Gottschalk, who have shown that atrophy occurs in human beings after castration and that development ceases in the young, or that even an actual decrease in size occurs as has been

shown by Hegar. These statements were, as has been said, well corroborated by this case in which there was found to be a lack of development of the nipples, breasts, vulva, vagina and uterus, which last was no larger than in the new born. Histologically there was found a marked lack of development of the muscle of the uterus and also of its mucous membrane, there being but few glands to be seen in the latter which were straight and short, with epithelium of poor quality. The breasts showed an almost complete absence of gland tissue and were composed of fat and connective tissue and corresponded to a hypoplasia and not a true atrophy.

As contrasted with this condition seen after castration the following report is of great interest. In the case designated in the series by the letter A, the author after castration transplanted the ovaries to a position under the skin of the abdominal wall. This animal lived and was killed at the same time as the other just reported, a year and a half after the operation. Its uterus was found to correspond in size to that of the normal animal as ascertained by a control test. Absolutely no remains of ovarian tissue could be found at the normal site. The breasts were well developed and the vagina and external genitalia were normal. In the position of the transplanted ovaries was found a body whitish in color containing a macroscopic cyst. The microscopic examination of this body showed the presence of ovarian tissue united above with subcutaneous tissue and below with muscle. Graafian follicles were found in different stages of development containing ova. Corpora lutea were also found, together with germinal epithelium. The ovarian tissue as a whole was sparse and there is no doubt that a considerable portion of the ovary had perished. Attached to the right ovary was found the piece of uterine horn which for anatomical reasons had been removed with it. This had retained its lumen and cubical epithelium, though there had been some flattening of the latter. The uterine glands found in this fragment were in a small measure cystic but the majority were well developed and contained normal epithelium. The musculature was well developed and corresponded to that found in the normal uterus. On the other side of the same ovary was found a piece of the tube which had been removed with it. Its lumen was also normal as was its general appearance and ciliated epithelium was found on the cylindrical cells of its mucous membrane. The breasts were also well developed and were histologically perfect. As explaining the evident partial degeneration of the ovarian tissue the author calls attention to the investigations of Gobell and Ribbert

who showed that the organs are nourished after transplantation by adhesions and that therefore the inner portions are for a time deprived of blood. Bearing in mind the results obtained by the author in the case of the ovaries and portions of uterine horn and tube, it is interesting to remember that transplantation of other organs as the thyroid and lymphatic glands, is likely to occasion the formation of new growths, while other organs, as the kidneys, muscles and nerves undergo involution and that the tracheal and conjunctival mucous membranes lose their specific characteristics. It is to be particularly noted that the uterus, tubes and ovaries not only do not atrophy after transplantation of the latter, but that an actual development occurs corresponding in every way to the normal except as regards a loss of a small portion of ovarian tissue. It is certainly a peculiar circumstance that the surrounding connective tissue does not by closure convert the tubal and uterine horn remnants into cystic sacs. As this was not the case it follows that their secretion must have been absorbed by the lymph spaces in the connective tissue.

The hypoplasia of the breasts reported by Halban, which is the correlative of the atrophic changes observed in these organs after castration, may be due either directly to the loss of the ovarian influence, or its primary cause may be the non-development of the uterus after castration. The latter seems empirically the more probable, on the ground of the close relationship which exists between the breasts and the uterus, as is shown by the changes occurring in the breasts in pregnancy and also the influence exerted by suckling upon uterine contractions. Halban, in conclusion, states his belief that there is a secretion of the ovary which entering the blood not only prevents atrophy of the other sexual organs but also exerts a marked influence on their development.

McCone reports some interesting experiments in the *American Journal of Obstetrics* for August, 1899. In this series of ovarian transplantations pregnancy occurred twice in six cases, and further he showed that the ovary may be successfully transplanted from one species to another by grafting from the bitch to the rabbit. In this experiment a pocket in the mesosalpinx was prepared and also a denuded surface on the omentum for the reception of the ovaries. Three and a half months after the operation, an examination showed that the uterus was in a healthy condition as were also the tubes, while the ovaries were functioning. There was no excess of fat found. From his experience he concludes that both homoplastic and heteroplastic transplantation are possible

and that in the latter the organs transplanted may be either obtained from an animal of the same or different species. If the animals are of the same species pregnancy may be expected in a proportion of the cases while if their species are diverse the post castration atrophic changes will be prevented.

