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Controlled Release for Hormone Therapies by LHRH Analogue Containing Polymer Needles and Testosterone Containing Artificial Testis

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Introduction

The author's group has studied and developed drug-polymer composites of various forms and applied to various therapeutic uses by the implantation.[1)-5)] Among them the implantable needles have been used successfully for hormone therapy against prostatic cancers and the artificial testis has been also effectively applied for testosterone-lacking patients for long periods. This kind of technique is simple and conveniently extensible to various hormone therapies, immuno-therapes and neurological therapies. In this report, the recent results of hormone therapies using the implantable composites were reviewed.

Experimentals

The implantable drug-polymer composites are classified to a non-biodegradable type and a biodegradable type. The former composite was prepared by molding a mixture of drug and vinyl monomer (acrylate or methacrylate) and polymerizing it with gamma-ray or electron beam. The latter one was prepared by molding a mixture of drug and biodegradable polymer powder and hot-pressing under heat and pressure. These processes are shown in Fig. 1.

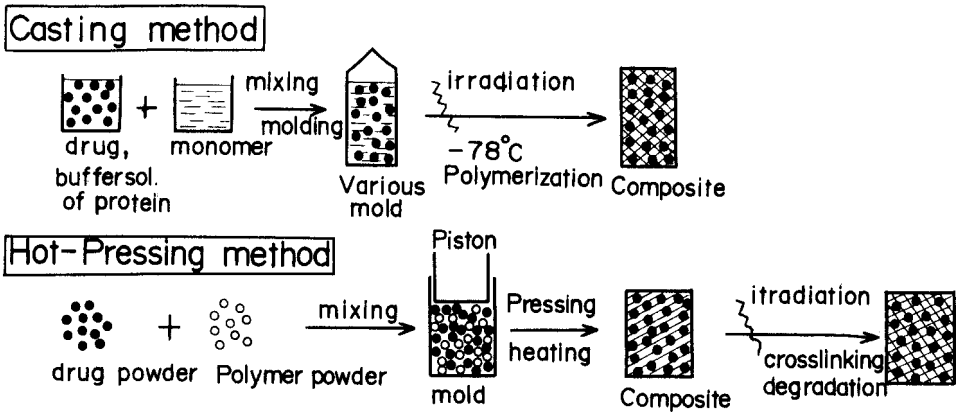

Fig. 1 Two fundamental immobllization methods for proteins and drugs by physical entrapping using radiation

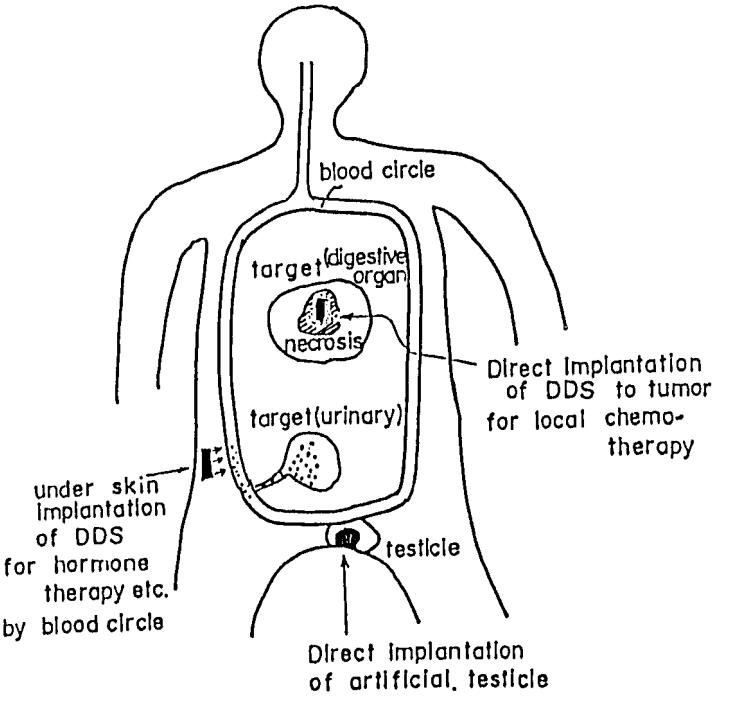

Fig. 2 Model scheme of various therapeutic administration of implantable drug delivery systems (DDS)

