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Clinical Trial on Reversible Male Contraceptive With Long-Acting Sex Hormones

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INTRODUCTION

This clinical trial is designed to develop a reversible supression of spermatogenesis with combined injections of long-acting medroxyprogesterone acetate and testosterone cypionate on 30 normal fertile male volunteers for 15 months. The objective of this trial is to ascertain the period of time to induce infertility, the minimum maintenance doses, the period of time to recover fertility, and various adverse side effects such as clinical side effects, biological side effects, sexual side effects and hormonal side effects.

MATERIALS AND METHODS

Subjects:

Through preliminary screening examinations with the following parameters, 30 healthy fertile male volunteers were selected and divided into 3 trial groups. Group I consisted of 10 cases and received 200mg of long-acting medroxyprogesterone acetate (Depo-Provera, D-P) and 200mg of long-acting testosterone cypionate (Depo-Testosterone, D-T), group Ⅱ, 10 cases, received 400mg of D-P plus 200mg of D-T, and Group Ⅲ, 10 cases, recvived 200mg of D-P plus 400mg of D-T.

Their mean age was 38 (39~40); weights, 58kg; heights, 163cm; duration of marital life, 11 years; numbers of children, 3; frequency of coitus, 2 per week; educational levels, 9 grades; and mean sperm counts, 120 million/ml (40~290 million/ml).

This clinical trial was divided into 3 phases, during which the subjects were instructed to use conventional contraceptive method. During control or pre-treatment phase, placebo injections were given to the subjects monthly for 3 months. During drug or treatment phase, various doses combinations of D-P and D-T were administered once a month intramuscularly and suppression of spermatogenesis were observed for 6 months. During recovery or post-treatment phase, nothing was given to them but recovery of spermatogenesis was investigated for 6 months.

Parameters:

The following parameters were investigated thoughout the trial period.

Semen analyses (16 items): Semen was obtained by masturbation after more than 3 days' of abstinence and analysed twice a month by conventional techniques.

Seminal fructose was also measured twice a month by Selivanoff reaction method.

Hormone assays: Serum follicle stimulating

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hormone (FSH), luteinizing hormone (LH) and testosterone were determined monthly by radioimmunoassay technique in Dr. Paulsen's Hormone Laboratory in Seattle, U.S.A.

Toxicology assessments: Analyses of blood biochemistry (18 items), hematology (8 items) and urinalyses (12 items) were carried out for assessment of adverse side effects monthly by the ordinary laboratory techniques.

General health and sexual activity: Clinical evaluations of general health and sexual activity were performed monthly by routine physical examinations and by subjective assessments of the subjects.

Psychiatric interviews: Psychiatric examinations and Minnesota Multiphasic Personality Inventory (MMPI) for personality analyses were attempted before and after the clinical trial.

RESULTS

Spermiogramme:

Changes of sperm concentration: Overall sperm counts of total subjects reduced from mean control counts of 143 million/ml to the lowest mean counts of 9 million/ml after drug administration and recovered to the highest mean counts of 105 million/ml after drug discountinuation. (Fig. 1).

Suppression of spermatogenesis: Sperm counts dropped less than 1 million/ml in 18 cases (complete azoospermia in 15 cases and 1 million/ml in 3 cases) out of the 30 subjects after 5 months (3-6 months) of drug administration, 2-9 million/ml in 7 cases after 5 months (4-6 months), 10-19million/ml in 2 cases after 5 months (4-6 months), and more than 20 million/ml in 3 cases after 7 months (6-7 months). These 3 cases whose sperm counts tended to drop persistently after drug exposure but never suppressed less than 20 million/ml were as follows: 1. subject no. 12 in group I, the lowest count was 138 million/ml in control phase and 39 million/ml after drug exposure. 2. subject no. 24 in group III, the lowest count was 254 million/ml in control phase and 26 million/ml

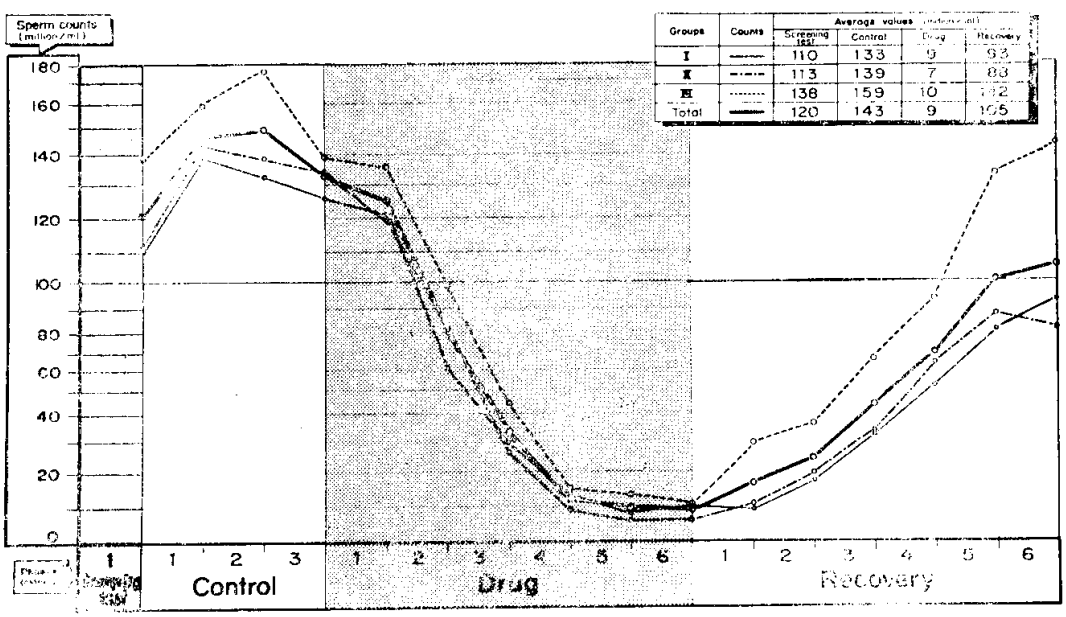

Fig. 1. Changes of Mean Sperm Concentration by Groups and by Month (million/ml)

after drug exposure. 3. subject no. 26 in group III, the lowest count was 189 million/ml in control phase and 24 million/ml after drug exposure. (Figs. 2 and 3).

Recovery of spermatogenesis: Sperm counts recovered greater or equal to the lowest counts of control phase in 24 cases out of the 30 subjects after drug discontinuation during recovery phase. The remaining 6 cases, 2 cases each group, whose sperm counts never restored to the lowest counts of control phase by the last month of recovery phase, had further 4 months of additional semen analyses. Subsequently full recovery to control levels occurred 5.5 months (3-10 months) after drug cessation. (Fig. 4).

Other items of spermiogramme: In general, volume, motility, active cell counts, live sperm, velocity, endurance tests, activity grade, motility index, and fertility index of control levels decreased slightly after drug exposure, but restored slowly to control levels during recovery phase. No marked changes were observed on morphology, pH, and liquefaction time throughout the trial period. No significant differences were noted among the trial groups on the above items of spermiogramme. (Figs. 5, 6, and 7).

Seminal fructose levels: Overall mean values of seminal fructose decreased control values of 3.2mg/ml during drug phase and increased to 3.3mg/ml during recovery phase. No distinct differences were observed among the trial groups. Accordingly, fructose levels decreased to 80% from baseline levels at the 3rd month of drug phase, thereafter, increased to 116% of baseline levels at the first month of recovery phase but decreased again to 88% of baseline at the end of recovery phase. (Fig. 8).

Hormone levels:

Serum FSH levels: Overall mean values of serum FSH fell from control levels of 4.0 IU/L

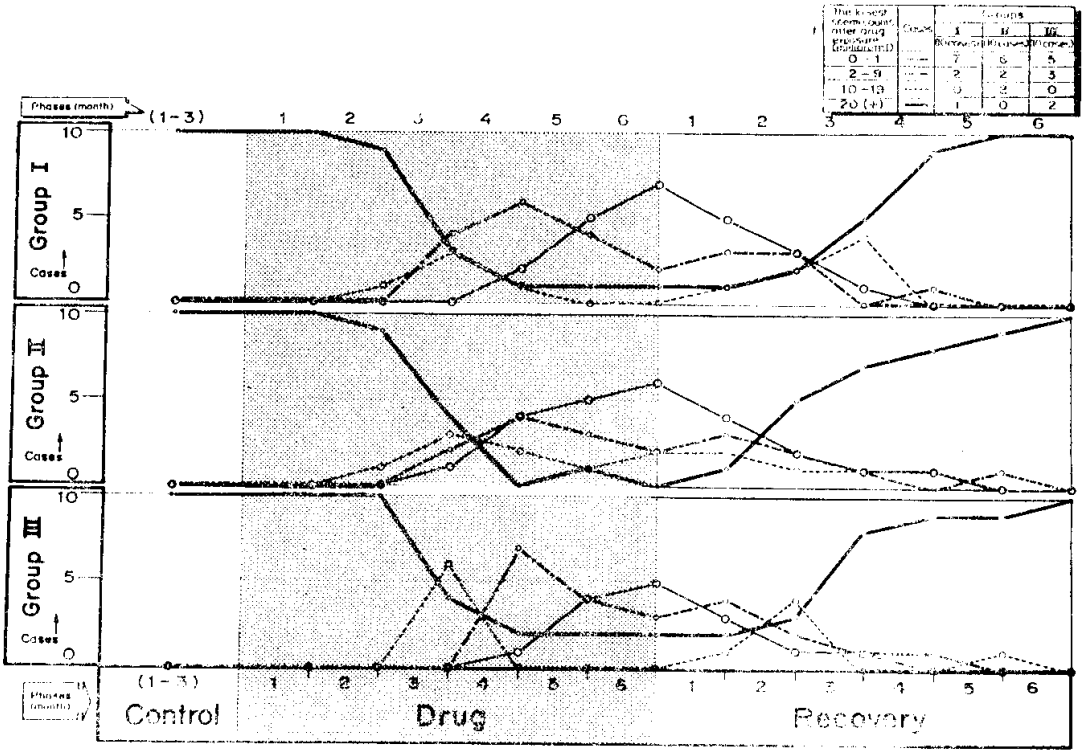

Fig. 2. Changes of Sperm Concentration by 4-Categories and Groups (cases)

