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Abstract

Homogenous grafting of the ovary to patients of ovarian dysfunction all proved to be effective, but the degree of the effectiveness and the time of appearance of effect of the grafting were not fixed. Moreover, there was no relationship between the effectiveness of grafting and the type of blood. If the various conditions at the time of grafting are taken into· consideration as above mentioned, this operation utilizing as it does the ovary usually discarded at operation may be expected to bring about quite a satisfactory therapeutic result.

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STUDIES ON HOMOGENOUS GRAFTING OF THE HUMAN OVARY

PART 2. HOMOGENOUS GRAFTING OF THE OVARY TO THE PATIENT WITH DYSFUNCTION OF THE OVARY

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There are many reports concerning the homogenous grafting of the ovary to the women with dysfunction of the ovary such as those by MORRIS, UNTERBERGER, GUNSTER, SCHULTZE, and OHNO. Differing from the case of grafting to the castrated women, in this case we are after the cure of peculiar ovarian function by grafting. Because success or failure of grafting itself was described in Part 1, in the present paper an attempt has been made to evaluate the efficacy of grafting by pursuing the effect for a long period of time continuously with the use of as many examination methods as possible.

MATERIALS AND METHODS

Subjects receiving grafting : Homogenous grafting of the ovary was performed on 16 cases who first had been diagnosed as dysfunction of the ovary and finally diagnosed definitely after follow-up examinations for two months by various methods of examination mentioned in the following manners (Table 2).

Donors of the ovary : Ovaries were selected exactly in the same manner as in Part 1 from women of 28 to 45 years old.

The method of grafting : In principle the method of grafting was the same as used in Part 1, except for a larger ovary which was sliced into thin section before grafting. Namely, immediately on removing the ovary is immersed in penicilin solution and is treated in the same manner as previously reported and is grafted after local anesthesia. The patient is made to rest for 5 to 8 hours before going home and having her recuperate at rest for five days, strings are removed a week afterward.

The site of grafting : Following the examples of YAGI, BUXTON-

WONG, and SIPPEL, the rectal muscle has been selected for the site of grafting.

The methods of determination : As reported in Part 1, methods conventionally used in the determination are menstruation, the length of uterine cavity, subjective symptoms, findings of the endometrium biopsy, vaginal smear method, estimation of urinary hormones, urinary VAKAT iodate index, the basal metabolism, basal body temperature, and histological examinations. Each of these has its advantage and disadvantage, but since histological examination of the ovary runs counter to the purpose of the present experiment, and as the determination of urinary hormones of outpatients is difficult to carry on continuously for a long time, these two were omitted and the other seven methods were employed. Briefly speaking of examination methods, no special mention seems to be necessary for menstruation, the length of uterine cavity and subjective symptoms, and as for the smear method it has been applied in the same manner as mentioned in Part 1. Concerning the basal body temperature already mention was made, but in order to solve the problem presented in the case where the basal body temperature and the ovarian or the progesterone cycle did not coincide with one another as pointed out by WHITLAW[50], and WATANABE[51], findings on the endometrium biopsy were referred to. Extirpation of the endometrium is conducted at high temperature in the case of the basal body temperature in biphase, while in the case the basal body temperature is in monophase, it is done at intervals of 15 to 20 days in the following manner : with a small modified form of Meigs curet in order to avoid this manipulation from affecting the ovarian function small pieces of endometrium are extirpated from three places, the anterior and the posterior wall of the uterine cavity, and the site of cancer, without enlarging the cervical canal. These samples are histologically examined, and those showing identical secretion picture in the range of $\pm$ 3 days by dating biopsy of WATANABE[52,53] are taken as normal while others are considered to be insufficient.

With the use of Knipping apparatus after Saito's method the basal metabolism is measured every two weeks, and the basal body temperature in biphase is measured both at high and low temperature ; and likewise ovarian function has been determined all by his method.

OBSERVATION AND RESULTS

In the follow-up examinations carried on continuously for two months before and about six months after operation to the total of eight months

by the methods mentioned above it as been found that the grafting proves to be efficacious in all as shown in Tables 2 and 3, but the results are not by any means uniform, varying as they do under various given conditions of an individual case.

