Effect of induced intrascrotal hyperthermia on testicular function in man

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THE CONCEPT that the scrotum regulates testicular temperature was first suggested by Crew[1] in 1922, on the basis of observations on temperature gradients made earlier by Benedict and Slack.[2] This view has been amply confirmed by studies on animals, first in 1923 by Moore and his associates[3-6] and by Fukui.[7-9] Further experimentation corroborating the adverse influence on spermatogenesis of intrascrotal hyperthermia continued in Moore's laboratory for many years.[10-13] More recently, Steinberger and Dixon[14] and, in our own laboratory, Zañartu, Maillot, and Scheer[15] and Naville and Scheer[16] have elucidated various aspects of the deleterious effect on spermatogenesis of wet heat applied to the scrotum of the rat. Similar results have been reported in the monkey.[17]

In the human, hyperthermia has been recognized as injurious to spermatozoa since the time of Hippocrates who mentioned this factor in two of his *Aphorisms*. During the past few decades, much supporting evidence has accrued. This includes the suppression of spermatogenesis in certain disorders, i.e., in cryptorchidism,[18, 19] varicocele,[20] and acute febrile diseases[21, 22]; the depressing effect of hot weather on conception rates (even though libido is not simultaneously affected)[23]; and a decrease in male fertility said to be associated with occupations carried out at high temperatures.[24]* In addition, there have been a few reports relating oligospermia to the wearing of tight Jockey shorts and suspensories which might increase intrascrotal temperature.[20, 25] One special case has come to our attention (reported by Fukui[7] in 1923), in which treatment with scrotal applications of hot paraffin in a young man suffering from epididymal tuberculosis was followed by testicular degeneration.

However, it was not until 1941 that experiments demonstrating the injurious effect of environmental heat on spermatogenesis in man were documented in the literature. MacLeod and Hotchkiss[26] obtained their results by utilizing dry heat in a fever therapy cabinet which enclosed the entire body of the subject.

As far as we know, the first attempt to determine the effect on human spermatogenesis of heat applied to the scrotum alone was made in 1955 by Dr. Clarence J. Gamble,[27] at Harvard Medical School. He found a decrease in sperm count in two cases, but did not pursue the subject further. Then, in 1959, Akira Watanabe[28] of Kyushu University in Japan described an ingenious apparatus for immersing only the scrotum in hot water. Our own experimental pro-

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*Dr. Stephen Plank has just called our attention to a more recent report on this aspect by O. A. Fomio et al. (Rev. Fac. Med. Tucuman 3: 139, 1961). Among approximately 700 men working under conditions of extreme heat, no adverse effects on spermatogenesis were observed in those whose scrota were structurally and functionally normal.

cedure for inducing intrascrotal hyperthermia by wet heat stemmed largely from his detailed reports of tests performed on 18 young men. In the early 1960's, we also began to investigate another method of increasing intratesticular temperature, i.e., by the wearing of insulating underwear. The suppressive effect of scrotal insulation on spermatogenesis, first demonstrated in the ram as far back as 1923,[4, 10] was more recently called to our attention as a possible etiologic factor in certain cases of human oligospermia.[20, 25] Preliminary studies on this aspect, carried out in our Clinic by Dr. Aloys H. Naville and Dr. Kenneth Scheer, were reported in 1963 by Dr. Naville.[29]

Our specific aim in pursuing this investigation was to explore the function of the scrotum in temperature regulation, as well as to study the effect of temperature changes on spermatogenesis. If it can be shown that induced intrascrotal hyperthermia is a cheap, easily available, harmless, and effective means of suppressing spermatogenesis without change in sexuality, yet permitting complete recovery of the former, a simple way of increasing temperature should prove readily acceptable to large numbers of men resistant to other more disturbing or expensive methods of reducing fertility.

The earliest mention of the possible applicability of this method to birth limitation which we have encountered was a statement made by Dickinson[30] that he had discussed the matter with Moore in 1930, "but at his [Moore's] suggestion, postponed for three years the urging of such tests on men until he [Moore] could say that recovery of function is demonstrated by study of several generations of progeny among experimental animals and that the test was therefore ready for transfer to man."