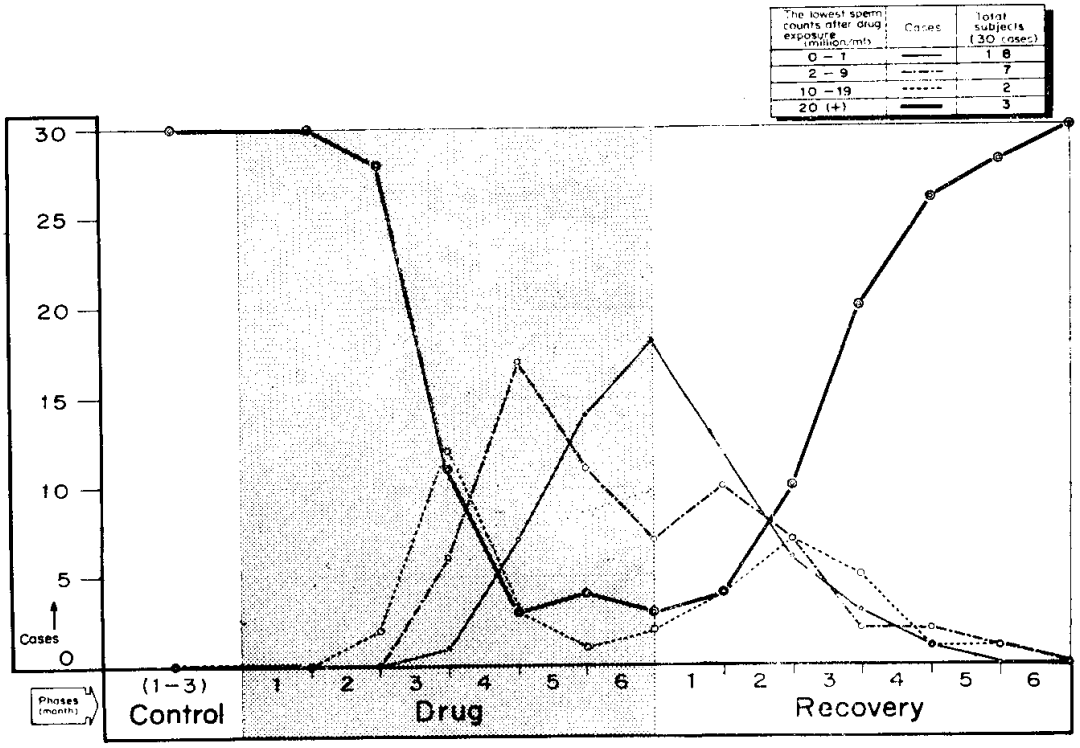

Fig. 3. Changes of Overall Sperm Concentration by 4-Categories (cases)

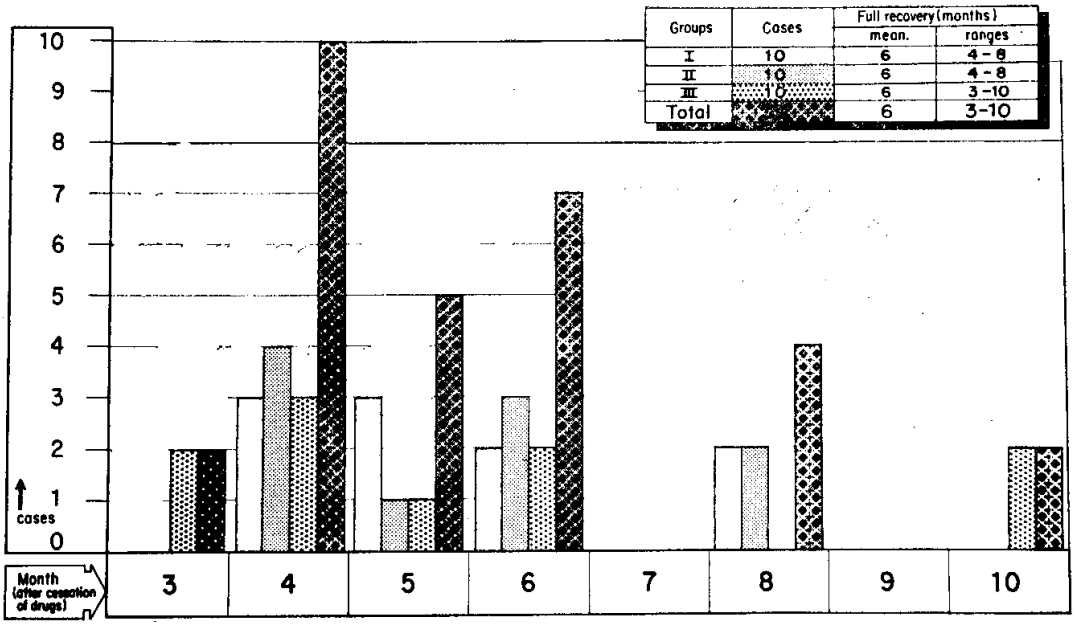

Fig. 4. Full Recovery of Sperm Concentration to Control Levels (cases)

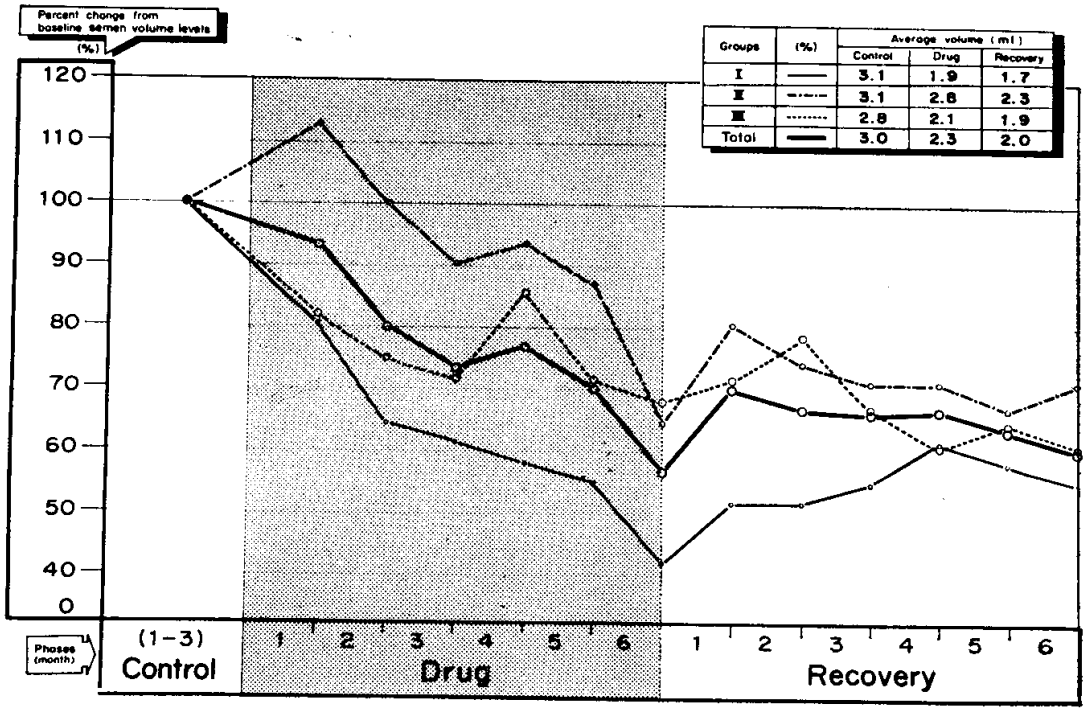

Fig. 5. Changes of Mean Semen Volume from Baseline Levels (100%)