Having now considered the subject from the experimental side it is well to consider the practical bearing of the subject on the daily work of the operator. The most complete paper yet published upon this side of the question is one by Robert T. Morris, in the *Medical Record* of January 1, 1901. In this paper the author details his experience in ovarian grafting in a series of twelve cases. Of these two have been previously reported. The author only bases conclusions upon six of the cases as the remainder were lost sight of too soon to determine whether or not the operation had any lasting influence. All patients menstruated subsequent to operation, but this in those of the cases which escaped from observation may have been simply the bleeding which takes place so often after complete removal of the adnexa. The six cases which were fully studied were operated on for diverse conditions mostly of an inflammatory nature and of such a grade that the ordinary plastic work was impossible. In one case pregnancy was observed after the transplantation, abortion occurring at the third month as in a case reported by Frank. In another case which had never menstruated, because of an infantile condition of the genitalia, menstruation was established after the operation. The site of the grafting was as a rule the broad ligaments, though in his earlier work he chose the mesometrium, the ovary being so implanted that its uncut surface projected into the cavity of the uterus while the cut surface was in contact with the muscle. Three of the cases were homoplastic grafts while the remainder were the recipients of portions of ovaries from other patients, subjected to operation at the same time. The author preserved the ovaries in a basin of salt solution kept at a temperature of 100° by an assistant. He found that the insertion of the ovary into the split broad ligaments in such a way that its cut surface was in contact with the cut surface of the ligament and that the uncut portion of the ovary projected into the peritoneal cavity, gave the best chance of a successful transplantation.

The results noted have been most valuable in the relief or rather avoidance of the menopausal symptoms. While there was only one case of pregnancy reported, the author feels that there are great possibilities in this direction based on the reports of animal experimentation. He is of the opinion that it would

be perhaps possible to treat some of the cases of operative menopause by the transplantation of ovaries from other women on the ground of the experiments of Halban and others, which have shown the great influence which these organs exert on the development of the whole generative system. The bad results noted in his experience have been one case in which the ovary continued to degenerate (a homoplastic case), another in which there was a suspicion of thrombo-phlebitis, and still another in which an extrauterine pregnancy was suspected but not proved, as the woman disappeared before the exact diagnosis could be settled. He believes that extrauterine pregnancy must be reckoned as a possibility in a certain proportion of the cases of transplantation.

A case is also reported by A. Palmer Dudley, in the *Post-Graduate* for April, 1900. The patient was a prostitute in whom a double salpingo-oophorectomy was demanded by the presence of gonorrhoeal pus tubes. At the operation the right ovary was left attached to the ligament until a place had been prepared for its reception by cutting into the uterine wall. A small portion of the wall was removed to give space for the ovary which was then inserted. Sutures closed the uterine wall and cul-de-sac and drainage was used as a precautionary measure.

In this case there had been a great deal of pain during menstruation before the operation. Three weeks after the section the flow occurred at its proper time and showed all the characteristics of the normal period, being moderate in amount and lasting but three days. An examination of this patient two months later showed a uterus normal in size and position, and free from tenderness. No pelvic tenderness could be elicited and the patient reported that she had suffered no pain, no reflex symptoms, no leucorrhoea, that nothing had been expelled from the uterus, that sexual intercourse was not painful and that her subsequent menstruation was without pain and less profuse than before operation.

Another paper which treats of the subject from the practical side is contributed by Glass in the *Medical News* of April 29, 1899. The author only has one case to report but it is interesting, not alone when taken in conjunction with the group of cases reported by others, but also from the fact that implantation was performed through the vagina. The patient was a woman aged thirty-nine, upon whom a double oophorectomy had been performed a couple of years before. She was presenting the symptoms of the menopause with loss of sexual activity and anemia. The uterus was fixed and retroflexed and smaller than normal.

A ventrosuspension was performed. Three days after the above operation a woman aged seventeen was operated upon, and the ovaries were removed in order to prevent the possibility of conception because of vaginal contractions. Vaginal section was then performed on the first case and the ovary of the second was placed in as nearly the normal position on the broad ligament as possible. This was effected by elevating the peritoneum and retention was secured by closure of the wound canal by layers of catgut and packing the vagina. The recovery was normal and a few days later the patient experienced an erotic dream. Sixteen days after operation menstruation occurred and lasted two days. After this there was a period of amenorrhoea for several months and then menses appeared again for three days, the color and consistence being normal and there being no pain. Patient's health greatly improved and her mental equilibrium was regained. She again menstruated in the early part of 1899.

