HEREDITY IN OVARIAN CYSTOMA: HISTORY OF A MOTHER AND HER TWO DAUGHTERS SUBJECTED TO OVARIOTOMY.

By Professor A. R. Simpson.

Dr Lever, recording observations made in the Midwifery department of Guy's Hospital in *Guy's Hospital Reports* for 1855 (Third Series, i. 79), has a paragraph entitled "An account of seven deaths in one family from Ovarian Disease, showing

the Hereditary Nature of the Malady." The disappointingly brief account reads as follows:—

"There is much diversity of opinion amongst writers whether ovarian disease is hereditary or not. I have not the slightest difficulty in giving my opinion, and emphatically state it is. As certain as I am that malignant disease of the uterus is transferred from generation to generation, so from experience I am convinced that ovarian disease is transmissible. It is true that ovarian mischief more often attacks the unmarried and the sterile, but it is also true that women who have borne children, and have ceased to conceive, may become the victims of this disease. With respect to the exciting causes, I must leave that question to a future communication.

"The following persons were all of one family and allied by blood, and they were all the subjects of ovarian disease:—

M. F., died at the age of 79 years.
M. A., „ 77 „
M. S., „ 48 „
E. S., „ 28 „ inspected by Mr Callaway.
M. D., died at the age of 49 years.
E. D., „ 20 years, operated on unsuccessfully by Mr Key.
M. S., an out-patient at Guy's, and who ere long will die."

In what relation, or with what degree of consanguinity the seven individuals stood to each other is not stated.

Sir J. Y. Simpson, in his *Clinical Lectures on the Diseases of Women* (p. 409), says: "In some few and rare cases ovarian dropsy seems to be hereditary, being developed in one or two females in successive generations of a family. I have known the disease affect three sisters in a family."

Dr Rose writes to *The Lancet* of December 22, 1866, ii. 696, that there had been in Kidderminster Infirmary two sisters, both suffering from ovarian dropsy, who stated that their mother's sister had the same disease.

Olshausen, with characteristic thoroughness, refers to these cases in his *Krankheiten der Ovarian*, 1879, p. 76. Discussing the allegation of Köberle, that where there is a hereditary disposition the disease is bilateral, he states that in two pairs of sisters that had come under his own observation the disease had in all been unilateral.

Von Winckel (*Lehrbuch der Frauenkrankheiten*, 1886, p. 644) speaks of these instances of ovarian cystomata occurring in sisters, and says he had seen such cases.

In Veit's *Handbuch der Gynaekologie*, 1898, iii. 412, Pfannenstiel says: "We still know but little as regards hereditary predisposition to ovarian tumours. The number of cases of ovarian tumours in sisters or other blood relations is indeed strikingly small in comparison to the frequency of ovarian neoplasms in general. Still, a hereditary disposition, such as is generally recognised in regard to cancers, is also here not improbable, if one keeps in view disposition in general, and not merely the disposition to development of special tumours in special organs."

The late Professor Löhlein gave an interesting history (*Monatsschrift für Geburtshilfe und Gynaekologie*, iii. 91, 1896) of three sisters who had all been subjected to ovariotomy for proliferating cystomata of both ovaries. He removed both ovaries in the case of one of the sisters. Köberle performed the same operation on another. In the third sister, Köberle removed a cystic ovary and noted that the other ovary was healthy. Fifteen and a half years later she came under Löhlein's care, when he performed for her a second ovariotomy, her remaining ovary having now degenerated into a cystoma. He could not ascertain that there was any further history in the

family of development of the disease, but considered that some hereditary influence might be at work.

Pozzi, in his *Traité de Gynékologie*, 1897, p. 818, says: "Curious cases have been noted of cysts in the same family among sisters," without recording any instances.

Martin (*Krankheiten de Eierstöcke*, p. 118, 1899), referring to Löhlein's article, says: "Undeniably, too little attention has hitherto been given to this kind of hereditary burden, so that we must confine ourselves to collecting separate observations. I can myself refer to two examples of ovarian neoplasms in sister-pairs; in both instances we had to do with glandular cystomata."

Except for the supposed ovarian cystoma in the aunt of Dr Rose's pair of sisters and the indefinite possibility of varying ranges of generation among Dr Lever's group of seven relatives who died of the disease, all the illustrations of heredity in ovarian neoplasms have been drawn from their development in sisters—usually two, more rarely three, as in Sir James Simpson's and Löhlein's cases, having developed the mischief.

The three patients whom I show to the Society on this occasion have the relationship of mother and two daughters. I give you their histories, taken from the ward record by Dr Barnetson, resident physician, in the order in which they came under observation.

I.—Mrs S., married, æt. 25, ii.-para, admitted 18th November 1899.

Complaint.—Swelling coming down front passage since January 1899.