Studying from the standpoint of examination method, in the case menstruation examination despite a good effect of grafting discernible of the case without menstruation some occasionally demonstrated no menses for a short period of time after grafting, proving the menstruation to be an inadequate method for a precise determination. Although menses were observed in all the 8 cases without menstruation to start with, every one of them revealed merely mense-like bleeding 3 to 6 months after grafting as shown in Tables 3 and 4. As for the subjective symptom all the cases complained somewhat prior to operation, but within one month of operation they were either completely cured or ameliorated. However, in this instance one can not overlook psychological factors of the grafting on the patient.

Next turning to the length of the uterine cavity, of the patients with dysfunction of the ovary quite a few had normal-size ovary, namely,. 8 cases ; and even in the cases showing an insufficient growth or atrophy of the uterus, the enlargement of the uterus itself seems to occur as a secondary phenomenon to the recovery of ovarian function. Therefore, though showing a certain degree of the enlargement, it occurred invariably 3 to 5 months after operation and only to a slight extent. The vaginal smear, as emphasized by LEWIN, BUXTON-WONG, and WATANABE, has been found to reflect the ovarian function most sensitively (Figs. 3, 4, 5), and even by this method alone it seems possible to know the total alteration of the ovarian function.

There was not one case that showed the typical biphase in the basal body temperature prior to operation. After grafting, however, the return to normal conditions such as typical or atypical biphase, in the patients indicating a tendency rather slightly toward dysfunction, was observable, and in those apparently advanced cases the stability of the fluctuation curve could only be discerned but no biphase.

In the determination of the basal metabolism after SAITO's[54] method in our clinic, although it seems to have been possible to grasp rather well the changes in the ovarian function, it yields unstable values during the postoperative period. This is apparently due to the stress, grafting, which affects the thyroid gland as well as the vegetative nerve system.

As for the finding on the endometrial biopsy, in the proliferation

phase it more or less parallels with the cornification index, and all the cases whose basal body temperature is in biphase present secretion type, while those in typical biphase the finding mostly coincides with dating diagnosis and those in atypical biphase most of findings do not coincide with the dating diagnosis. Those in monophase and having menstruation present a picture less advanced than that of dating diagnosis, namely, a secretion type indicating insufficient growth of the ovary.

In reviewing these results individually, it seems that often there is a certain degree of variation in dysfunction according to different method employed. Therefore, in the consideration of the degree of dysfunction in the ovary it seems that over-all judgement of entire results obtained by various methods needs to be taken into consideration. Looking over the extent of dysfunction prior to operation and the course of recovery of the grafted ovary from this view-point, they can be divided into three grades according to the extent of effectiveness of grafting (Figs. 2, 3, 4).

The first grade effectiveness : Those that recovered the ovarian function to the extent almost normal from the cycle immediately after grafting and who had repeated almost normal cycles for six months (Fig. 2).

The second grade effectiveness : Those who had shown a certain degree of effectiveness immediately after grafting but required several months to return to the normal level ; or those whose function returned to relatively normal but still remained unstable ; or those who had shown no effect after grafting but about two months later began to show some effect and returned to the normal level by six months later (Fig. 3).

The third grade effectiveness : Those who seemed to get no effect after grafting began to show some improvement of the function about third month and though they continued to improve but did not reach the normal level by six months afterward (Fig. 4).

Effects of grafting to the various degrees were observable in every case as shown in Table 2 ; but those who were considered to have dysfunction in advanced stage showed the third grade effectiveness and those with slight dysfunction tended to show the first grade effectiveness. Moreover, those whose function recovered back to the normal level maintained that state up to six months later ; and even in those who had shown the third grade effectiveness the effect of grafting, improving gradually up to six months later, has never been found to lose its effectiveness on the way to recovery, that is, to revert back again to a highly dysfunctioning state.

On the other hand, with a view to study the relationship between the type of blood and the effectiveness of grafting, all the 16 cases were

Table 2.