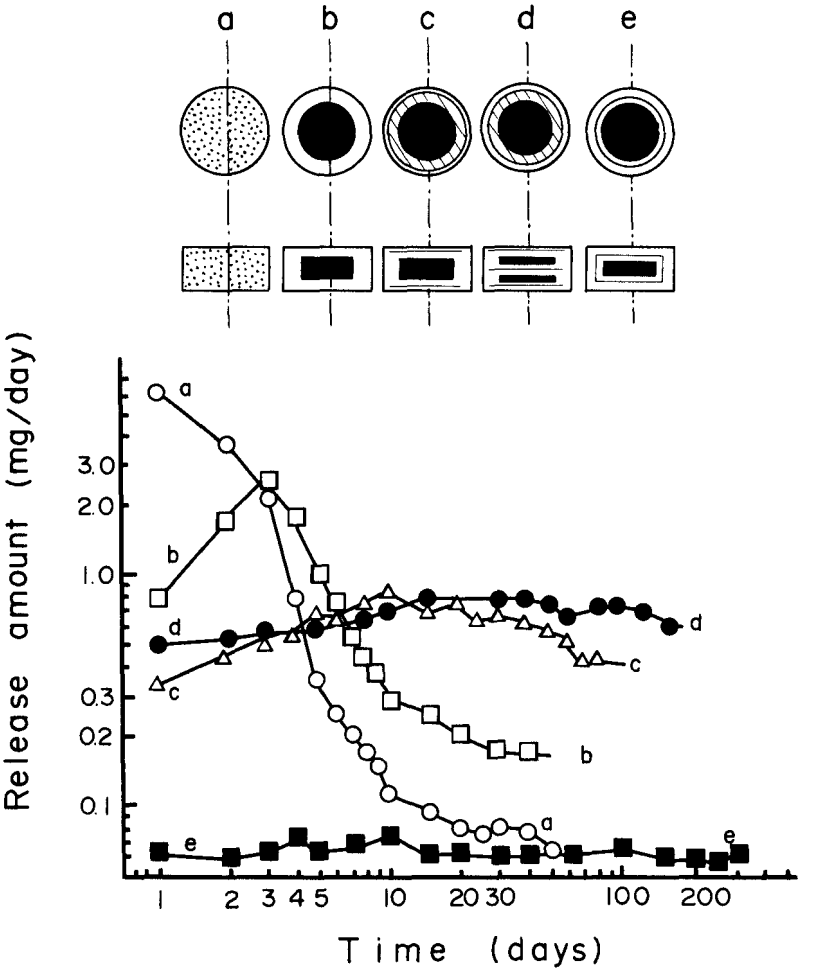

Fig. 3 Effect of various multi-layers (sandwich) structures on the release profile of LHRH analogue as a hormone.

a : drug was homogeneously distributed in the polymer matrix,

b : pure drug layer was entrapped by the polymer layer,

c : drug layer was covered by two polymer film layers and one matrix layer,

d : two drug layers were covered by three films and one matrix layer,

e : one drug layer was covered with a surrounding film and a polymer matrix.

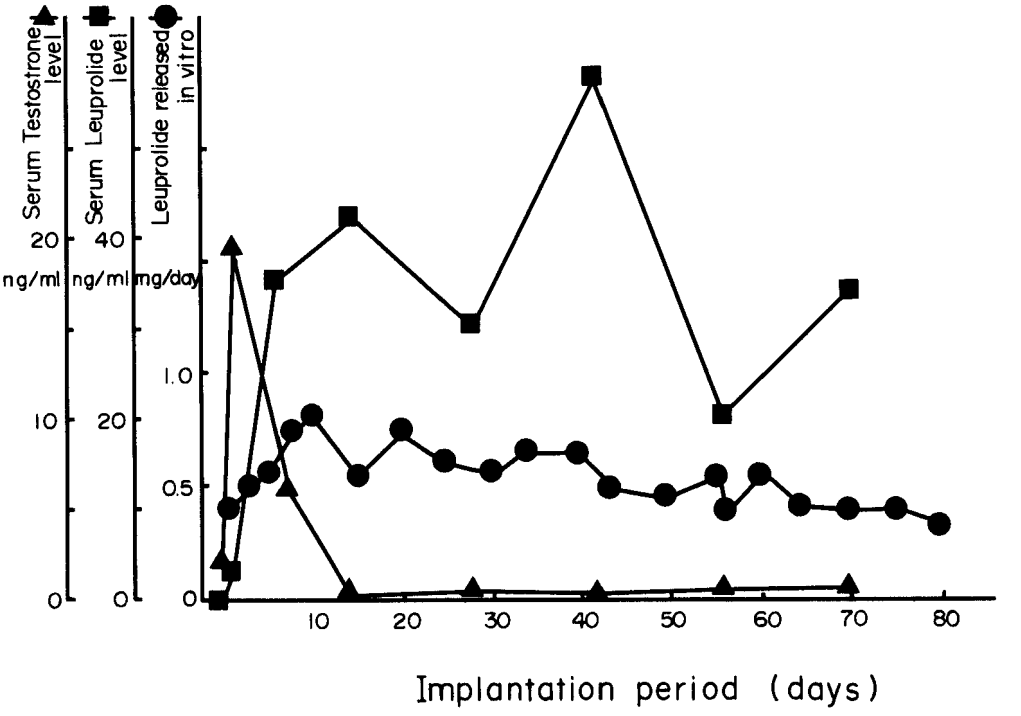

Fig. 4 Transition of serum concentration levels of various hormones by the implantation of LHRH analogue (Leuprolide) containing needle into Whister rats

The in vitro release profile was evaluated by immersing a composite in physiological saline solution and measuring an absorption intensity of the drug in a small portion of the solution spectroscopically at intervals. The in vivo test was carried out by subcutaneous implantation of a composite under the skin of back or body in rats. The LHRH analogue containing needle was inserted just under the skin of body by an injector with or without small cutting of skin in the clinical studies. This operation is simple and easy, giving no pain on the patients. The removal and renewal of the samples were easily carried out periodically. The artificial testis was implanted in the local organ position by a surgical operation. Fig. 2 shows a model scheme of therapies using the implantabnle compesites.