In a recent, excellent review, Glover and Young[31] advocate further investigation in this field with the aim that becomes increasingly urgent of providing a feasible means of alleviating the augmenting threat to civilization of accelerating population growth rates. With this problem in mind and encouraged by our preliminary results,[29] we were prompted to continue our studies on this aspect.

Plan of investigation

In order to obtain criteria for gauging the efficacy of various artifices to induce intratesticular hyperthermia, determinations of differences between intrascrotal and rectal temperature (hereafter referred to as S-R differentials) were carried out in three series of subjects as follows:

1. S-R differentials of normal individuals chosen at random were measured at room temperature in different postures, i.e., supine, sitting, standing, etc. (Series 1).

2. A comparison was made of the S-R differentials obtained at room temperature in euspermic and in oligospermic subjects and in those with varicoceles (Series 2).

3. S-R differentials were determined in euspermic individuals immersed below the neck in bath water at temperatures ranging between 38 and 43° C. (Series 3).

The effect of induced intrascrotal hyperthermia on spermatogenesis was investigated in: (1) euspermic subjects wearing various types of insulating underwear (Series 4); and (2) oligospermic husbands treated by intermittent immersion of the scrotum in hot water usually at temperatures of 43 to 45° C. (Series 5).

Materials, methods, and procedures

Intrascrotal-rectal temperatures (S-R differentials). Intrascrotal temperatures were uniformly determined by a thermistor probe.*

With the subject supine, 70 per cent alcohol followed by 2 per cent tincture of iodine was applied to the skin, usually of the left side of the scrotum. An area about 2 cm. in diameter was then desensitized with procaine. Through this and the subcutaneous tissue, a No. 14 gauge, open-grooved needle was passed until its point lay near the upper pole of the testicle. The ther-

*These were at first obtained from Yellow Springs Instrument Company, Yellow Springs, Ohio. Other probes capable of responding to at least 40° C. were furnished by Victory Engineering Corporation, Springfield, New Jersey, and by Fenwal Electronics, Inc., Framingham, Massachusetts.

mistor on the tip of a thin conductor cord was threaded through the needle up to its pointed end, either before or after its insertion into the scrotum. After placement in the scrotum, the needle was gently removed, leaving the probe in place. The conducting cord was fixed to the skin at the point of entry with narrow strips of adhesive tape.

To make sure the thermistor tip stayed in place, conductors were later modified by a separable prong-and-socket electrical joint placed about 12 inches from the tip. Thus, only a short part of the cord needed to be attached to the suprapubic skin of the subject who was to move about.

The conductor, whether in one or two sections, led to a telethermometer.* Readings on this were then converted to degrees Centigrade, each probe having been previously calibrated for voltage response to known temperatures.

Rectal temperatures were at first obtained by an ordinary glass thermometer inserted just beyond the internal anal sphincter.† Later, rectal temperatures were similarly measured by use of a thermistor which, with its cord, lay in a glass or polyethylene tube with one closed rounded end. The conductor cord, emerging from the open end, was connected with the telethermometer.

Intermittent heat treatments. In Series 3, where the entire infraclavicular body of the subject was immersed, the water in the bathtub was gradually heated from 38 to 43° C. The temperature of the water was monitored by a glass laboratory thermometer.

In these tests, the subject remained in the bathtub for periods of up to 2 hours.

In Series 5, only the scrotum was kept submerged, as carefully as possible, while the subject sat comfortably with an ordinary water-filled baby-bottle warmer between his thighs. The temperature of the water was regulated by the use of a rheostat within the range usually of 43 to 45° C., and was measured by a thermistor suspended close to but not touching the scrotum.

Intermittent heat treatment of the scrotum alone was carried out for half an hour on 6 alternate days.

Insulation tests. In Series 4, we tested the effect on spermatogenesis of various scrotal coverings, and correlated these findings with changes in S-R differentials.