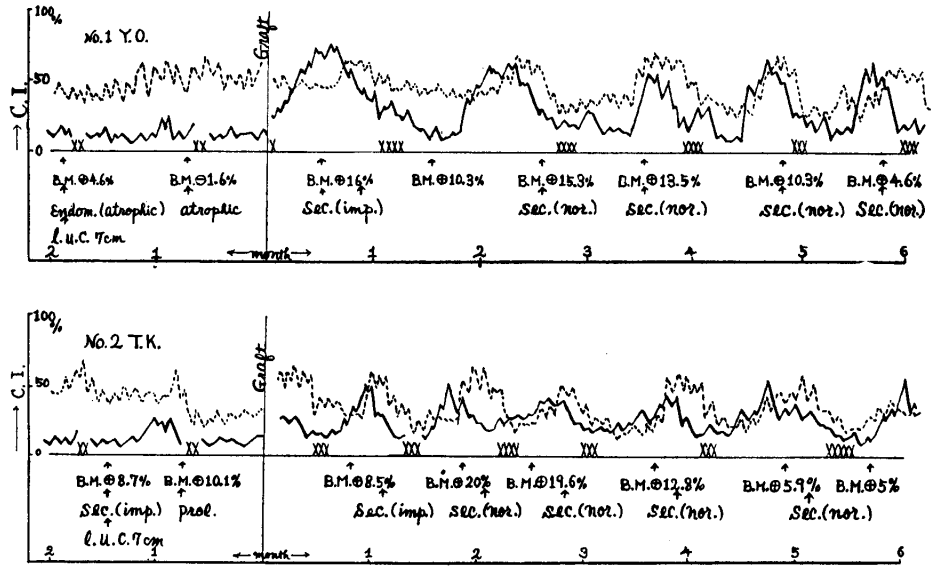
No.	Name	Recipient					Donor				Effect
		Age	Para	Blood type	History	Degree of dysfunction	Age	Para	Blood type	Diagnosis	
1	Y. N.	26	0×	O	hypomenorrhea, intermittent menses dysmenorrhea, essential sterility	light	38	4×	O	cancer St. I	1st grade
2	T. K.	28	1×	B	hypomenorrhea, irregular menses (for the past 3 yrs)	do.	41	7×	A	cancer St. II	do.
3	M. G.	28	1×	B	intermittent menses (once in every 3—4 months, for the past 3 yrs), dysmenorrhea	do.	28	3×	O	cancer St. II	do.
4	S. T.	33	5×	B	hypomenorrhea (very small amount of menses for two day, starting 5 mos previously marked headache, dizziness, humming in ear	do.	45	9×	AB	cancer St. II	do.
5	F. B.	25	0×	A	hypomenorrhea (from 3 yrs previously, menses once in every 4 mos), sterile for 13 yrs after marriage, dysmenorrhea	do.	37	8×	O	erosion endomet.	do.
6	N. K.	24	0×	A	hypomenorrhea (once every 3—4 mos), dysmenorrhea, sterile for 3 yrs after marriage	do.	32	3×	B	cancer St. I	do.
7	A. F.	24	0×	O	hypomenorrhea (menses twice a year), marked headache and nausea	interm.	41	7×	O	cancer St. II	2nd grade
8	T. H.	30	2×	A	hypomenorrhea (about twice a year), sterile for 7 yrs	do.	37	8×	B	erosion endomet.	do.
9	S. K.	37	2×	A	menses stopped ten mos previouly, headache, poor memory, adiposis	do.	42	5×	A	cancer St. I	do.
10	T. H.	37	0×	O	no menses for the past 4 yrs, when she had menstruation, it was difficult m.	do.	41	1×	B	cancer St. I	do.
11	Y. M.	25	0×	A	no menses for past 6 mos., hypomenorrhea, sterile (3 yrs since marriage)	do.	42	5×	A	uterine myoma	do.
12	N. K.	25	2×	A	no menses for the past 2 yrs.	do.	42	3×	A	cancer early St.	do.
13	Y. N.	30	0×	B	no menses for the past 4 yrs. received treatment both before and after that period, without any effect.	high	41	1×	B	cancer early St.	3rd grade
14	K. M.	31	0×	O	menses stopped 11 mos ago, sterile (7 yrs since marriage)	do.	42	3×	B	do.	do.
15	I. N.	31	1×	B	no menses ever since 25 yrs old marked stiff neck	do.	32	5×	B	do.	do.
16	F. T.	29	0×	A	no menses since she was 25 yrs old	do.	42	2×	AB	cancer St. II	do.

