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Abstract

The grafting itself can be successful only when the type of blood between the recipient and the donor of the ovary meets the requirements for blood transfusion. In the case of success in the grafting, a marked activity of the grafted ovary can be observed about two months afterward by the vaginal smear method, but no cyclic phenomenon can be recognized nor biphasic picture suggestive of the progesterone activity in the basal body temperature.

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STUDIES ON HOMOGENOUS GRAFTING OF THE HUMAN OVARY

PART 1. HOMOGENOUS GRAFTING OF THE OVARY TO CASTRATED WOMEN

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In case of grafting exogenous ovary to a young castrated woman its purpose can be fulfilled only when the grafted ovary continues to secrete hormones, because the ovarian functions all depend on the ovary so grafted. Since CROON reported a normal delivery after homogenous grafting of the ovary in 1906, SHAW (1936), KUHN (1943), and PHILLIP (1943) histologically proved successful grafting. There appeared numerous works by UNTERBESGER, SIPPEL as well as those by OHNO and MORIYA in our country. However, there is no detailed report concerning the rate of successful grafting and post-operation functions of the ovary. This seems to be due mainly to the lack of satisfactory method for the determination of the function of the grafted ovary.

The present studies have been undertaken in an attempt to determine whether or not such a grafting would be a success and to find out what factors are responsible if it is successful and also to learn the activity of the grafted ovary, using the vaginal smear method and the determination of the basal body temperature as recommended by BUXTON and WONG, LEWIN, and WATANABE.

MATERIALS AND METHODS

Subjects of the grafting : Ten patients 28 to 43 years old with cervical cancer of the uterus in early stage admitted to the clinic of Obstetrics and Gynecology of the Okayama University Medical School, whose general conditions were good and whose menstrual cycle and the results of follow-up examinations by smear method for one week previous to operation proved to be normal. Namely, those were the patients whose ovaries on both sides had been excised in radical extensive hysterectomy by Okabayashi's method. Besides these, two cases 43 and 44 years old

on whom castration only had been performed but no grafting were selected as the control.

Donors of the ovary : Donors were selected from woman 28 to 43 years of age with cervical cancer in early stage, whose menstrual cycle before operation was normal and those who had been attested to have no special abnormalities on both side ovaries upon laparotomy. The ovary on the side which had shown the corpus luteum was taken out for grafting. Every one of them was negative to Wassermann's test.

The method of grafting : The method of the grafting have been already described in detail by YAGI^{1,2,3}, and I have also divided the removed ovaries into two, and selecting the more suitable one, grafted it with cut-surface on the outside.

The site of grafting : As for the site of graft there are various opinions, but I have selected the rectal muscle which had been first chosen by TUFFIER⁴, followed by YAGI¹, SIPPEL⁵, WAGNER⁶, and BUXTON and WONG⁷, and which presents no handicaps as reported by WATANABE⁸ and HOSAKI.

The method of determining the ovarian function : In judging the function of the grafted ovary histological investigations are carried on hormonal assay of urine, the index of Vakut iodate titer, the basal body temperature, basal metabolism, vaginal smear method, endometrial biopsy, the size of the uterus, menstruation, and subjective symptoms. It is advisable to use as many of these means as possible and at the same time from the standpoint of cyclic nature the observation of the ovarian function should be continuously carried out for a long period of time. Having selected outpatients for this investigation, I employed the basal body temperature and vaginal smear method. For instance there are many studies such as by MATSUMOTO^{10,11}, RUBENSTEIN⁹, and others based on the basal body temperature. DAVIS-ABARBANEL¹², and MARTIN¹³ by endometrial biopsy, DAVIS and FUGO each verified an intimate relationship between the basal body temperature and the progesterational phase by measuring pregnandiol excreted in urine; while LEON and SHNELLER¹⁴ have proved that the corpus luteum hormones are responsible for the increment in high temperature phase of the basal body temperature by recognizing an elevation in the body temperature after progesterone injection to castrated women, and at the same time they contend the existence of the uterus has nothing to do with the temperature raising mechanism.

Concerning the vaginal smear method by series of works¹⁹⁻³¹ starting with those of STOCKARD-PAPANICOLAOU¹⁵, there is no room for doubt that the vaginal body temperature is closely associated with the ovarian func-

tion, especially with excretion of estrogen; and BUXTON-WONG⁷, LEWIN²⁶, and WATANABE⁸ consider this method to be an excellent one for pursuing the function of the grafted ovary.