The suspensories worn were of closely woven cotton and nylon cloth. The shorts were of the ordinary, loosely hanging, cotton variety ("boxer" shorts). The Jockey shorts were the more closely woven, closely fitting, commercial kind. At first, we used ordinary elastic jock straps, sometimes worn over a form-fitting pad of plastic and the kind of paper tissue found in surgical pads. Later, we preferred athletic supporters with an anterior pocket in which we inserted a properly shaped, folded piece of oilcloth. The two layers of this held between them a piece of surgical plastic and paper tissue of appropriate size and shape.

Observations were made of the effect on spermatogenesis of insulating materials when worn almost constantly, sometimes day and night, usually for periods of about 6 weeks. Obviously, temperatures were not consistently recorded during these insulation studies. In most cases, recordings were made on the same subject from which were calculated the extent of temperature change caused by the particular insulation.

In 2 of the 3 cases of insulation here reported, as also in four similar tests as yet uncompleted, the pretreatment level of sperm production was known from studies of at least two ejaculates with continence intervals of 2 to 3 days. In all experiments in Series 4, specimens at the same continence interval were promptly examined each week during the insulation and for several weeks following, until at least usual testicular function had been re-established.

Results

S-R differentials as influenced by various conditions.

Normal individuals chosen at random

*YSI Thermistemp Tele-thermometer, Model 43 TP, Yellow Springs Instrument Company, Yellow Springs, Ohio.

†We are indebted to Johan W. Eliot, M.D.[32] for advice to avoid higher rectal areas where approximation to large blood vessels might conceivably give falsely high readings.

studied at room temperature in different postures (Series 1). After 10 minutes of lying nude and supine, with scrotum resting on the anterior-median surfaces of thighs ordinarily separated, the average S-R differential of 36 normal subjects chosen at random was 2.38° C. (range: 0.8 to 5.2° C.; median: 2.64° C.). With one exception, the same individual showed only slight variations in S-R differentials on different days. In this one exceptional case, the variation of as much as 4.2° C. was thought to be due to a faulty use of the thermistor.

The ages of these 36 subjects ranged between 18 and 35 years with 3 exceptions (2 men in their early forties and one in his seventies). There was no evidence that age had any effect on S-R differentials.

Scrotal temperatures were influenced mildly by room temperature and by whether or not the penis was resting on the scrotum. Also, scrotal temperatures were found to decrease by about 1° C. if the subject, formerly supine, stood for about 7 minutes. Again, when the subject sat for 9 minutes, the temperature was likewise decreased according to the extent of contact between scrotum and both thighs: i.e., it was lower when the thighs were widely separated than when they were approximated to the scrotum.

Comparison of S-R differentials at room temperature of euspermic and oligospermic men and those with varicoceles (Series 2). The mean S-R differentials in the three groups of Series 2 were obtained under the same conditions as described for Series 1. The respective averages of 1.75° C. in 21 euspermic individuals, 1.93° C. in 37 oligospermics, and 2.0° C. in 8 men with varicoceles must await interpretation pending the