Table. 3

		Name	Subjective symptoms	Menstruation
Prior to operation	No. 3	M. T.	systemic ennervation	hypomenorrhea, intermittent menses, dymenorrhea
	No. 4	S. T.	headache, ringing ear	hypomenorrhea (a small amount for 2 days)
	No. 5	F. B.	do.	menses once every 4 mos., dysmenorrhea
	No. 6	N. K.	headache,	menses once evry 3—4 mos., dysmenorrhea
	No. 9	S. K.	headache hypomnesia	menses stopped ten mos. previously
	No. 10	T. H.	headache	menses stopped 4 yrs. ago
	No. 11	Y. N.	diziness	menses stopped 6 mos. ago, hypomenorrhea
	No. 12	M. K.	stiff neck	menses stopped 4 yrs. ago
	No. 13	Y. N.	do.	menses stopped 4 yrs. ago
	No. 14	K. M.	heaviness of head	do.
For 3 mos after operation	No. 3	M. G.	(−)	menst. cycle 40 days, amount normal
	No. 4	S. T.	(−)	do. , amout medium
	No. 5	F. B.	(−)	menst. cycle 30—40, no dysmenorrhea
	No. 6	N. K.	(−)	do. , amount normal, no dysmenorrhea
	No. 9	S. K.	(−)	a small amount of menses once a month
	No. 10	T. H.	(−)	an intermediate amount of menses to two days and a very small amount for another day
	No. 11	Y. N.	(−)	a very small amount of menses once in a cycle
	No. 12	M. K.	(−)	none
	No. 13	Y. N.	(−)	none
	No. 14	K. M.	(−)	none
For 6 mos after operation	No. 3	N. G.	(−)	menst. cycle 35 days, normal amount
	No. 4	S. T.	(−)	normal
	No. 5	F. B.	(−)	do.
	No. 6	N. K.	(−)	do.
	No. 9	S. K.	(−)	a small amount for one day
	No. 10	T. H.	(−)	an intermediate amount for 3 days
	No. 11	Y. M.	(−)	a small amount for one day
	No. 12	H. K.	(−)	do.
	No. 13	Y. N.	(−)	a very small amount for a day
	No. 14	K. M.	(−)	for a days in a small amount

Basal body temperature	Vaginal smear (cornification index)	Basal metabolism	Size of uterus	Finding of the endometrium
monophase (irregular)	non-cyclic (20—30%)	(+)20—27%	7cm	secretion stage (insufficient)
atypical biphase	cyclic (+) (max. 50%)	(+) 13%	7cm	do.
do.	cyclic (−) (max. 35%)	(+)15—20%	6cm	do.
do.	cyclic (−) (max. 41%)	(+) 25%	6.2cm	do.
monophase	cyclic (max. 26%)	(−) 5.8%	5.6cm	proliferation stage (slight atrophy)
irregular type	cyclic (−) (max. 32%)	(+) 30%	5.8cm	do.
do.	cyclic (±) (max. 32%)	(+) 8—10%	5.4cm	complete atrophy
do.	cyclic (±) (max. 29%)	(+)24—31%	6cm	do.
monophase	cyclic (−) (max. 20%)	(+) 15%	5.0cm	do.
do.	cyclic (−) (max. 32%)	(+) 18%	7cm	atrophy intermediate
typical biphase	cyclic (+) ovulation p. 70%	(+) 12%	7cm	normal (secretion stage)
do.	do.	(+) 5%	7cm	do.
do.	cyclic (+) ovulation p. 72%	(+) 17%	6.2cm	do.
do.	cyclic (+) (max. 48%)	(+) 18%	6.4cm	do.
monophase	cyclic (±) (max. 38%)	(+) 18%	5.7cm	insufficient (secret stage)
atypical biphase	cyclic (+) (max. 50%)	(+) 17%	6.0cm	do.
typical biphase	cyclic (+) (max. 30%)	(+) 22%	5.5cm	slight atrophy secretion insuffi.
do.	cyclic (+) (max. 45%)	(+) 27%	6.3cm	slight atrophy no secretion
monophase	cyclic (+) (max. 58%)	(+) 24%	5.2cm	do.
do.	cyclic (−) (max. 32%)	(+) 8.1%	7cm	do.
typical biphase	cycle (+) ovulation 55%	(+) 12%	7cm	secretion period normal
do.	do. 57%	(+) 3.2%	7cm	do.
do.	do. 62%	(+) 13%	6.4cm	do.
do.	do. 46%	(+) 12%	6.5cm	do.
atypical biphase	do. 42%	(+) 20%	5.8cm	secretion period insufficient
do.	do. 55%	(+) 12%	6.2cm	do.
typical biphase	do. 43%	(+) 20%	5.6cm	slight atropy secretion insufficient
do.	do. 38%	(+) 24%	6.4cm	do.
atypical biphase	do. 46%	(+) 26%	5.3cm	do.
biphase	do. 65%	(+) 16%	7cm	