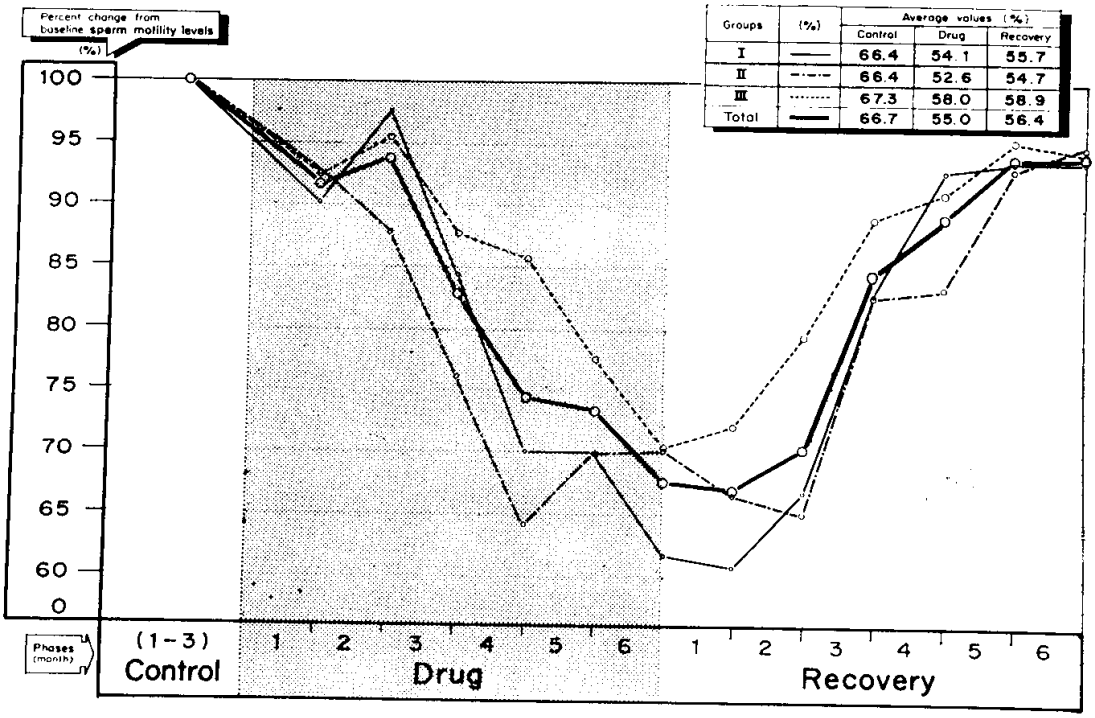

Fig. 6. Changes of Mean Sperm Motility from Baseline Levels (100%)

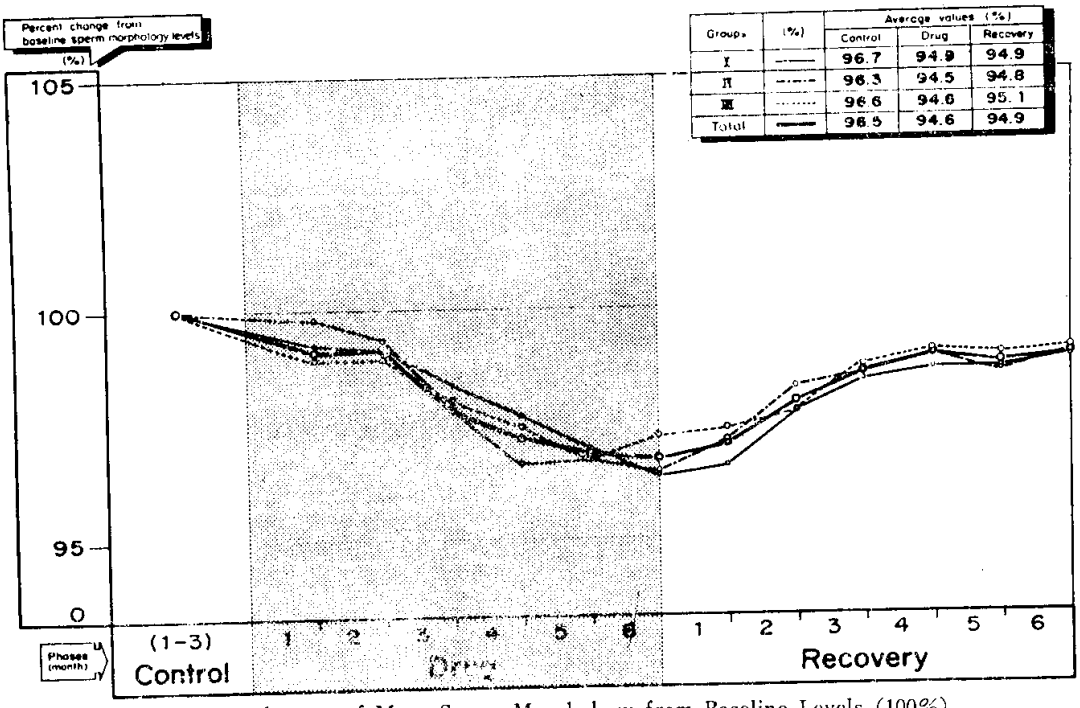

Fig. 7. Changes of Mean Sperm Morphology from Baseline Levels (100%)

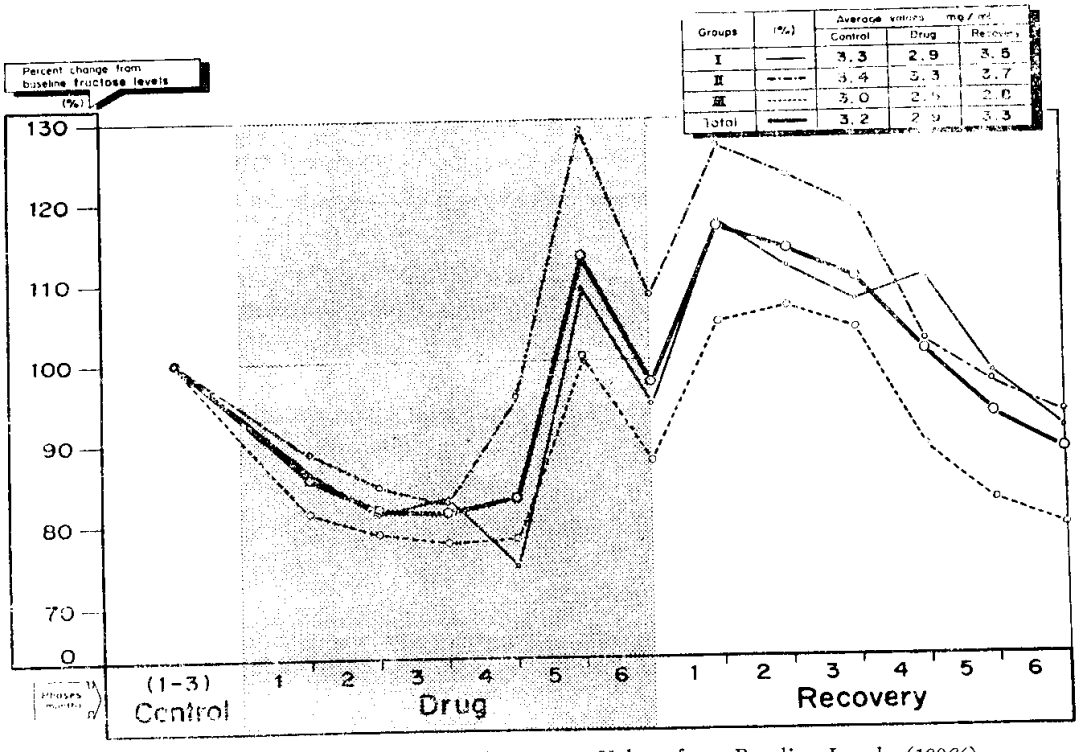

Fig. 8. Changes of Mean Seminal Fructose Values from Baseline Levels (100%)

to 1.9 IU/L during drug phase and subsequently recovered to 3.2 IU/L during recovery phase (FSH mean values of the last month of recovery phase was 4.9 IU/L). Accordingly, serum FSH levels dropped to 33% from baseline levels during drug phase, but recovered 123% of baseline levels at the end of recovery phase. The decreasing tendency of FSH titers after drug administration was marked in subjects of group II who received D-P 400mg plus D-T 200mg. However, none of these subjects demonstrated that FSH levels fell below normal male ranges of 0.8~10.4 IU/L. (Fig. 9).

Serum LH levels: Overall mean values of serum LH dropped from control levels of 2.9 IU/L during drug phase and subsequently recovered to 2.3 IU/L during recovery phase (LH mean values of the last month of recovery phase was 3.3 IU/L). Therefore, serum LH levels fell to 35% from baseline levels during drug phase but recovered 121% of baseline levels at the end of recovery phase. The individuals of group II demonstrated a significant decrease in LH titers but none of these subjects revealed that LH levels fell below normal adult male ranges of 0.6~7.3 IU/L. (Fig. 10).

Serum testosterone levels: Overall mean values of serum testosterone fell from control levels of 33.24 nmol/L to 27.34 nmol/L during drug phase and further decrease to 16.69 nmol/L during recovery phase (testosterone mean values of the last month of recovery phase was 21.48 nmol/L). Consequently, testosterone levels dropped to 58% from beseline levels following durg administration but recovered 65% of baseline levels at the end of recovery phase. The decreasing tendency of testosterone titers was more pronounced in subjects of group II. Testosterone values fell to lower limits of normal adult male ranges of 14~42 nmol/L in some individuals of group II. (Fig. 11).