Results and Discussion

Cancer therapy on the prostates with the LHRH analogue-polymer composites[6)-9)]

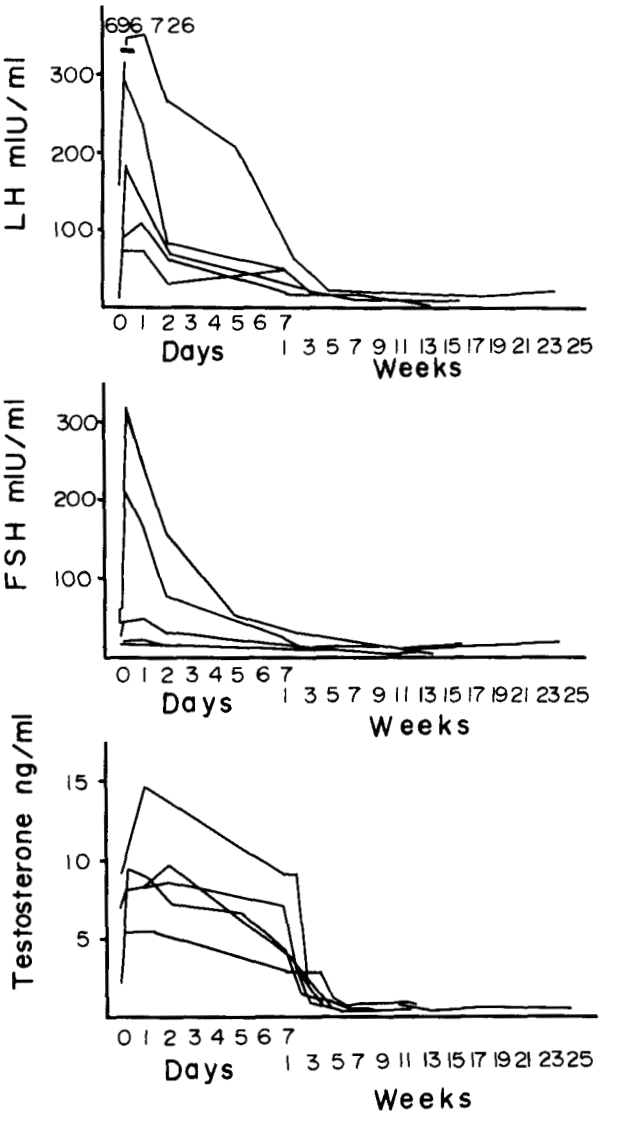

Fig. 5 Trandition of serum concentration levels of various hormones by the implantation of LHRH analogue containing needle in the clinical tests

LHRH analogue (Luteinizing Hormone Releasing Hormone analogue, Leuprolide) is noticing for cancer therapy against prostatic organ cancer without secondary reactions. However, daily injection of the hormone is a problem to give a trouble to the patient and doctor for a long period. The technique of implantable needle and the subcutaneous administration has been applied to the hormone cancer therapy on the prostate with the LHRH analogue containing needles.

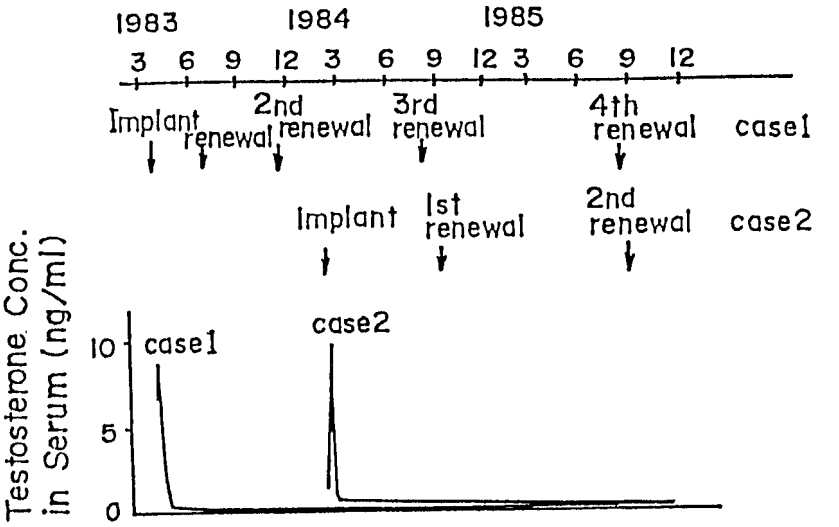

Fig. 6 Long period transition of serum concectration levels of testosterome in the continueous therapy with LHRH analogue-non-biodegradable vinyl polymer needles by implantation and successive renewals