Fig. 2. The first grade effectiveness



X = Menstruation ····· Basal body temperature

——— Cornification index (C. I.) Sec. = Secretory type of the endometrium

Prol. = Proliferative type of the endometrium

nor. = Normal, imp. = Imperfect type

l. u. c. = Length of the uterine cavity

Fig. 3. The second grade effectiveness

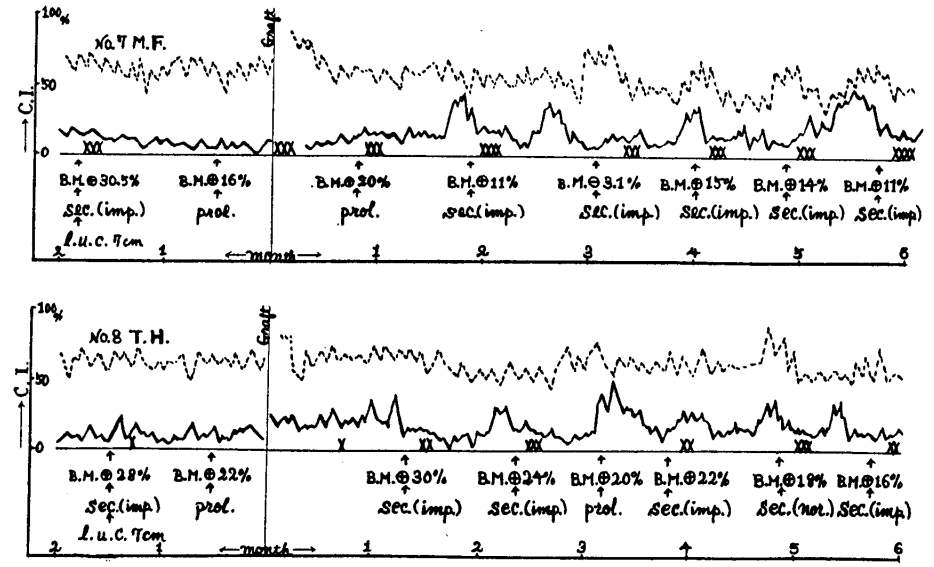
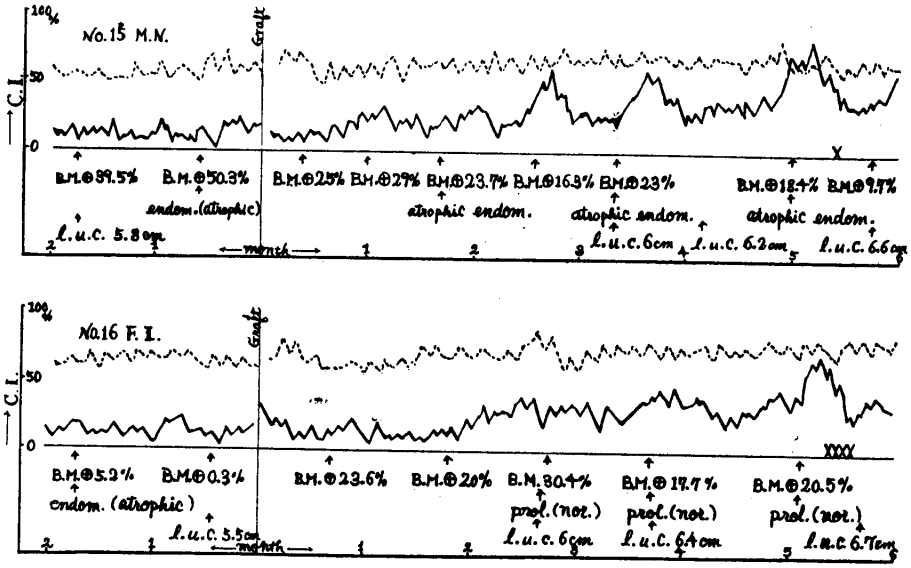