Blood biochemistry:

SGOT values: Some alterations such as elevated values in group II and decreased values in

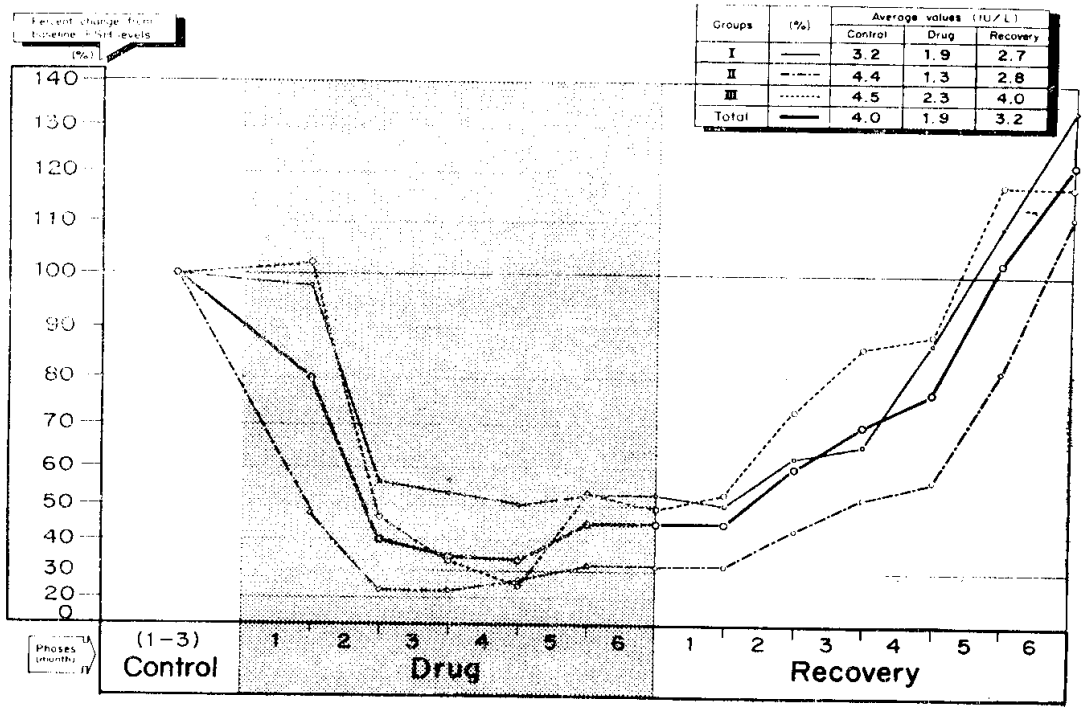

Fig. 9. Changes of Mean Serum FSH Values from Baseline Levels (100%)

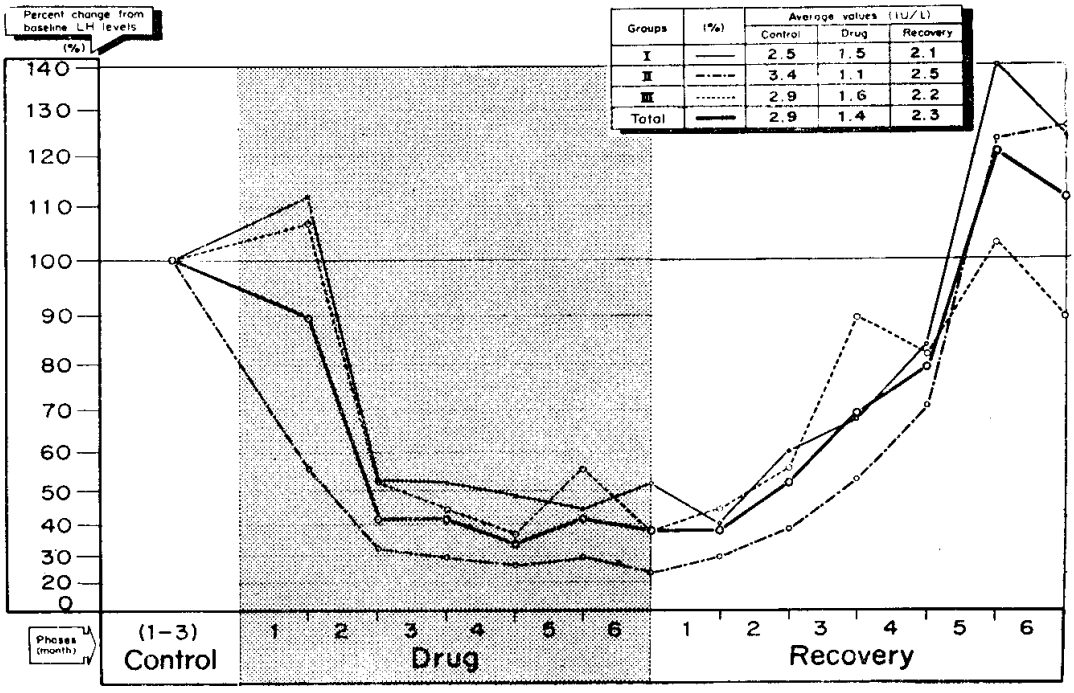

Fig. 10. Changes of Mean Serum LH Values from Baseline Levels (100%)

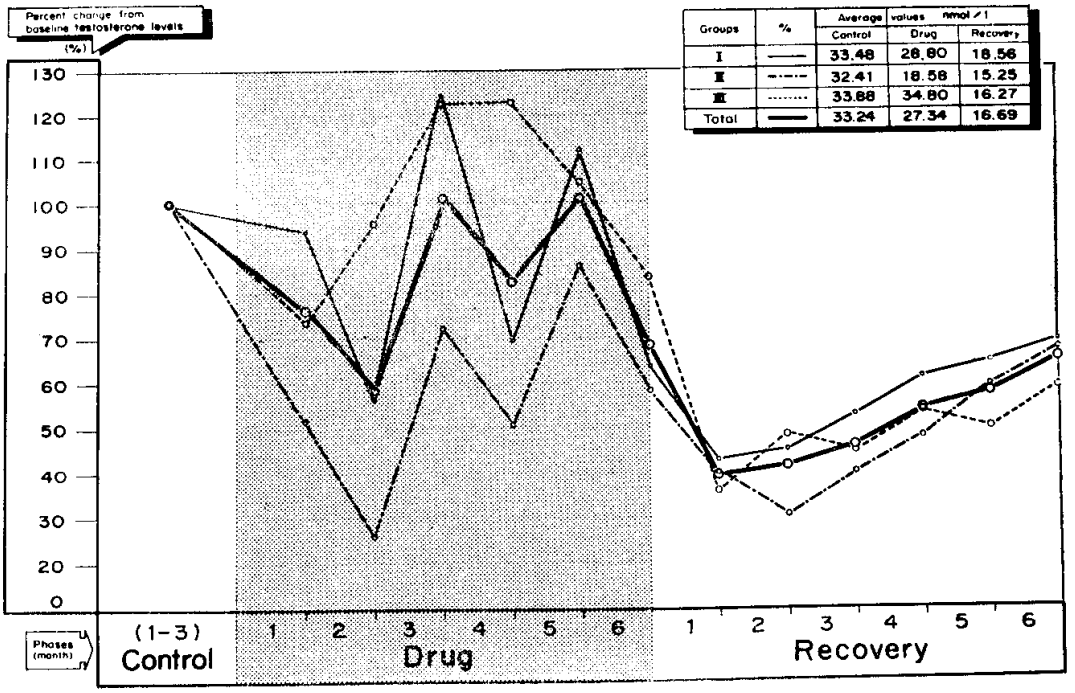

Fig. 11. Changes of Mean Serum Testosterone Values from Baseline Levels (100%)

group I from baseline levels were noted but these were within normal ranges of 3.84～19.20 IU/L. (Fig. 12).

SGPT values: No significant alterations from baseline levels were noted. These values were within normal limits (2.40～16.80 IU/L).(Fig. 13).

Alkaline phosphatase: Some fluctuations from baseline levels were found but no significant differences existed among the trial groups. These fluctuations were still within normal limits (1.04～2.34 IU/L). (Fig. 14).

Serum total protein levels: No significant alterations from baseline levels were noted.(normal ranges: 60～80 g/L). (Fig. 15).

Serum creatinine levels: Overall mean creatinine levels elevated 144% of baseline levels at the second month of recovery phase, thereafter, returned slowly at the end of recovery phase. However, these elevations were within normal ranges (62～133 micro mol/L). (Fig. 16).

Slight surges in the remaining items of blood biochemistry and eletrolytes, such as TTT, LDH, acid phosphatase, cholesterol, glucose, uric acid, albumin, globulin, magnesium, calcium, phosphorus, and BUN were observed during the trial period. One individual (no. 17 of group I) in a total of the 30 subjects, who was negative to the HBsAg (Australia antigen) on the preliminary screening test, had been positive to the test throughout the trial period. However, he had not been excluded from the trial programme as his remaining toxicological parameters remained within normal limits and as he was wanting to cooperate our trial programme.