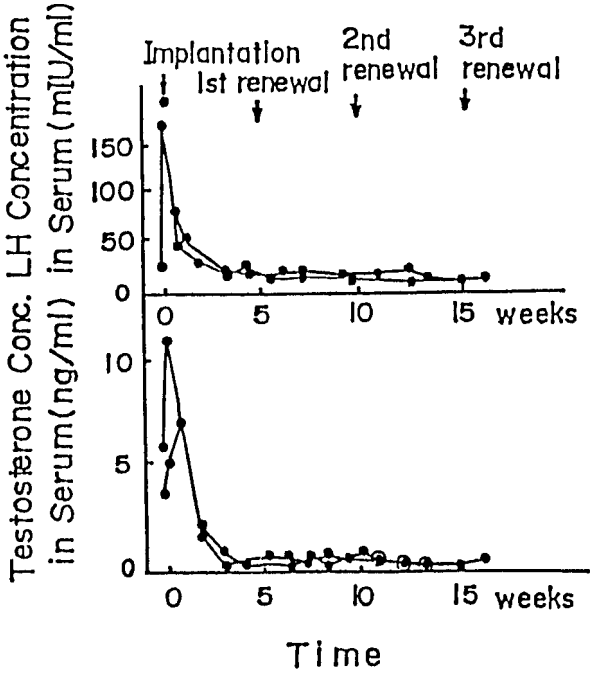

Fig. 7 Long period transition of serum concentration levels of hormones in the continueous therapy with LHRH analogue-biodegradable poly-lactic acid needles by an implantation and successive renewals

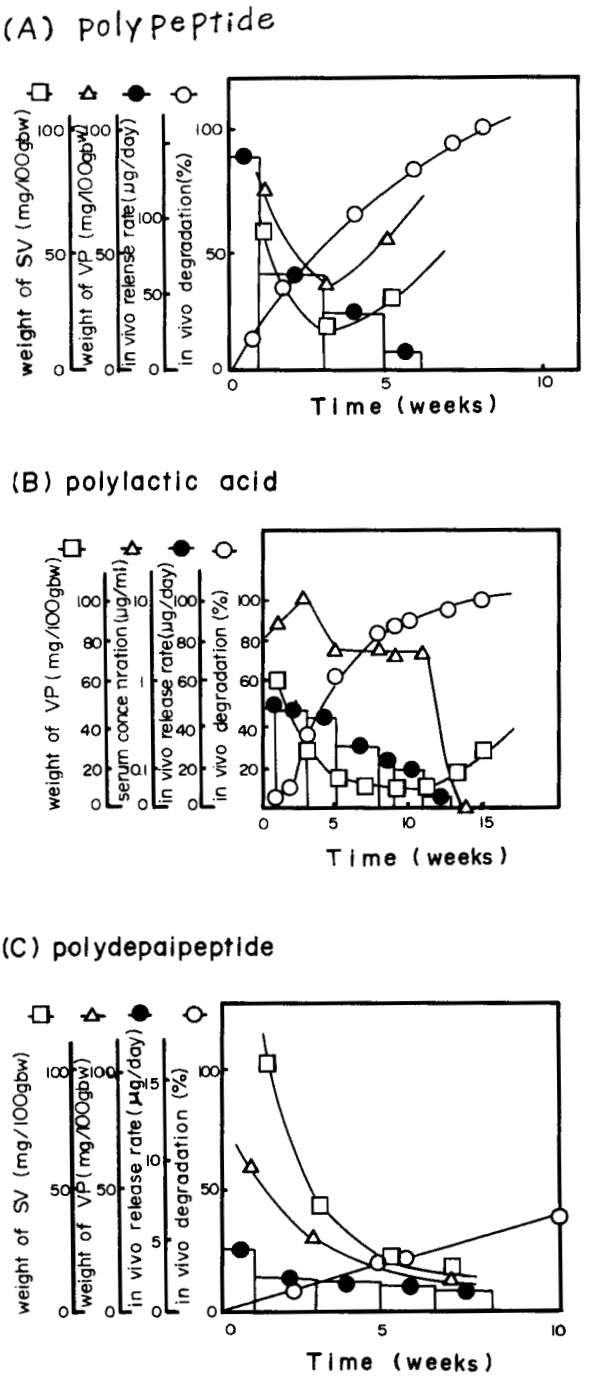

Fig. 8 Comparison of corelationship between drug release, polymer degradation and pharmacological effect (weight change of Ventral Prostate and Seminal Vesicle), in polypeptide, polylactic acid and polydepsipeptide needles by the implantation