The method for preparing vaginal smear specimens : Various methods have been tried for extracting vaginal smear depending on the purpose for which it is used^{19,21,22,27}. Following WATANABE's method as used in the case of auto-transplantation, I have had the patient prepare clean cotton applicator the size of the tip of thumb at her home and by having her put it deep into the previously cleaned vagina and taking smear on object glass with this applicator which she turns once around before taking out, and have the smear fixed in 95% alcohol before drying, and then let it dry. Smear specimens are prepared in this manner every other day for one month, and these are gathered monthly and in turn placed again in 95% alcohol, and are stained by Papanicolaou E. A. 36-staining²⁸ and some are stained by hematoxilin-eosin staining.

The calculation of cornified cells : Although there are many classifications of the vaginal epithelial cells such as by PAPANICOLAOU²⁹, MURRAY²³ and ISHIKAWA¹⁶, I have used Ishikawa's classification, and classifying those under the cells with dense nuclei as cornified cells, their percentage is taken as the cornification index. Namely, by counting 100 epithelial cells each from four different parts of five specimens to the total of 400 and taking the percentage of cornified cells in each specimen as the cornification index, a graphical representation is made after MURRAY de ALLENDE²³.

OBSERVATIONS AND RESULTS

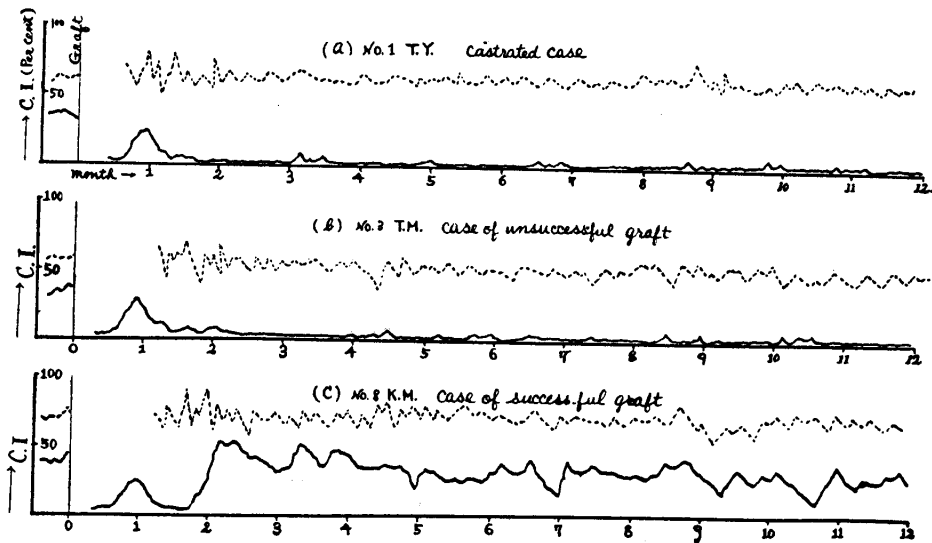
These experimental subjects are divided into three separate groups for observation. Namely, the first is the control consisting of two castrated women without grafting as shown in Table 1. The second group is consisted of five cases whose blood type do not conform to the requirements of blood transfusion between the recipient and the donor of the ovary; and the third consists of 5 cases whose blood type conforms to the above mentioned conditions of blood transfusion. The results of observations are presented in Table 1, and the details of which are as follows (see Fig. 1).

On the castrated women : Although there are some fluctuations in the curve of the basal body temperature after operation, in about the third post-operative month when mentally and physiologically the unstable stage appears to have passed, the curve assumes its stability and there-