Hematology:

Complete blood cell counts including differential white blood cell counts remained within normal ranges throughout the trial period. No significant alterations from baseline levels of both Hgb and Hct were observed during the trial period. (Figs. 17 and 18).

Urinalyses:

Routine urinalyses showed no abnormal findings during the trial period in all subjects.

Clinical evaluation of general health:

Physical examinations: Routine physical examinations for general health revealed no particular abnormal findigs throughout the trial period. No changes on testicular sizes and prostate nor gynecomastia were observed. However, mild tenderness or discomfort on breast was reported by 3 individuals after drug exposure.

Subjective feelings of general health: Excellent general conditions were felt more than once by only 1 subject for 3 months during control phase(total of 90 months), by 12 subjects for 54 months during durg phase(total of 180 months), and by 9 subjects for 29 months during recovery phase (total of 180 months). Subjects in group II felt less excellent conditions on general health after durg administration.

Body weight: Eighty per cent of the 30 subjects gained 2～13kg of body weights following durg administration and the remaining 20% showed no marked changes on body weights. Mean body weight gained 113% of baseline levels at the last month of durg phase, and subsequently returned slowly to 109% of baseline levels at the last month of recovery phase. (Fig. 19).

Clinical evaluation of sexual activity:

Libido and sexual potentia: In general, 17% of the total subjects reported a slight increase in libido and potentia, 20%(9% from group II) of them reported decrease, and the remaining subjects, no change after durg exposure. However, no subjects discontinued cooperation with this trial because of sexual problems.

Frequency of coitus per week: On the whole, there were wide variations from baseline levels of coital frequency among the trial groups.

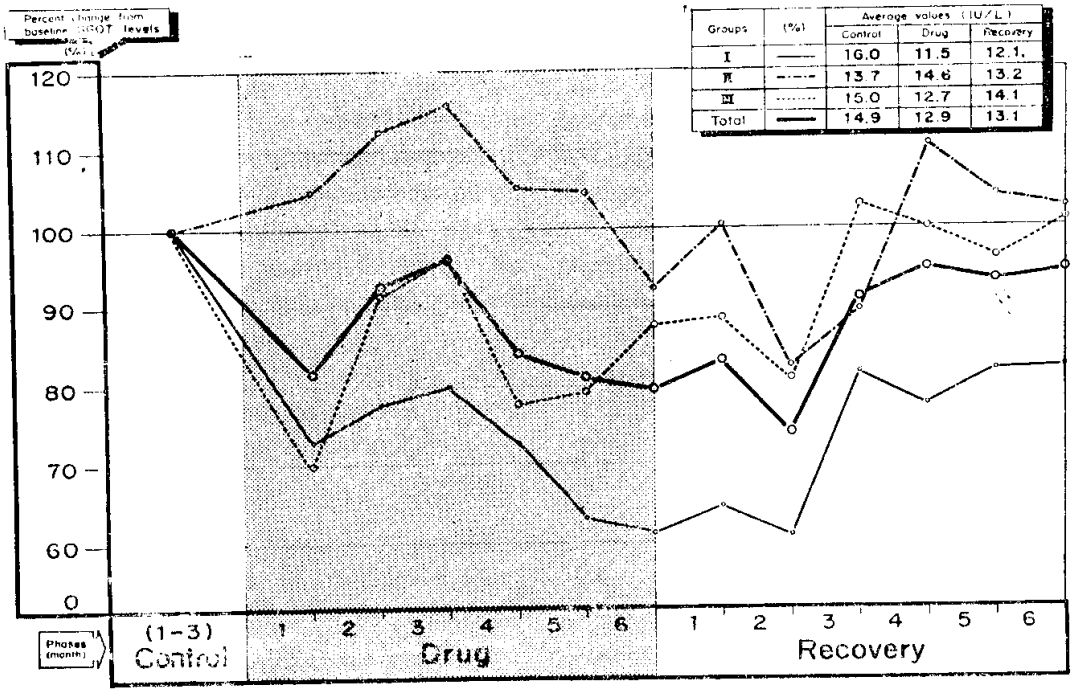

Fig. 12. Changes of Mean SGOT Values from Baseline Levels (100%)

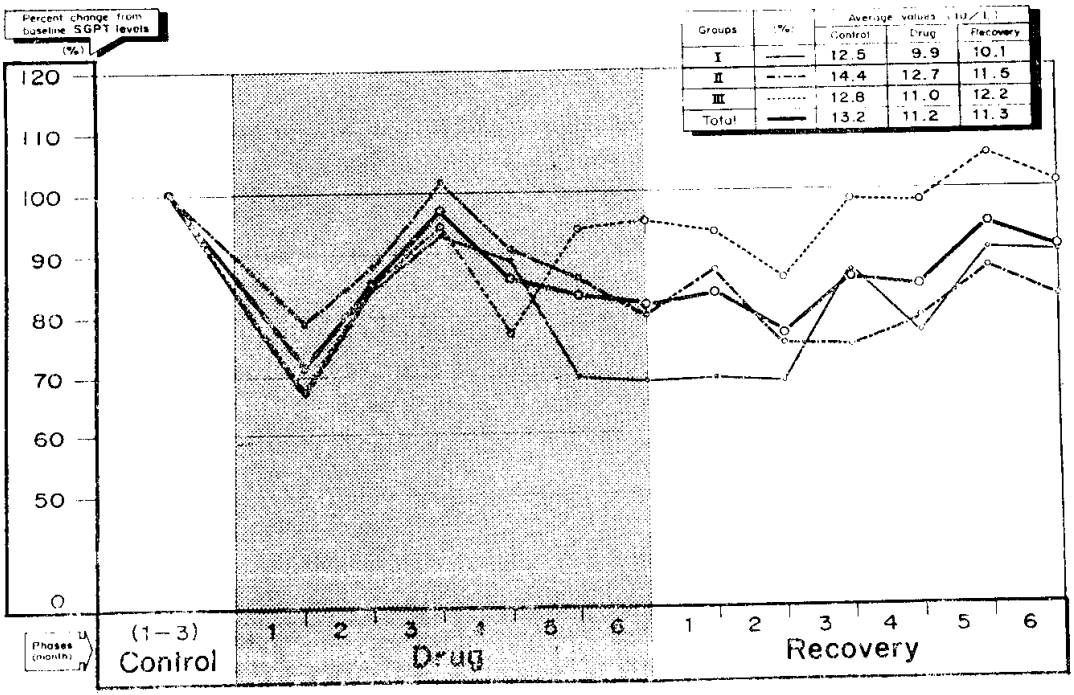

Fig. 13. Changes of Mean SGPT Values from Baseline Levels (100%)

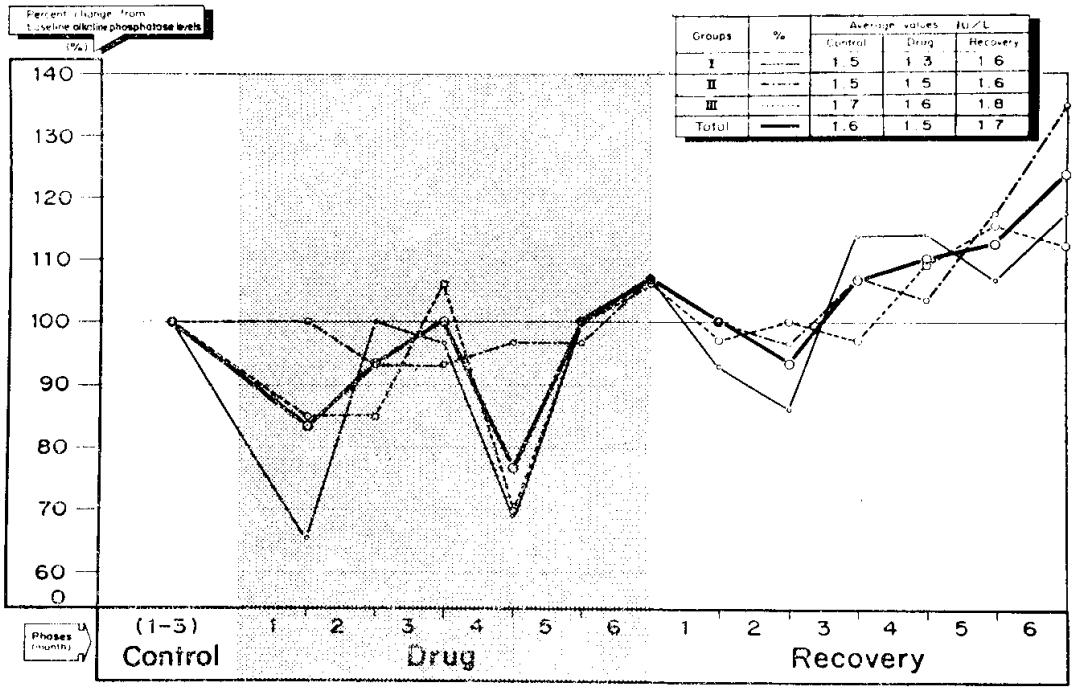

Fig. 14. Changes of Mean Alkaline Phosphatase Values from Baseline Levels (100%)