History.—In January 1899, when three months pregnant, was blown over and fell on her right hip, and for two weeks suffered from an intermittent pain in right groin. In May, noticed something coming down the vagina which proved to be

a rectocele. On 1st August, child was delivered with forceps, a face case. Rectocele did not interfere with birth. No swelling was observed when a vaginal examination was made after labour. On 23rd September was seized with a sudden sharp throbbing pain on right side of abdomen, spreading across to left side—this confined her to bed for four weeks—pain grew less. Three days after severe pain began, had a slight red discharge from front passage lasting two days. In November she ceased nursing, and menstruation returned and lasted five days, attended with some degree of pain.

Pregnancies.—Two, eldest child two years of age, youngest four months old. Both labours were instrumental. The patient nursed the eldest for thirteen months and the youngest for two months.

Physical Examination.—The lower part of the abdomen is distended by a swelling, rising out of the pelvis as a rounded mass, regular in outline, firm in consistence, slightly movable and somewhat sensitive. It reaches to within two inches of the umbilicus. There is percussion dulness over this area, and no bruit is heard.

Per Vaginam.—Posterior wall protrudes on straining. The body of the uterus lies posteriorly, and in front of it is a large elastic swelling continuous with the abdominal tumour and extending to both sides of the pelvis. *Sound* passes in $2\frac{3}{4}$ inches with concavity backwards.

Operation, 22nd November 1899.—On opening abdomen, a brownish-coloured spherical tumour was found on right side of abdomen. After some adhesions of bowel were separated off, the pedicle was seen to be twisted four or five times. Pedicle crushed with Doyen's angiotribe, ligatured with a thin silk thread, and the tumour cut away. The tumour was multilocular, with thick congested walls, and contained quantities of extravasated blood, some of which was organised. The Fallopian tube was greatly distended. As the left ovary was

found to be undergoing cystic degeneration and enlarged till it measured three inches by two, it was removed.

II.—M. M., single, æt. 19, nullipara, admitted 29th November 1902.

Complaint.—Swelling of abdomen for four months. Pain on right side, six weeks.

History.—About four months ago she noticed a swelling on the right side, soft in character, and about size of a fist. Since this time the swelling has gradually increased and extended to the left side. About six weeks ago she experienced for the first time a dull aching pain which lasts for a few hours, then leaves her. She has always enjoyed good health. Her periods are perfectly regular and of usual amount, and do not cause her pain.

Physical Examination.—The swelling extends in rounded form above the umbilicus and tails off into the flanks. There is a distinct thrill on tapping. It feels elastic and is not tender. It extends to the tip of the ensiform cartilage and to the costal margins laterally. Its upper margin is distinct. There is dulness all over on percussion. No bruit heard on auscultation. In anterior and right lateral fornix was a soft bulging which with the bimanual gave a thrill. In the left fornix a resistant body is felt which probably is the body of the uterus. Bimanually the fundus could not be felt.

Operation, 6th December 1902.—Abdomen opened, cyst punctured and an albuminous-looking fluid escaped. There were no adhesions. The broad pedicle was ligatured and the tumour removed. It was formed mainly by one cyst, with some smaller cysts and a healthy portion of the ovary close to the pedicle. As the left ovary was enlarged and cystic, it was at once removed.

III.—Mrs M., married, æt. 60, x.-para, admitted 3rd January 1905.

Complaint.—Great heaviness along lower part of abdomen.

History.—For the last ten years patient has noticed abdomen gradually swelling. For the past five years has not worn stays, as they caused her difficulty in breathing. About one year ago she experienced a bearing down in the lower part of abdomen, more marked on the right side. She also felt her legs weak. She was able to continue her household duties until October 1904, when she laid up for a few days' rest. She continued well after getting up until the end of November, when she was attacked with severe pain, most acute on the right side and extending across the abdomen. The pain continued severe for two days and then gradually went away. The pain was accompanied by vomiting. Ten days ago the patient became "faintish" and had an escape of dark-coloured blood from the vagina. Except for scarlet fever, the patient has had excellent health.

Family History.—Mother died at 74; father died at 64. Has five sisters who present no history of any gynæcological condition, and ten children—five boys and five girls. Of the daughters, the eldest is married, is in good health, and has five children—two boys, three girls. The second is Mrs S., who was the first of our three ovariotomised patients. The third died in childhood. The fourth is our second case of double ovariotomy. The fifth is a healthy unmarried girl of sixteen.

Sexual History.—Menstruation ceased 15 years ago. Never had menorrhagia, metrorrhagia, or dysmenorrhœa. She nursed all her children, and has generally been in the enjoyment of good health.

Physical Examination.—Abdomen is very corpulent, slightly bulging on the right side. The abdomen is very tense on palpation, the muscles being held very tightly. A large tumour, somewhat tense, round in outline and perfectly smooth, and with a distinct fluid thrill, can be felt rising out

of the pelvis and occupying the right iliac and lumbar region and part of the hypochondrium, and extending into the umbilical and hypogastric regions. Percussion showed this area to be dull all over. No bruit was heard.