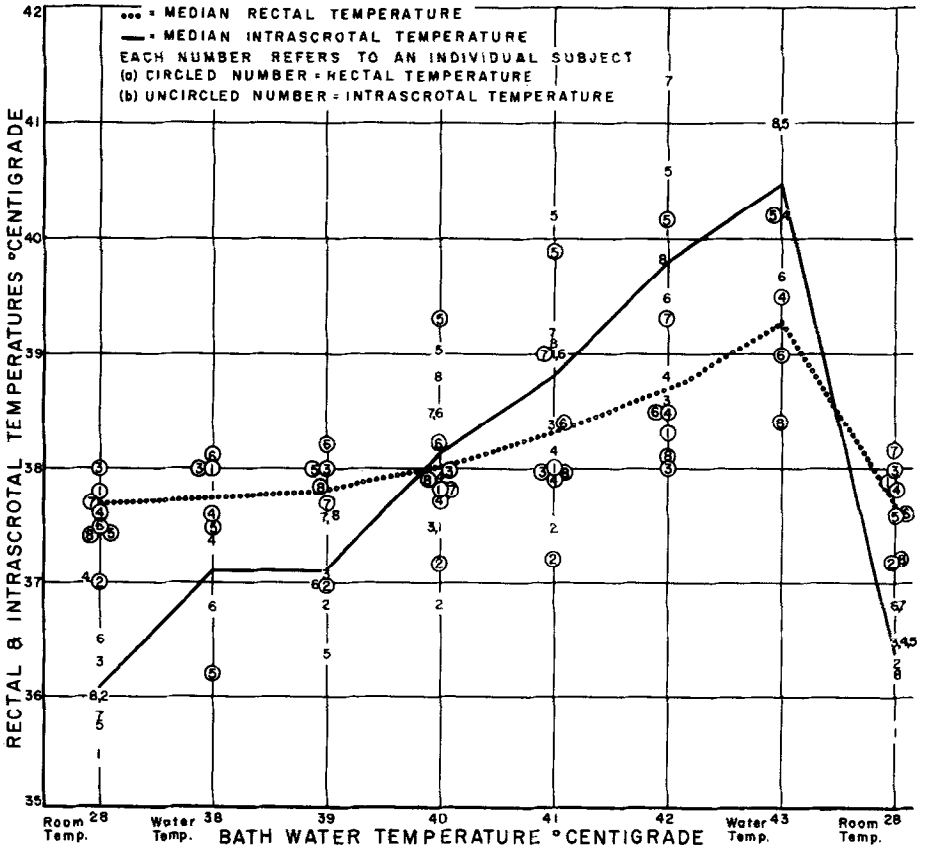

Fig. 1. Rectal and intrascrotal temperatures of 8 euspermic subjects immersed below the neck in bath water (38 to 43° C.).

accumulation of sufficient data to warrant statistical evaluation.

Effect on S-R differentials of infraclavicular immersion in hot baths. In another group of 8 euspermic subjects (Series 3, Fig. 1), immersion of the body below the neck in baths of 38 to 43° C. gave a most dramatic change in S-R temperature differentials. As the water became progressively hotter from 38° C., rectal temperatures remained fairly constant up to a water temperature of 39° C., at which they gradually rose. At about this point, the scrotal temperature began a steep incline, until, at about 40° C. water temperature, it started to exceed body temperature. When the water was at 43° C., the body temperature had risen from a median value of 37.7 to 39.3° C. The scrotal temperature during this change in water heat rose from 36.1 to 40.5° C., i.e., an inversion of the ratio of scrotal:rectal temperatures from 0.96 to 1.03, or a change in the S-R differential of 2.8° C. (from −1.6 to +1.2° C.).

Effect of induced intrascrotal hyperthermia on spermatogenesis.

Euspermic subjects wearing various types of insulating underwear. Series 4 was concerned with the effect on spermatogenesis of fairly constant insulation of the scrotum for about 6 weeks in each of 6 euspermic individuals, and in a seventh subject for approximately 14 weeks.

The concentration of spermatozoa began to decrease at about the third week after the start of insulation. The volume of semen, however, remained practically unchanged, reflecting the expected lack of deleterious heating effect on the Leydig cells as observed by Moore and Oslund[10] in the ram and, more recently, by Zañartu, Maillot, and Scheer[15] and by Naville and Scheer[16] in the rat.

The lowest concentration of sperm was reached from the fifth to the ninth week after the beginning of insulation, the sperm counts ranging between 5 and 25 million per cubic centimeter. The minimal level was largely determined by the subject's normal pretreatment count.

It was perhaps surprising that the quality of spermatozoa was not markedly influenced except in the one subject who had worn insulated jock straps for about 14 weeks; he showed a high degree of dyspermia.

All the men remained oligospermic from 3 weeks up to as long as 8 weeks after omitting insulation, and then, with one exception, gradually returned to their characteristic preinsulation sperm output. This level they all reached, at the latest, by the twelfth postinsulation week. In one exceptional case (Fig. 2), the sperm count rose, receded, and rose again before final recovery to a level even exceeding the preinsulation value. Two others have already shown a short-term rebound to levels well above those preceding insulation; the rest are still being followed.