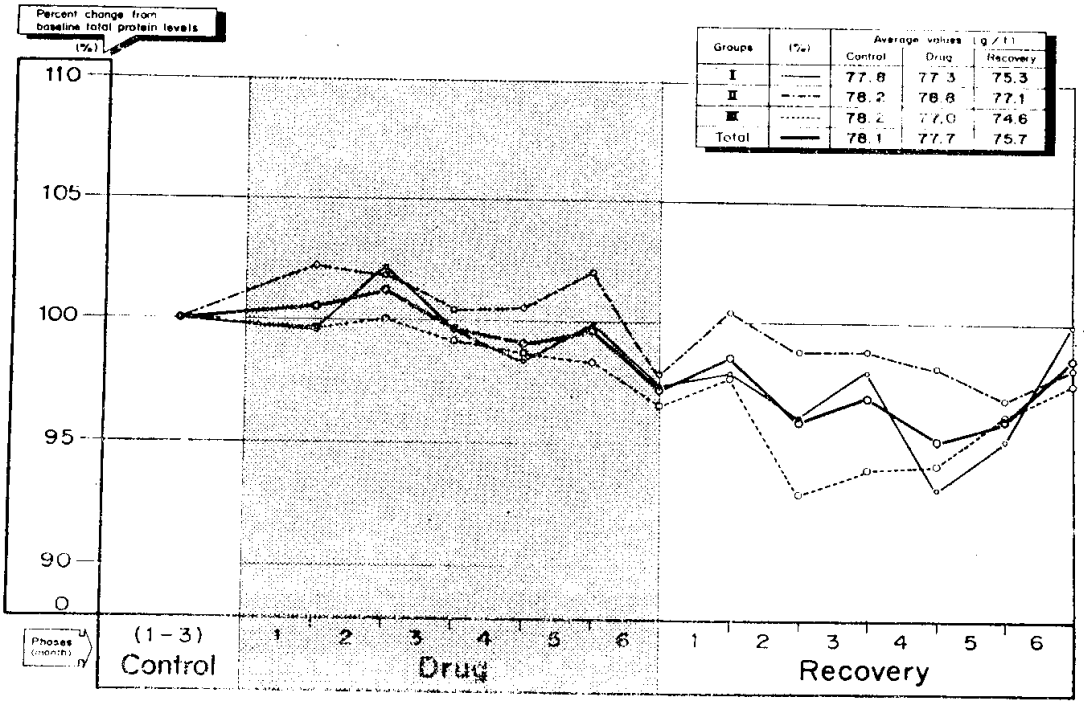

Fig. 15. Changes of Mean Serum Total Protein Values from Baseline Levels (100%)

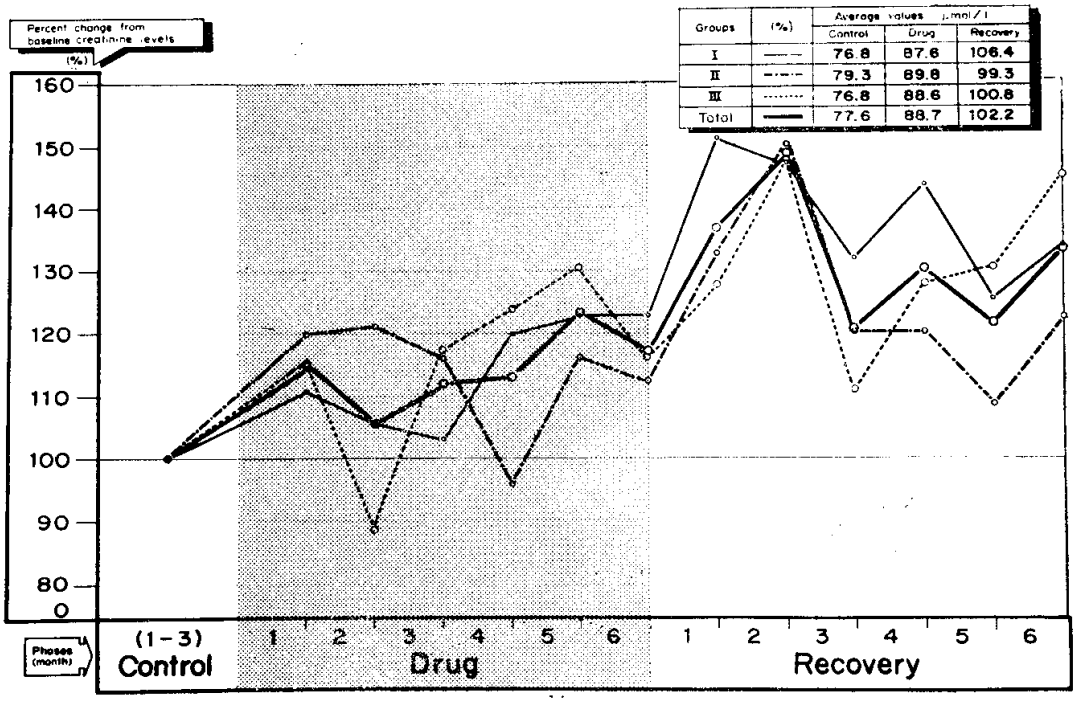

Fig. 16. Changes of Mean Serum Creatinine Values from Baseline Levels (100%)

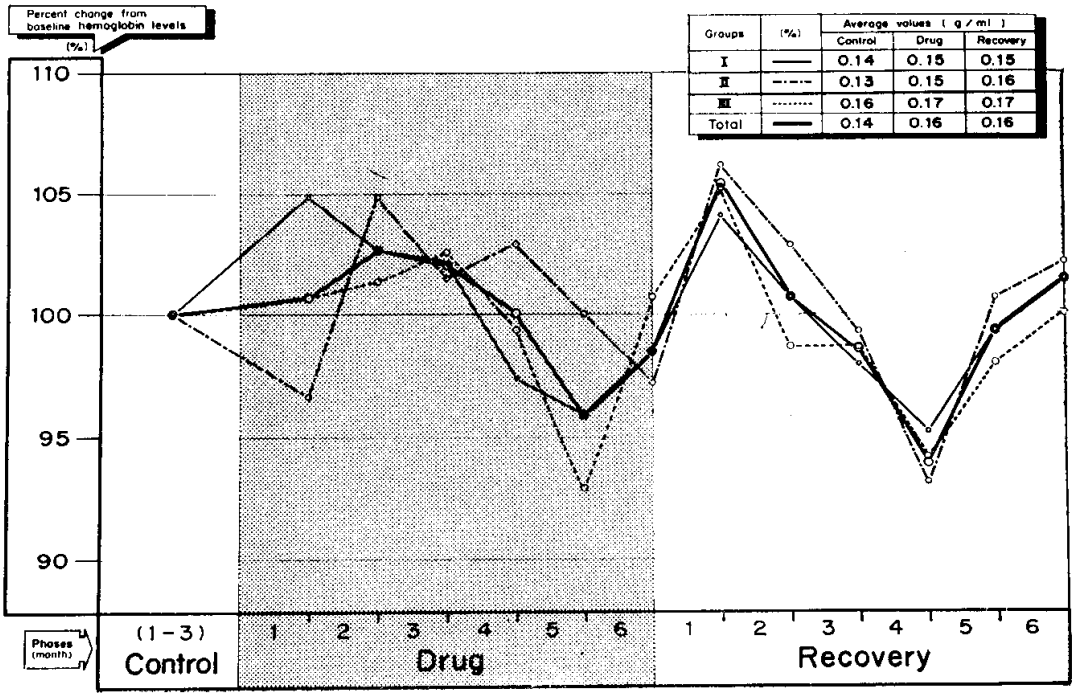

Fig. 17. Changes of Mean Hemoglobin Values from Baseline Levels (100%)

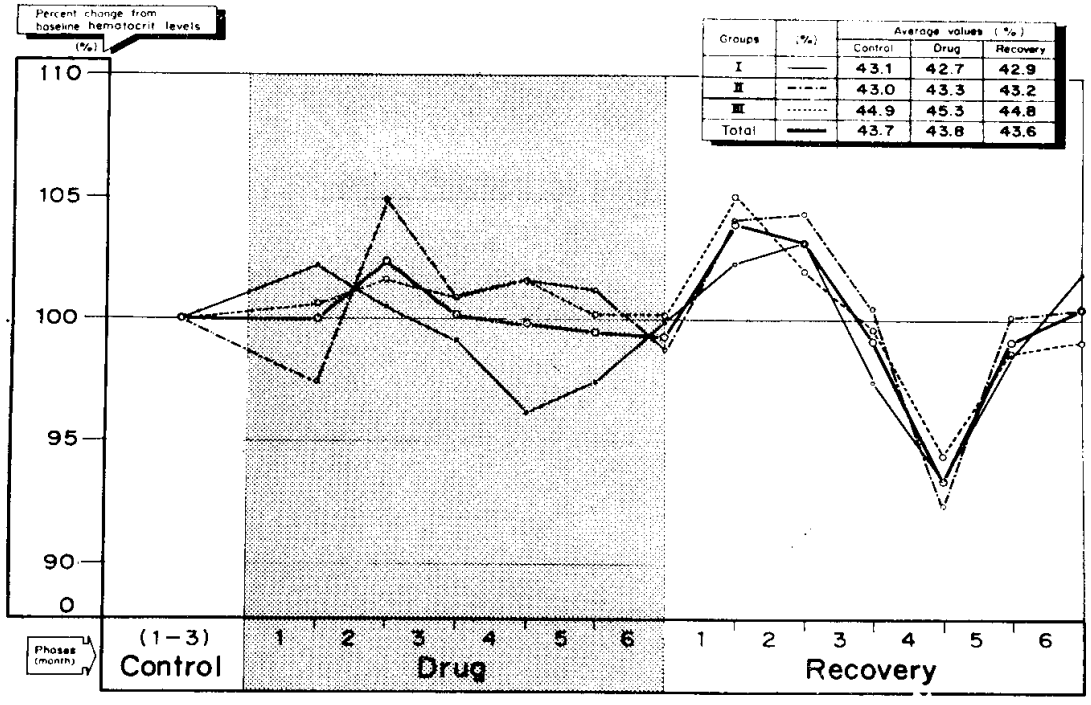

Fig. 18. Changes of Mean Hematocrit Values from Baseline Levels (100%)