Table 1. Recipient, Donor, and the Experimental Results

	Recipient				Donor				Syat. Menopa	Basal body temp.	V. smear f. Hormonal activity	Result	
	Age	Pa-ra	Blood type	Diag.	Age	Pa-ra	Blood type	Diag.					
Group 1 (control)	1 T. Y.	43	8×	B	P. K. I				Mode-rate do.	Mono-phasic do.	Inactive do.	Cast-rated do.	
	2 T. H.	44	0×	B	P. K. I								
Group 2	3 T. M.	35	1×	B	P. K. II	43	4×	A	P. K. I	(-)	do.	do.	Unsuccessful do.
	4 N. M.	43	4×	A	P. K. I	35	1×	B	P. K. II	Light	do.	do.	do.
	5 Y. N.	37	5×	O	P. K. I	43	10×	A	P. K. I	do.	do.	do.	do.
	6 A. K.	28	3×	O	P. K. I	32	5×	B	P. K. II	do.	do.	do.	do.
	7 S. Y.	36	6×	O	P. K. II	36	2×	A	P. K. I	do.	do.	do.	do.
Group 3	8 K. M.	32	5×	B	P. K. II	28	3×	O	P. K. II	(-)	do.	Active from 60 d.	Success
	9 I. K.	40	3×	A	P. K. II	42	3×	A	P. K. I	(-)	do.	Active from 50 d.	do.
	10 H. O.	41	7×	A	P. K. I	46	2×	O	P. K. I	Light	Irregular	Active from 60 d.	do.
	11 Y. T.	43	10×	A	P. K. I	37	5×	O	P. K. I	(-)	Mono-phasic do.	Active from 70 d.	do.
	12 T. I.	40	4×	B	P. K. II	38	3×	B	P. K. II	(-)		Active from 40 d.	do.

Fig. 1 Graphic representation of the basal body temperature and the cornification index



after it shows hardly any change (Fig. 1a).

For the general changes in the picture of vaginal smear findings, examinations are started one week after operation. The period up to the commencement of postoperative irradiation therapy is characterized by the lowering of cornification and the appearance of parabasal cells. In the same period the cytoplasm and nucleus degenerate so that along with a decrease in stainability the specimen as a whole presents an unclean appearance; and an increase in leucocytes can be observed as well. The radio active therapy is given for 12 days from the 21st day after operation, and during this period with the appearance of basal vaginal epithelium turns acidophilic and irradiation degeneration of cytoplasm can be recognized, being stained rather light and clear with an increase still in leucocytes. After the completion of the radio active therapy, irradiation degeneration gradually recedes, and the subsurface and basal cells increase in number, being generally poor in stainability and losing basophilic tendency but they still show the increase in leucocytes. In other words, this is a picture of atrophy, that is, the so-called colpitis is often encountered. Such conditions persist up to one year after the operation.

The cornification-index curve tends to fall markedly during the period between a week after operation and the initiation of irradiation, but rising rapidly with start of the therapy, it again commences to fall about the time the therapy is over, and by 10 to 15 days after cessation of irradiation the cornification index almost reaches zero. Thereafter the condition is maintained almost constant, except for temporary and irregular appearance of cornified cells, which is not so significant (Fig. 1 a). Menopausal symptoms of intermediate degree were observed in both of the control.

In five cases with unsuitable blood type for blood transfusion between the recipient and the donor of the ovary: The curve of the basal body temperature proved to be almost the same as that of group 1, and no biphasic suggestive of hormonal activity of the corpus luteum could be recognized (Fig. 1 b). Changes in general findings on the vaginal smear took almost the same course as that of group 1; and likewise the curve of the cornification index moved within the same range, maintaining almost zero for one year with transient and irregular appearance of cornified cells as was the case in the group 1 (Fig. 1 b).

Menopausal symptoms in this group were intermediate in degree in four cases and hardly any in one case. As is clear from these, most findings being almost identical with those in group 1, it is assumed that the grafting in the group 2 turned out as a failure (Fig. 1).

On the five cases whose blood type agreed with the conditions for blood

transfusion between the recipient and the donor of the ovary: The curve of the basal body temperature in this group, showing no marked change, was identical with that in groups 1 and 2. Therefore, no biphasic indicative of hormonal activity of the corpus luteum could be detected (Fig. 1 c).

General changes of vaginal findings during the period from the operation to the completion of irradiation therapy do not differ greatly from those in groups 1 and 2. About 15 days after cessation of irradiation these approach to those of normal vaginal smears, but staining for the deformation of epithelial cells and clarity of the specimen surface are still low. An increase in erythrocytes can be seen as well, but no cyclic changes in the general picture can be discernible. However, in comparison with groups 1 and 2, the vaginal smears were far clearer and nearer to those of the normal, and showing no marked atrophic findings, they indicated the activity of estrogen distinctly.

Changes in the cornification index chart during the period up to the completion of irradiation were almost identical with those in the groups 1 and 2; lowering temporarily after the cessation of irradiation, the curve about 60 days after again clearly shows the cornification index suggestive of the estrogen activity. Namely, none in this group showed a marked lowering as observable in two groups though there was a light fluctuation and the stage where it remained standstill as shown in Figure 1; and even after one year still the curve indicative of estrogen activity could be observed. However, it was not so marked as in the case of women with normal cycle nor cyclic phase could be detected (Fig. 1 c). Slight menopausal symptoms were recognized in one case.