Fig. 4. Cases showing the third-grade effectiveness



divided into groups each of which had similar preoperative history and examination results such as A, A′, B, B′, etc. (Table 2). The group, ABC, was given grafting in conformance with requirements for blood transfusion, and A′B′C′ group was operated on counter to the requirements of blood trnsfusion : and as the result although some difference could be observed between the two groups, it is believed that there was no effect due to the type of blood (Table 2, refer to Figs. 2, 3, 4).

COMMENT

Homogenous grafting of the ovary to the patient with ovarian dysfunction has been tried by UNTERBERGER[30], SIPPEL[32,36], MANCLAIR[56], GUNSTER-SCHULTZE[57], CRAMER[58], LEOSER ALFRED, OHNO[43], NAKAYAMA, etc[59]., and every one of them report the efficacy of such a grafting. Not all, however, are clarified about its effectiveness and there still remain many problems to be solved. On the other hand, despite its complex nature hormonal therapy as applied to the patient of ovarian function seems, though not so conclusive as yet today, to play an important rôle in the clarification of the problems arising out of re-examinations with various methods on the efficacy of grafting the ovary that is usually discarded at the time of gynecologic operation.

In every case, needless to say, a good effect of grafting has been

recognized but there is no literature available explaining properly the mechanism of appearance of this effect. In my experiment it has been effective irrespective of success or failure of grafting itself, and also it has been found the good effect appears at the stage immediately after grafting, namely, before the grafted ovary begins its activity. From this it would appear, as OHNO and SIPPEL[55] contend, that the tissue of the grafted ovary in some manner stimulates the indigenous ovary, leading its function back to normal ; and therefore, the recovery of the function should not be considered as due to the secretion of hormones by the grafted ovary. It is believed that the ability to react to such a stimulation and the degree of dysfunction of the indigenous ovary are the deciding factors on the effect of grafting, and that difference in the combination of these factors makes the time of appearance and the degree of effect variable. That the case of severe dysfunction mentioned previously tended to show the third grade effectiveness seems to lie in the fact that the majority of these ovaries possessed a weak-reaction power.

As already mentioned no relationship can be recognized between the type of blood and the effectiveness. However, in Group ABC where the grafting was supposedly successful and consequently whose grafted ovary was thought to be secreting hormones, yet it was difficult to distinguish the activity of the grafted ovary from that of the indigenous ovary ; and there is no literature available explaining this point. Again, despite the fact that the indigenous ovary is assumed to be acting in conjunction with the grafted ovary, the reason why there is not any appreciable difference between the successfully grafted group and the group of failure seems to be due to the fact that activity of the grafted ovary in the presence of an indigenous ovary, as in the case of the activity of the grafted ovary in castrated woman, is not so marked.

Finally, as regards the danger of transplanting cancer cells at the time of grafting, by the investigations of NAGAI[60] of our department and by the fact that in 946 cases of auto-transplantation conducted in the Gynecology Department of Okayama University at the time of extensive hysterectomy without any cancer growth, it may be said there is no such a danger. However, as a matter of assurance in my own experiment I have taken out small pieces from ovarian tissue and verified histologically that there is no cancer infiltration.

SUMMARY

Homogenous grafting of the ovary to patients of ovarian dysfunction all proved to be effective, but the degree of the effectiveness and the time

of appearance of effect of the grafting were not fixed.

Moreover, there was no relationship between the effectiveness of grafting and the type of blood.

If the various conditions at the time of grafting are taken into consideration as above mentioned, this operation utilizing as it does the ovary usually discarded at operation may be expected to bring about quite a satisfactory therapeutic result.

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