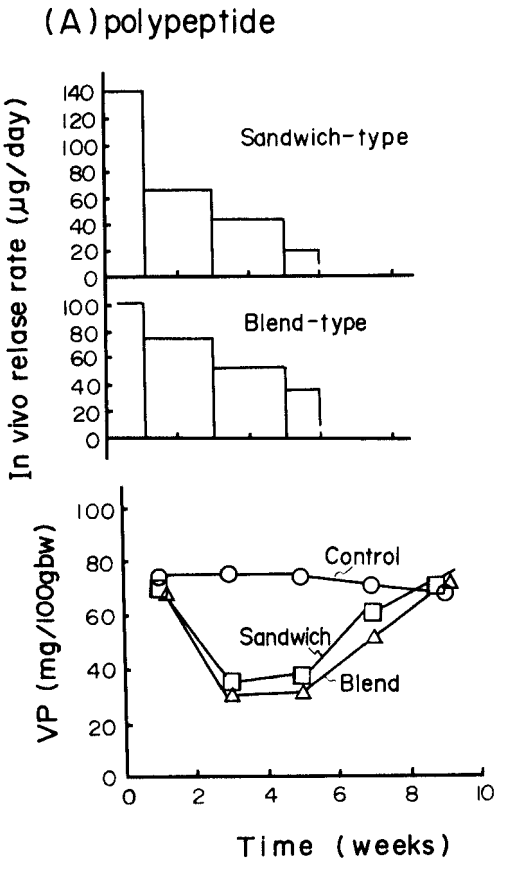

Fig. 9 Comparison of release profile and pharmacological effect in a homogeneous composite and sandwich structure composite in the two systems, polypeptide needle and polydepsipeptide needle

Fig. 3 is the in vitro release profiles of LHRH analogue from hormone-polymer composite having sandwich-like multi-layers structures. The daily dose of the released hormone can be varied widely by the kind of polymer and the structure of the composite. Fig. 4 is the result of implantation of composite in Whister rats and showed transitions of hormone concentration level in blood with the time. Testosterone level decreased with the implantation and kept a constant low value of castration level, while the LHRH analogue level continued a considerable level in the serum. Fig. 5 is the result of clinical tests by subcutaneous implantation for a relatively short time scale. The hormone levels in the

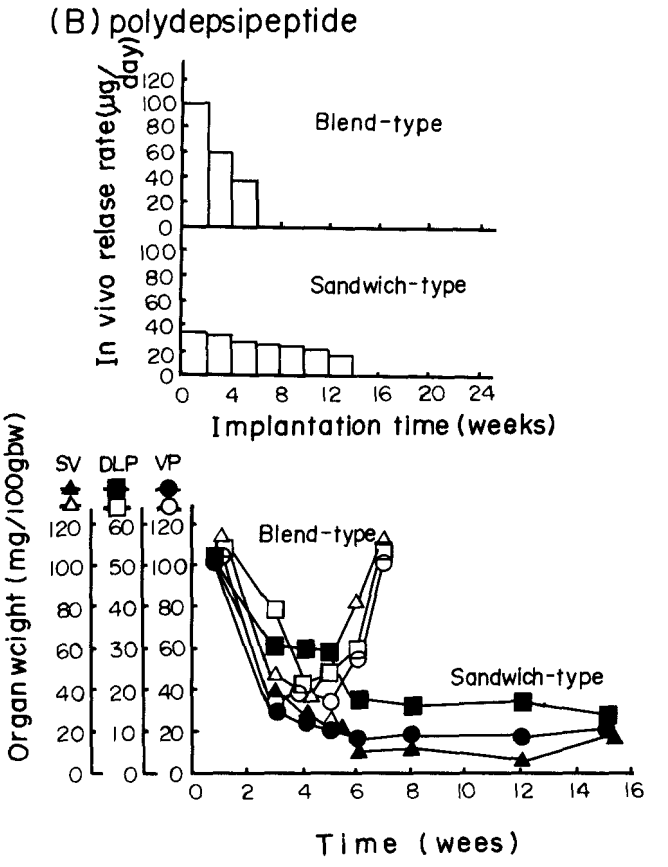

FIG. 9 CONTINUED

serum decreased after some weeks and then showed a continueous low level as the pharmacological effects. However, in thes technique the successive renewals of the needles at a suitable interval are possible. Therefore, a continueous long therapy has been carried out in the clinical treatments of cancer patients. Figs. 6 and 7 show the long period transitions of pharmacological effects by the successive implantation of needles of both types, non-biodegradable and biodegradable grades. As obvious in those results, testosterone, FSH and LH levels can be supressed for a long period continueously by the implantation and the renewals. The shrinkage of prostate organs was also observed remarkably. As already described, two types of composites, non-biodegradable needle and biodegradable needle, have been used for the relatively short period renewals and the long interval renewals