From these it is assumed that the estrogen activity lasted from about 60 days after operation for one year; and therefore, it is believed that grafting was successful. However, this activity was not so remarkable as that in the normal women, and no progesteron activity due to the same cyclic changes and the basal body temperature could be recognized.

COMMENT

Since CROON in 1906 first performed homogenous grafting to the castrated women, there are many follow-up reports by UNTERBERGER³⁰, SIPPEL³¹, KUHN³³, TUFFIER⁴, MARTIN^{34,35}, ESTS³⁶, SOLOMONS³⁷, ZONDECK³⁸, BLAIR³⁹, NORRIS, GRAVES⁴⁰, BICKENBACH⁴¹, COUNSELLER⁴², and in Japan by OHNO, MORIYA, SHIRAIISHI-YOKO-O, etc. However, these reports are not so uniform.

Concerning this point the lack in any satisfactory method of determin-

ing definitely success in grafting may be pointed out as has already been mentioned by OGAWA⁴⁶ and WATANABE⁸. Namely, the determination in the past has mainly depended on subjective symptoms and menstruation; and ZONDECK³⁸ alone applied the basal metabolism for it, while MORIYA⁴⁴ the estimation of urinary estrogen. I believe these are not adequate enough for exploring the function of the grafted ovary, and especially what is considered to be indispensable in pursuit of the cyclic ovarian function, i. e. prolonged examinations, is overlooked. Realizing this point to be of importance, BUXTON and WONG⁷, and LEWIN²⁶, have recently recommended the basal body temperature, estrogen content in urine, vaginal smear, menstruation, and subjective symptoms for the re-examination of the grafted ovary, and the vaginal smear method to be the most excellent one for the pursuit of the grafted ovarian function, in particular; and WATANABE likewise is of the same opinion.

On the other hand, OHNO and SIPPEL brought up the problem of grafting and the Type of blood; and SCHWARZMAN, by his detailed experiments, calls attention to agglutinin in the ovarian tissue; and OHNO also entertains the similar idea. MANDELSTAMM⁴⁸ likewise from this standpoint has been attempting to clarify the problem relative to grafting and the type of blood by devising his own simple method. The failure of group 2 in my experiment in all probability is attributable to the fact that agglutinin in the tissue of the transplanted ovary, being agglutinated by serum agglutinin, early has lost power to live, thus resulting in failure. On applying this method, it seems necessary not to neglect the problem of the type of blood.

Moreover, from the standpoint of the basal body temperature although monophase in the successful grafting contradicts the progesterone activity, TUFFIER⁷ and KUHN³³ histologically concede the existence of the corpus luteum; and COOPERMANN⁴⁹ states that the basal body temperature presents an irregular type when the corpus luteum is formed under the ovarian functional insufficiency or without ovulation. In view of these even in my experiment it may be said that the findings were not such as to completely deny the progesterone activity and yet the activity itself was not so remarkable as to show biphasic.

OHNO who has taken menstruation as the criterion for the time of the commencement of activity in the grafted ovary, observed the occurrence of menstruation early; and KUHN³³ and BUXTON-WONG⁷ state the time is about 2—3 months after the operation; BLAIR³⁹ thinks it requires a considerable length of time for the regeneration of blood vessels in the grafted ovary to be completed and before the ovary begins to function;

and MORIYA observed the discharged progesterone early in urine by quantitative analysis. In my study with the vaginal smear method the remarkable activity of the grafted ovary was observed about two months after operation, and the results were more or less identical with those of WATANABE in his autotransplantation.

Concerning the duration of the grafted ovarian function there are MORRIS' case of delivery 4 years after grafting, and those of OHNO, MARTIN, KUHN, and BUXTON-WONG with the duration of 2 to 8 years. In my experience I can see the marked activity still one year after grafting.

SUMMARY

The grafting itself can be successful only when the type of blood between the recipient and the donor of the ovary meets the requirements for blood transfusion. In the case of success in the grafting, a marked activity of the grafted ovary can be observed about two months afterward by the vaginal smear method, but no cyclic phenomenon can be recognized nor biphasic picture suggestive of the progesterone activity in the basal body temperature.

For bibliography refer to References in Part 2.