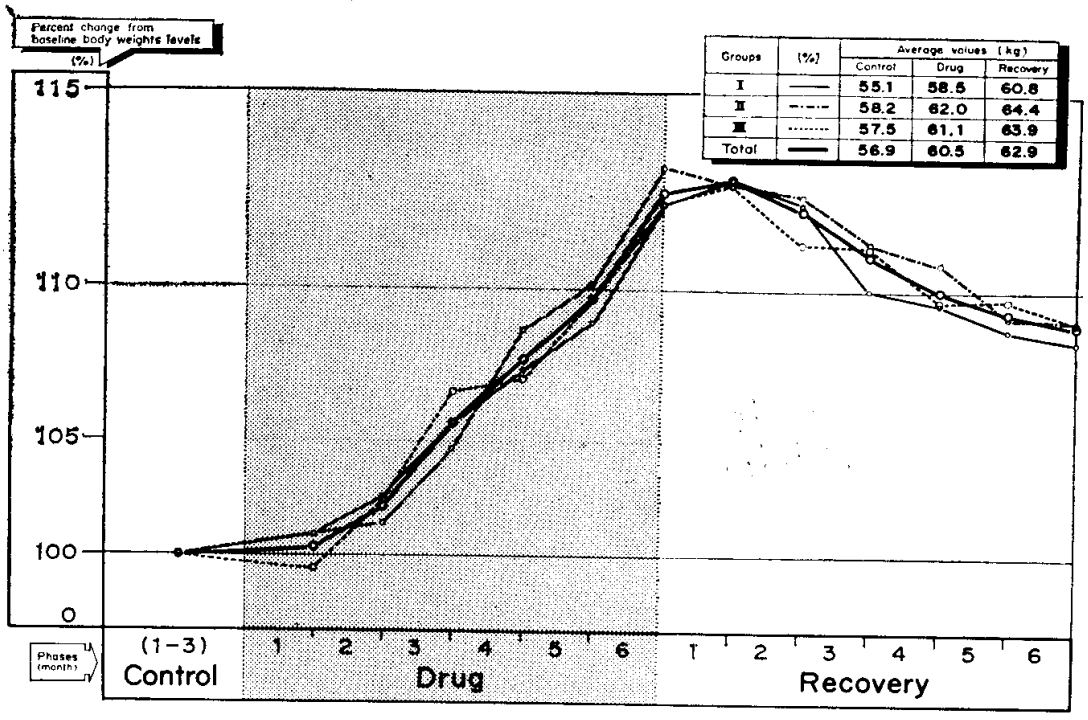

Fig. 19. Changes of Mean Body Weights from Baseline Levels (100%)

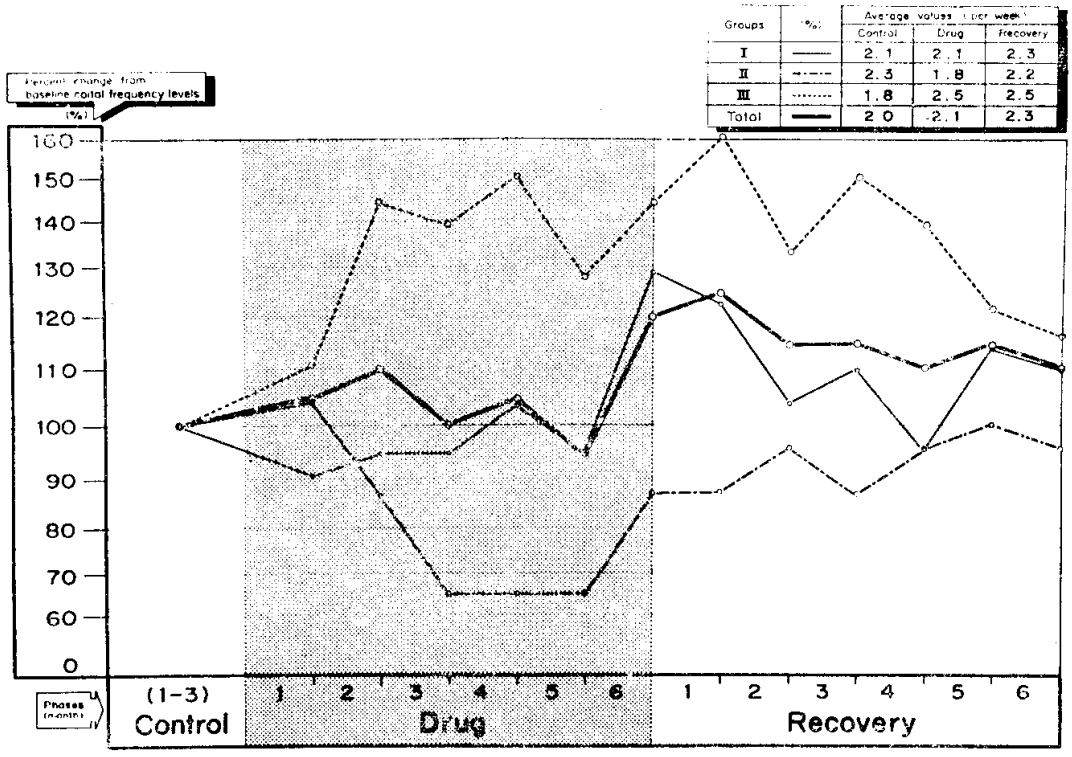

Fig. 20. Changes of Mean Frequency of Coitus from Baseline Levels (100%)

Table 1. Results of MMPI

Volunteer No.	Tendencies of pre-study score	Tendencies of post-study socre	Remarks
0001.	Depression, anxiety with obsession	hypochonirical tendency	no change
0002.	Depression with obsession	slightly obsession	much better
0003.	Psychosomatic disorder	within normal limits	much better
0004.	Depression, anxiety or adult maladjustment	tendency of personality disorder	much better
0005.	Hypochondrical or hystery	tendency of hystery	no change
0006.	Emotionally unstable	become stable	much better
0007.	Depression with anxiety	no change	no change
0008.	Sexual problem, mild	within normal limits	much better
0009.	Anxiety	slightly depressed	slightly better
0010.	Hypochondriasis	slightly better	slightly better
0011.	Depression	slightly better	slightly better
0012.	Behavior problem	much better	much better
0013.	Depression	much better	much better
0014.	Emotionally unstable	no change	no change
0015.	Depression	much better	much better
0016.	Somatization and obsession	slightly better	slightly better
0017.	Hypochondriasis	much better	much better
0018.	Deprssion	hysterical tendency	worse
0019.	Depression and anxiety	much better	much better
0020.	Depression	hysterical tendency	worse
0021.	Hystery	slightly better	slightly better
0022.	Depression with obsession	no change	no change
0023.	Agitated depression	slightly better	slightly better
0024.	Hystery	slightly better	slightly better
0025.	Enotionally unstable	slightly depressed	slightly better
0026.	Depression with anxiety	no change	no change
0027.	Anxiety with depression	slightly better	slightly better
0028.	Sexual problem	no change	no change
0029.	Depression with agitated	no change	no change
0030.	Depression with obsession	much better	much better

Actual coital frequency per week of control phase increased in groups I and III after drug exposure and again increased during recovery phase. However, the frequency of group II decreased after drug exposure but recovered during recovery phase. In other words, coital frequency per week apparently increased upto 150% of baseline levels in group III, on the other hand, the frequency decreased to 65% from baseline levels in group II following drug exposure, but these transient changes of coital frequency were subsequently returned to their control levels at the end of recovery phase. (Fig. 20).

Frequency of morning erection: Frequency of morning erection was also reduced in group II following drug exposure.

Results of personality analyses:

The abnormal tendency of personality analyses by MMPI technique before and after the trial revealed that the scores of post-trial analyses became better than that of pre-trial analyses in 20 subjects, remained the same scores in 8 subjects and became worse in 2 subjects after the trial. (Table 1).