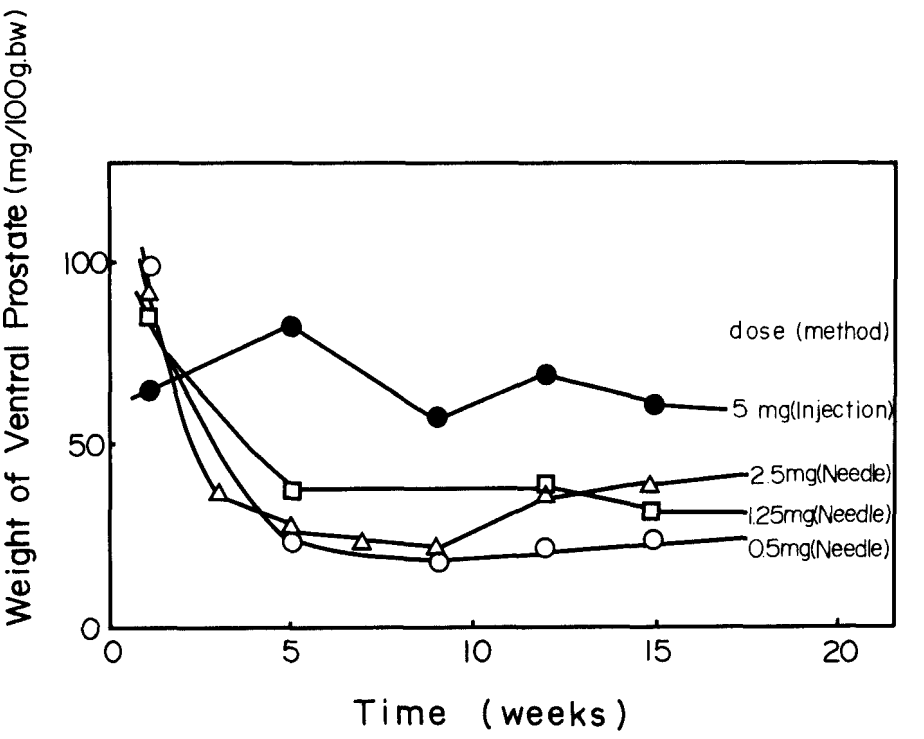

Fig. 10 Transition of Pharmacological efficacy with the implantation time in the needles containing various loading amount of LHRH analogue in the clinical tests

as shown in the figures. In the case of biodegradable needles, it is important to choose a polymer which is not so hydrophilic and erased gradually and smoothly from the surface for a relatively steady and durable effects of release and pharmacological efficacy. For examples, the comparisons of polypeptide as a strong hydrophilic carrier, and polylactic acid or polydepsipeptide as a much less hydrophilic carrier are shown in Figs. 8 and 9 in relation to the correspondence between drug release, biodegradation and pharmacological efficacy (organ shrinkage) in Fig.8 and to the difference in the same correspondence by the difference of composite structure, a homogeneous structure or a sandwich structure in Fig. 9. According to the result of Fig. 8, the hormone release and pharmacological effect began to decrease relatively fast in the middle stage of polymer degradation in the case of polypeptide, while the release and efficacy continued until the final stage of

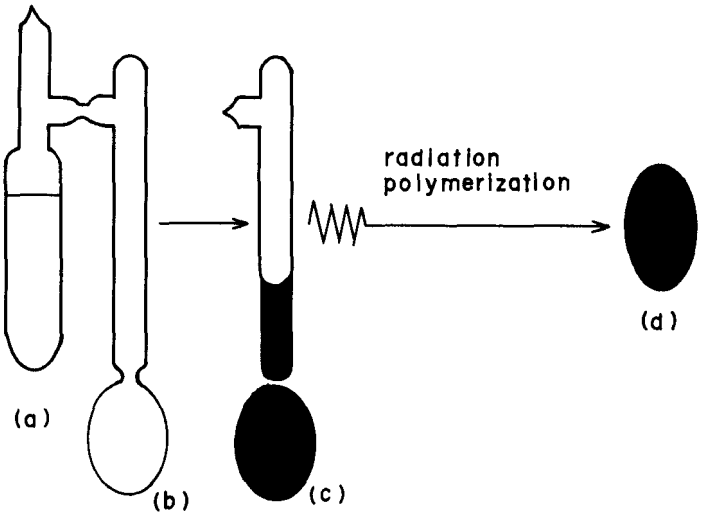

Fig. 11 Preparation of artificial testis
(a) monmer-testosterone mixture, (b) glass ampule (mold)
(c) sealing of casted mixture under vacuum,
(d) polymerized product

polymer degradation in polylactic acid. The results of Fig. 9 showed that the hormone release and efficacy seemed to be more steady and durable in the sandwich structure than in the homogeneous blend of drug and polymer, in the case of polydepsipeptide, while the release and efficacy showed the same patterns between the sandwich and the blend in polypeptide. Those results are due th the fact that an irregular and uncontrolled release of hormone occurred in the stark hydrophilic polymer owing to swelling and cracking of the sandwich structure.

One of the very advantages in this kind of long continueous therapy is an increase of bioavailability of drug and the resulting remarkable saving of hormone loading and dosage. Fig.10 showed the effect of change in the amount of hormone loading per one needle on the serum concentration of the hormone. According to this result, the dosage of only one tens of dosage amount in the injection caused the same effectiveness as in the injection.

Conclusively, it can be said that the technique of subcutaneous administration of implantable needle has been successfully applied to the hormone therapy against the prostatic cancers in the clinical tests of more than 20 patients. The