Encouraging as this report may be to those particularly interested in this subject there is certainly a need of caution lest in attempting to relieve one woman from the miseries of the menopause we inadvertently consign another to the identical state. Even if the most enthusiastic admirers of transplantation can make good their claims the operation of transplantation of the ovary from one woman to another will still be one of but little utility because of the rarity of the occasion for its legitimate employment. Without wishing to criticise, it still seems that in the case just reported the castration of a young girl was not actually demanded by the described condition, as Cesarian section offered a means of delivery but little if at all more dangerous than the castration, and, moreover, if in the opinion of the operator the special conditions of the case seemed to demand the prevention of conception, this end could have been reached with certainty by a salpingectomy with removal of a portion of the uterine horns, without subjecting the patient to the symptoms of the operative menopause at her early age.

To sum up the results of the work which has been reported on this subject up to the present time, it may first be stated that transplantation of the ovaries either homo- or hetero-plastically is possible and that pregnancy will follow in a small proportion of cases. Further, it may be authoritatively stated, that there is without doubt an influence inherent in the ovaries beyond the mere process of ovulation which is very important for the development of the genitalia and also for their conservation. Whether this is strictly an internal secretion or not, remains to be proved,

but certainly there seems to be a considerable number of facts pointing to this as the solution. Further than this it is at present not possible to go if one demands actual proofs. Without doubt there is some evidence leading to the belief that the influence of transplanted ovaries may be most beneficial in the prevention of degenerations of the genitalia, but as yet there have been far too few cases reported to formulate any conclusions as to this fact. Finally, all the evidence adduced tends to strengthen the position held by the so-called conservative school that the whole ovary or, if that be impossible, at least a portion of it should be left in all operations in which such conservatism will not tend to subject the patient to a greatly increased danger.

OBSERVATIONS ON THE NATURE AND DIAGNOSIS OF ACUTE OR INFECTIVE ENDOCARDITIS.

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During recent years our ideas concerning the nature of acute endocarditis have undergone considerable modification. Formerly it was customary to distinguish two forms of acute inflammation of the endocardium: the one, a benign, non-infective process, ending in recovery of the patient, though it usually led to permanent damage to the valves affected—the so-called benign, verrucose, or warty endocarditis; the other, a malignant, destructive, infective process running a comparatively short course and leading to death of the patient—the so-called malignant, ulcerative, mycotic, diphtheritic, or infective endocarditis. However, for a long time it had been observed that clinically the differential diagnosis between the two forms of the disease is sometimes attended with considerable difficulty; that the benign process does not always result in recovery of the patient, but that, apparently beginning benignly, it sooner or later assumes malignancy, and leads to death of the patient; that, on the other hand, the malignant form of the disease—from clinical evidence at least—does not always result in death of the patient, but that, losing its malignancy, it sometimes terminates favorably—at least as regards the life of the patient; that the malignant form of the disease sometimes becomes engrafted on the benign form—some cases of so-called recurring endocarditis; that some cases of clinically benign endocarditis are attended by more or less ulceration; that ulceration is common in chronic endocarditis, especially in the so-called atheromatous variety; and that some cases of malignant endocarditis run a fatal course unattended by distinct ulceration. Finally when it was ascertained that all cases of acute endocarditis are associated with, if not due to, bacteria, and that the same bacteria are found in those cases that reveal, as well as in those that do not reveal, ulceration, the necessity for revising and modifying our conceptions of acute endocarditis became apparent.

The most important addition to our knowledge concerning the nature of acute endocarditis during recent years has been the demonstrating of the intimate causal relationship that bacteria bear to the disease. Bacteria have been isolated from the lesions of the heart, from certain associated lesions in other organs, and from the blood. In most cases but a single organism has been found, but in a certain proportion of cases more than one organism has been found. In most cases the organisms found are such as occur in the well-known infective diseases—and this is not surprising when we consider that acute endocarditis usually is secondary to some other disease. In some cases, however, bacteria have been isolated that, as far as we know, are unassociated with other diseases. The bacteria most frequently found are the staphylococcus pyogenes aureus, streptococcus pyogenes, and diplococcus pneumoniae—bacteria that we might expect when we recall that acute endocarditis is most frequently associated with pyococcic infection (pyemia, septicemia, puerperal infection, wound infection, abscesses, osteomyelitis, erysipelas, etc.), croupous pneumonia, meningitis, etc. In other cases, however, the following bacteria have been found: Staphylococcus pyogenes albus, the pneumobacillus of Friedlander, the typhoid bacillus, the tubercle bacillus, the diphtheria bacillus, and the gonococcus. The following bacteria that, as far as

¹ Read at the Fifty-first Annual Meeting of the Medical Society of the State of Pennsylvania, Philadelphia, September 17, 24, 25 and 26, 1901.