Per Vaginam.—The patient has a prolapse of the upper half of the posterior wall, which comes down on coughing. The uterus is felt in anterior fornix. Nothing is felt in other fornices. The abdominal tumour is thought to be ovarian, with a long pedicle.

Operation, 17th February 1905.—Tumour punctured. A few omental adhesions were separated. Pedicle, fairly long, clamped by angiotribe and ligatured. The tumour was polycystic ovarian, with one very large cyst and several smaller ones. The fluid which escaped on puncture was at first clear yellow, and then had a greenish tinge. The sediment was decidedly green. The fluid was albuminous. The other ovary was pulled up, and as it presented the usual appearance of a healthy senile ovary, it was not further interfered with.

When the younger of the sisters was admitted to the Infirmary it was recorded in her schedule that her sister had previously been subjected to ovariotomy. It would hardly have been worth while to record their histories as further illustration of heredity in ovarian disease, although I note they are on the side of Köberle as against Olshausen in that in both of the sisters the degeneration was bilateral. The history of the elder sister illustrates, further, how such tumours may co-exist with pregnancy and not awaken suspicion till pedicle-torsion is produced, as it often is, some time after labour. They both confirm the importance of examining the second ovary in all cases of removal of a cystically degenerated gland, for if in either of these two women only the large right-sided tumour had been removed, then there was the likelihood that the fate of the third of the Köberle-Löhlein sisters would have happened to them—they would almost

certainly, after a lapse of years, have come a second time under the ovariotomist's knife.

But whilst the occurrence of ovarian cystoma at an early age in the two sisters might have been noteworthy in relation to the question of the influence of heredity in this disease, their history acquires quite an exceptional value when there is added to it the history of the development of the same disease at an advanced age in their mother. I have not lit upon any other such clear record of its appearance in a mother and her daughters.

There are two considerations which help us to understand the rarity of observations as to heredity in ovarian disease, as compared with the illustrations met with of heredity in cancer.

First, in the transmission of cancer there is the possibility of its descent along two lines, the male and the female. This might suggest the possibility of attenuation of the taint, but assuredly it gives not only more chance of transmission, it also gives the possibility of intensification of the unhappy tendency. Thus I have known of a woman upwards of thirty marrying a husband more than ten years her senior. They had only one son, and the mother having died of cancer of the mamma about the age of sixty, and the father some years later having died of visceral cancer, the son died whilst still young of malignant disease of the testicle and liver. In regard to ovarian cystoma, on the other hand, the possibility of descent can attach only to the maternal predispositions, so that the chances of hereditary transmission are greatly lessened, and there is no possibility of intensification from the other side of the mischievous tendency.

Secondly, it is the germinal glands themselves that are the seat of the disease. Their degeneration involves lessened power of reproduction, so that married women who suffer from ovarian cystoma are barren in the proportion of one in three or four instead of one in eight or nine, as in the general

community. The very development of the disease thus lessens the chances of its descent to another generation, and whilst there is the bare possibility that some other of Mrs M.'s descendants may yet become the subject of an ovarian tumour, so far as concerns those whose history I have recorded, M. M. has no germ left to which she can transmit her malady, and the only other individuals who could possibly share some day in the *damnosa hereditas* would be Mrs S.'s little six and eight year old girls.

Dr Haultain said he had been very interested in the paper. He had never seen a similar case in his experience, and thought it must be a coincidence, and not hereditary. He had seen more cases in fibroid disease. He even preferred to think cancer of uterus was not hereditary. He did not think they could draw any deductions from the case. The paper was exceedingly interesting, and well worthy of being brought before them.

Dr Ballantyne said he was very pleased to have heard the paper. It was a clear case of heredity, and a very interesting one. He himself had found striking instances with regard to the heredity of fibroid and also ovarian tumours in working at antenatal pathology. It would be interesting to find out what exactly was transmitted. It was well known that large families were hereditary, and the daughters were likely to have large families or give birth to twins. In such cases Hellin had shown that the ovaries had large numbers of follicles, a persistence of the fœtal state; certain follicles might become cystic, and this tendency might be transmitted. There was also the interesting relationship of lutein cysts to cancer of the uterus.

The President thought that heredity might have an influence in producing ovarian disease. He had himself operated on three sets of sisters, and also on a girl whose grandmother,

two aunts, and two cousins were all operated on for ovarian tumour; and another with two aunts and two cousins. He remembered those cases, and doubtless there were more instances. The subject was well worthy of research.

Professor Simpson said Dr Haultain was quite justified in taking up the position he did, as every one was free to doubt the influence of heredity in disease, but it was more important to keep a record of observed cases where heredity was possible. He was glad to hear the President mention his cases, and was sure there were many cases of heredity in ovarian disease.