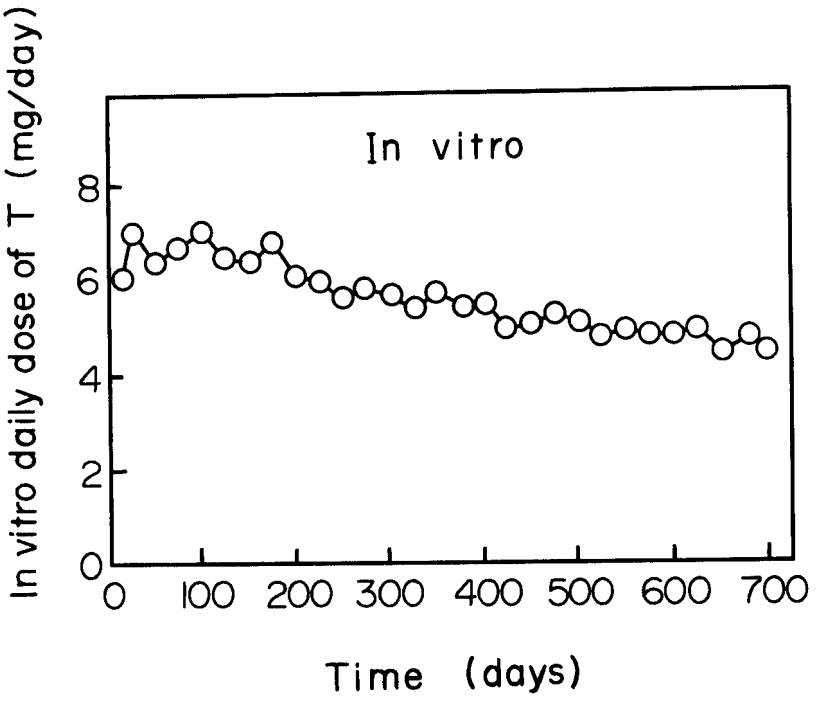

Fig. 12 Daily dose of testosterone (T) released from testicular prosthesis.
T: 7g, HEMA: 6.4g, irradiation: 1Mrad, -78°C, in vacuo

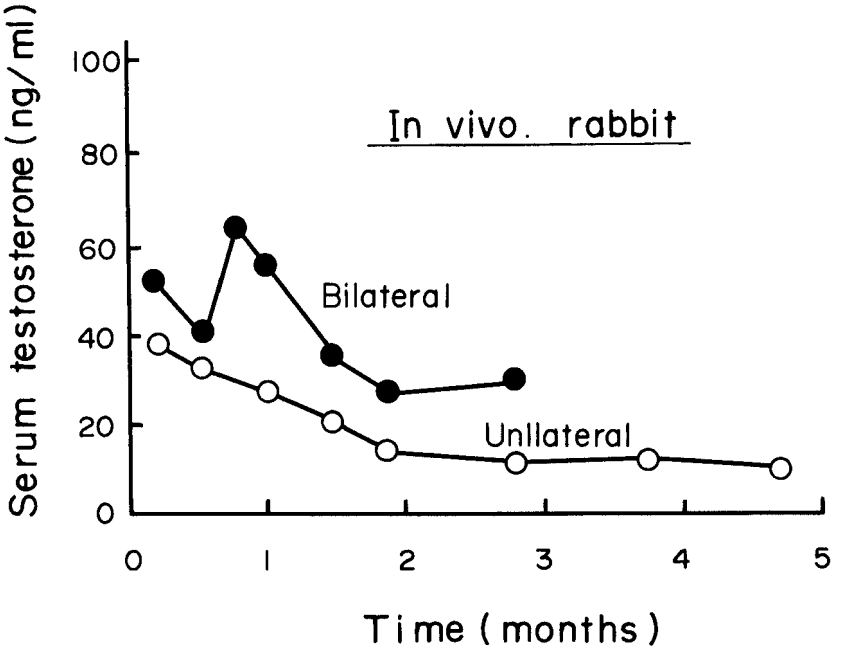

Fig. 13 Effect of the number of implants on serum testosterone level in castrated rabbits.

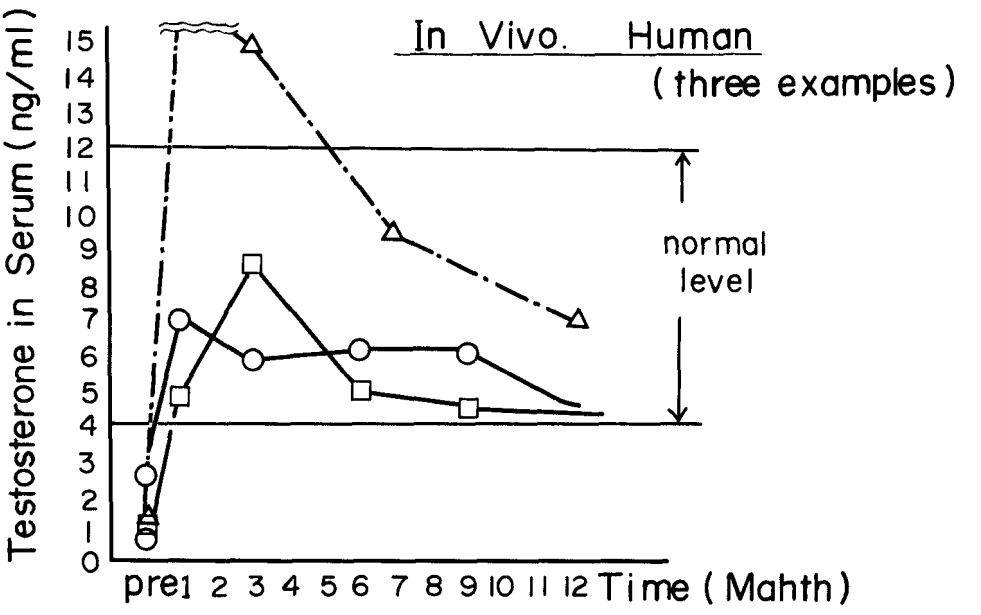

Fig. 14 Trasition of serum testosterone concentration in clinical tests

technique is very simple and easy and the efficacy has been proved remarkably.