DISCUSSION

Many studies have been demonstrated that progestin and large dose of androgen are each capable of suppressing spermatogenesis through the feedback control of hypothalamo-hypophyseal unit.[1,2,3] That is, progestin and androgen may produce suppression of spermatogensis through suppression of FSH in conjunction with LH in plasma and induce recovery of spermatogenesis on ceasing the therapy.[4] However, progestin may inhibit libido and sexual potentia and induce weight gain and gynecomastia. It is, therefore, suggested that progestin which is administered concurrently with androgen may suppress sperm production without producing these unacceptable side effects and may be reduced in total amount required for full suppression by achieving possible synergism.

The results of this trial revealed that azoospermia or near-azoospermia (less than 1 million/ml) was produced in 18 cases (60%), oligospermia (2-9 million/ml) in 7 cases (23%), and moderate suppression in 5 cases (17%) including 3 cases of more than 20 million/ml of sperm counts. The combimation with various doses of D-P and D-T even the large doses of these agents failed to achieve full suppression of spermatogenesis in all of the subjects investigated in this trial. Thus, great indiuidual variety in responsiveness to the agents have been noted in this trial. No distinct differences could be found between the subjects whose sperm counts never went down below 20 million/ml and the subjects whose counts reduced less than 1 million/ml on items of testis sizes, frequency of coitus, levels of serum FSH, LH, and testosterone, body weights and other parameters except higher control mean sperm counts in the subjects with more than 20 million/ml (mean counts: 261 million/ml to 120 million/ml). The failure of complete suppression to azoospermia observed in this trial may be due to too low dosage to maintain high blood levels of the agents, due to limited period of treatment phase (6 months of durg phase) or due to individual biological responsiveness to the agents. There were no significant differences among the trial groups on the length of time to reach azoospermia. In general, the period of time to suppress sperm production following drug administration was longer in this trial of 5 months than other's series of 3 months.[5,6] There may be some gap between time of injection and time of sampling in this trial.

Azoospermia continued for 2 to 6 months

with the maintenance doses given for 6 months in this trial.

Sperm counts recovered more than 20 million/ml in 29 cases out of the 30 subjects 3 months after drug cessation. However, full recovery of spermatogenesis occurred in 24 cases within 6 months and in the remaining 6 cases, within 10 months following drug cessation. So that, restoration of sperm counts to control levels following drug cessation was delayed in this trial of 6 months in comparison with 4 months of other reports,[7,8] even though the kinetics of spermatogenesis required 70~80 days in human. No relationship existed between the full recovery time and the trial groups, and also between full recovery time and various parameters investigated in this trial. However, mean sperm counts of control phase of slowly recovered 6 cases were lower than those of the remaining 24 cases (97 million/ml to 155 million/ml). Based on the results from this trial, the control phase might be cut from 3 months to 2 months, but recovery phase should be extended from 6 months to 10 months, because of delay in full recovery. (Table 2).

It has been also repoted by many investigators[1,2,3,4,7] that the occurrence of mild impairment of liver function treated with high dose of progestin and androgen. But in this trial, no evidence of drug related liver damages was observed by careful analyses of relevant parameters. Some alterations in the blood biochemistry to upper limits of normal ranges in soe mindividuals were supposed to be related to the excessive metabolic and catabolic load on the liver caused by the high doses of progestin and androgen.

It has been documented that in nearly all instances, declines of sexual urges and potentia were associated with the use of progestin due to suppression of endogenous testosterone production by the progestin.[6,7] Therefore, lower doses of progestin or combination of progestin with androgen may prevent the occurrence of these side effects. The side effects such as loss of libido and potentia, decreased coital frequency and morning erection were apparently higher in the subjects who received D-P 400 mg plus D-T 200 mg than the remaining subjects in this series. Besides these pharmaceutic actions, it is likely that psychological reactions to the trial were partially responsible for the impoten-

Table 2. Summary of Changes of Sperm Concentrations

Groups	Drug combination		Subjects	Suppression after durg exposure				Full recovery to control levels		
				sperm counts: million/ml				(6-months)	(4-months)	(10-months)
	D-P	D-T		0-1	2-9	10-19	20(+)	(recovery)	(add. tests)	(total period)
	mg		cases	cases (months after durg exposure)				cases (months after drug cessation)		
I	200	200	10	7 (5:4-6)	2 (4:4-4)	0 —	1 (7)	8 (5:4-6)	2 (2:2-2)	10 (6:4-8)
II	400	200	10	6 (4:3-6)	2 (6:6-6)	2 (5:4-6)	0 —	8 (5:4-6)	2 (2:2-2)	10 (6:4-8)
III	200	400	10	5 (5:4-6)	3 (5:4-5)	0 —	2 (6:6-7)	8 (4:3-6)	2** (4:4-4)	10 (6:3-10)
Total			30	18 (5:3-6)	7 (5:4-6)	2 (5:4-6)	3* (7:6-7)	24 (5:3-6)	6 (3:2-4)	30 (6:3-10)

(mean: ranges)

* The lowest counts of control: the lowest counts of durg exposure=1) 138:39, 2) 254:26, and 3) 189:24

** The lowest counts of control: the highest counts by the 10th month=38:34 in 1 case of 2 cases

tia. These transient decrease on the sexual activity returned spontaneously to normal during recovery phase.

Gynecomastia and shrinkages of testicle did not occur in this trial but mild tenderness or discomfort on the breast was reported by 3 individuals after drug exposure. This was disappeared spontaneously during recovery phase but was not annoying complaints.

In the majority of the subjects, body weight gained more or less following drug exposure since the steroids used in this trial both possess the anabolic properties. No significant differences could be observed among the trial groups on the incidence of these unavoidable side effects.

Occasional nightly sweats were reported by some individuals after drug exposure.

Consequently, this trial findings do suggest that the lower dose of D-P 200mg in combination with D-T 200mg was proved to be an adequate combination for the suppression of spermatogenesis and for avoidance of some types of side effects, since higher doses of combination of D-P 400mg plus D-T 200mg produced these side effects in some men and could not attain full suppression of sperm production.

CONCLUSION

In conclusion, for the development of an ideal method of reversible male contraceptive using sex hormones, a new combination with the lowest dosage of Depo-Provera and Depo-Testosterone should be developed by which full suppression of spermatogenesis could be attained in a limited period of time since occasional pregnancies had been documented with the sperm counts of less than 10 million/ml. The combined steroids compounds used in this trial suppress sperm production to azoospermia or severe oligospermia but could not achieve full suppression in all subjects even when high doses of D-P plus D-T were used. Full recovery of spermatogenesis should be achieved in all subjects following cessation of drug administration. Any types of side effects even transient loss of libido and sexual potentia should not be occurred by the drug administration in actually all age groups of subjects who are treated. The maintenance doses should be confirmed at which the subjects remained consistently infertile during the drug administration without any drug resistant phenomenon.

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》國文抄錄《

性호르몬 併用에 의한 男性 可逆性 受胎調節法의 臨床的 硏究

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남성 가역성 수태조절법을 개발하기 위한 15개월에 이르는 본 임상적 연구에서는 여러가지 양의 「데포—푸로베라」와 「데포—테스토스테론」 주사를 30명의 건강한 가임남성에게 매달 병용하여서 이렇다 할 큰 부작용

없이 정자형성억제는 5개월만에 그리고 정자형성회복은 약 투여 중지후 6개월만에 각각 일으킬 수 있었다.

REFERENCES

Alverez-Sanchez, F., Faundes, A., Brache. V., and Leon, P.: *Attainment and Maintenance of Azoospermia with Combined Monthly Injection of Depot Medroxyprogesterone Acetate and Testosterone Enanthate. Contraception*, **15**:669, *1977*.

Brenner, P.F., Mishell, D.R. Jr, and Bernstein, G.S., and Ortiz, A.: *Study of Medroxyprogesterone Acetate and Testosterone Enanthate As a Male Contraceptive. Contraception*, **15**:679, *1977*.

DeKretser, D.M.: *The Regulation of Male Fertility: The State of the Art and Future Possibilities. Contraception*, **9**:561, *1974*.

Frick, J., Bartsch, G., and Weike, W.H.: *The Effect of Monthly Depo-Medroxyprogesterone Acetate and Testosterone on Human Spermatogenesis. I. Uniform Dosage Levels. Contraception*, **15**:649, *1977*.

Hammerstein, J., and Brotherton, J.: *Methods for Evaluation of Antifertility Agents in the Male. Int. J. Androl., Supplement, 2, Part 2, July, 1978, p. 659.*

Melo, J.F., and Coutinho, E.M.: *Inhibition of Spermatogenesis in Men with Monthly Injection of Medroxyprogesterone Acetate and Testosterone Eenanthate. Contraception*, **15**:627, *1977*.

Paulsen, C.A., and Leonard, J.M.: *Clinical Trials in Reversible Male Contraception. I. Combination of Danazol plus Testosterone. Regulatory Mechanism of Male Reproductive Physiology. Edited by CH Spilman, et al. The Netherlands, Excerpta Medica, Armsterdam, 1976, p. 197.*

Schearer, S.B., Alvarez-Sanchez, F., Anselmo, J., Brenner, P., Countinho, E., Latham-Faundes, A., Frick, J., Heinild, B., and Johansson, E.D.B.: *Hormonal Contraception for Men. Int. J. Androl., Supplement, 2, Part 2, July, 1978, p. 680.*