Hormone therapy with the testosterone containing artificial testis [10)-13)]

The artificial testis including 10g of polymer and 6.4g of testosterone was prepared by radiation cast polymerization as in the procedure shown in Fig. 11. The release profiles of testosterone from the artificial testis are shown in Figs. 12, 13 and 14 for the in vitro test, in vivo test in animal and the clinical tests, respectively. The serum concentration level of testosterone can be kept in a normal value for a long period by the implantation as clearly seen in those studies. The testosterone release is expected to be durable for several years from a composite by theoretical calculation. The loading amount and releade rate of hormone can be varied widely by the choice of polymer based on the solubility of drug to the monomer and the hydrophilicity of the polymer. For example, the release rate of testosterone changed variously with the change of testosterone solubility to the monomer for polymerization to form a composite as shown in Fig. 15. It is needles to say that the use of non-

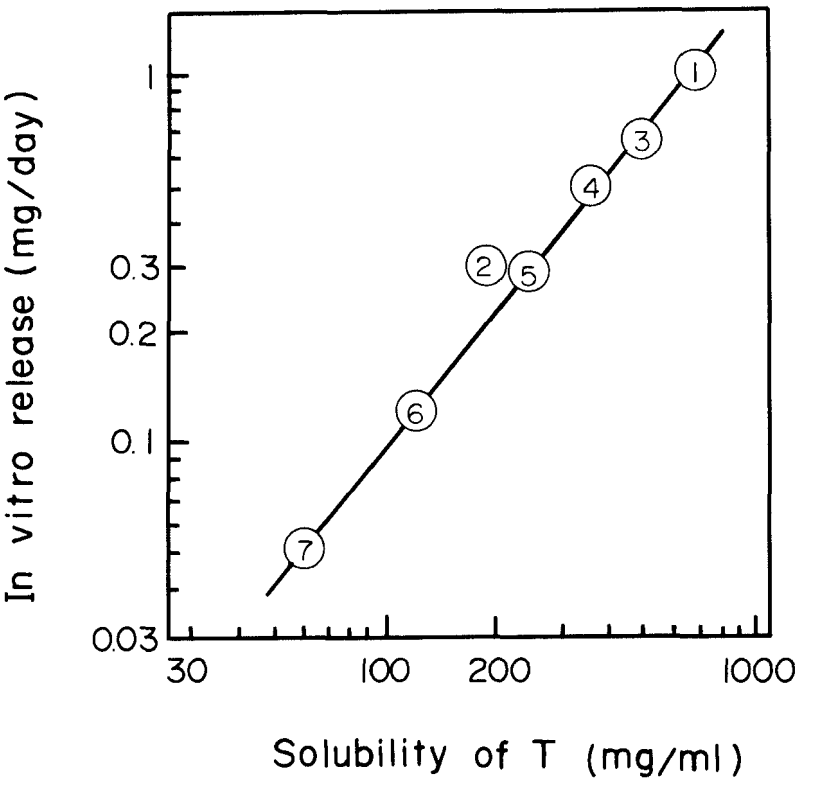

Fig. 15 in vitro release rate of testosterone (T) from the composite as a function of solubility of testosterone for vinyl monomer.
Composite: tablet form, T. 100mg, vinyl monomer. 0.3ml. irradiation: 1Mrad, -78°C, in vacuo
Carrier (dissolution condition of T): (1) 100% HEA (80°C, 1hr), (2) 100% HEMA (25°C, 1hr), (3) 100% HEMA (80°C, 1hr), (4) HEMA/2G, 80/20 (80°C, 1hr), (5) HEMA/2G, 50/50 (80°C, 1hr), (6) HEMA/2G, 20/80 (80°C, 1hr), (7) 100%/2G, (80°C, 1hr)

biodegradable polymer is suitable for carrier in the artificial testis.

Conclusion

The implantable drug-polymer composites was developed by means of radiation cast polymerization and hot pressing method. The composite has been applied to hormone therapies for a long continueous period. The LHRH analogue containing needle form composite has been used for cancer therapy of prostate cancers successfully by the subcutaneous implantation. The technique of

administration is simple and renewable. The non-biodegradable needle gave a longer period of duration of release and efficacy (for one year by one batch implantation) than in the biodegradable needle (for one month). Bioavailability of the hormone increased remarkably in the continueous long therapy than the daily injections. Another application has been done to the hormone therapy with implantable artificial testis also successfully. The duration of release of testosterone from the artificial testis continued effectively for two and three years by one batch implantation. Various male characteristics such as voice, hair and body line were recovered as the pharmaceutical responses remarkably by the implantation.

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