That the sperm suppression was attributable to a lowering of S-R temperature differentials is shown in Fig. 3. The insulated athletic supporters diminished these by 1° C. This seems to be sufficient to interfere with normal sperm production.

Three of our subjects were questioned in regard to sexuality. None reported any noticeable effect on libido or function, either during or after prolonged insulation. Glover,[33] likewise, had failed to find evidence of any significant influence on libido in the ram as a result of scrotal wrapping. Nor had Young[34] noted any change in sexual vigor in the guinea pig during about 10 weeks of impaired fertility following heat treatment of the scrotum which occasioned degeneration to the germinal layer.

Oligospermic husbands treated by intermittent immersion of the scrotum in hot water (Series 5). Tests begun in our Clinic in 1962 by Drs. Naville and Scheer corroborated the observation of Watanabe[28] that suppression of spermatogenesis by heat applied to the scrotum was followed by an upsurge in sperm concentration exceeding the pretreatment level. Further results including data on 20 oligospermic subjects, in whom the scrotum was submerged in hot water (43 to 45° C.) for half an hour on 6 alternate days, have been briefly reported from our Clinic by Rivo and Rock[35] and will

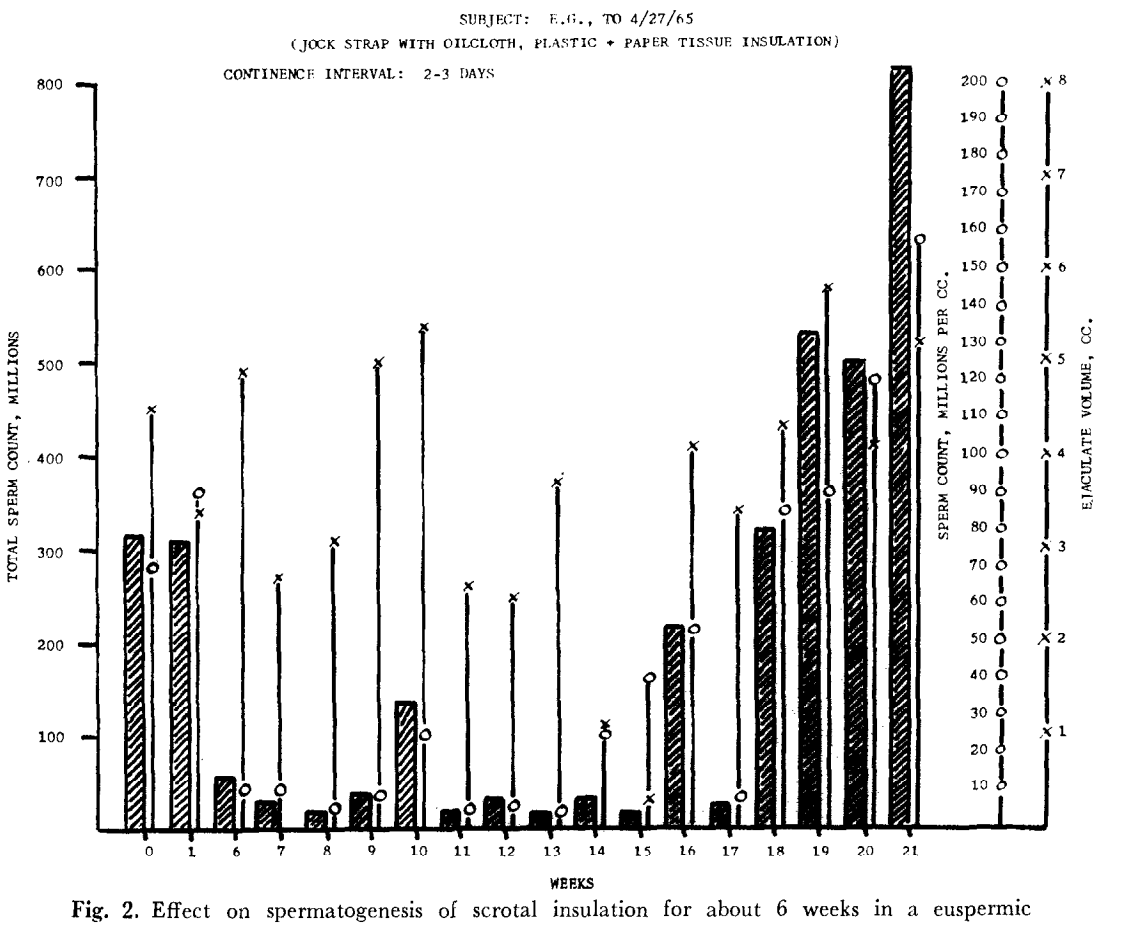

Fig. 2. Effect on spermatogenesis of scrotal insulation for about 6 weeks in a euspermic young man.

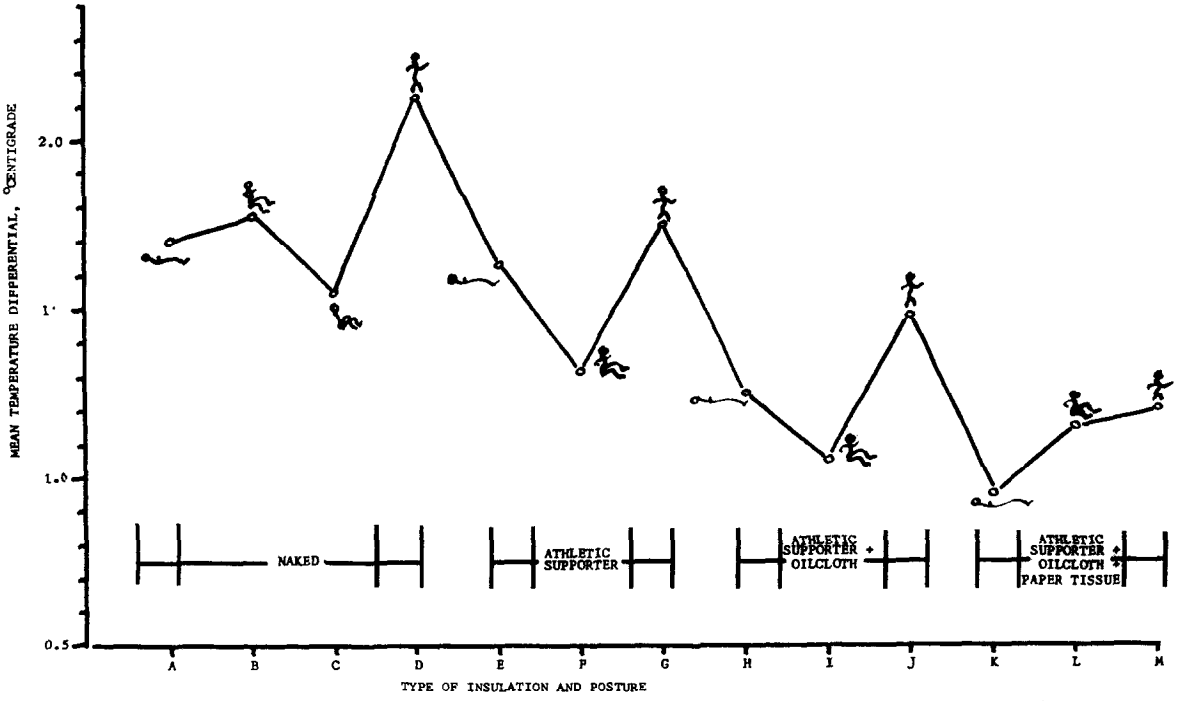

Fig. 3. Effect of insulation and posture on mean intrascrotal-rectal temperature differentials in euspermic subjects.

be described in detail in a forthcoming publication.

They found that the increase in temperature to which the scrotum was subjected was associated with a drop in sperm production within anywhere from 11 to 112 days. In 9 of the 20 men, the decrease in sperm count was followed by a rebound to levels higher than had prevailed prior to treatment. The peak of this rebound occurred, on the average, at about 8 weeks after cessation of therapy. The wives of 6 of these 9 men conceived 48, 61, 81, 114, 135, and 156 days, respectively, after the start of treatment. The pregnancies were all normal. This conceptive incidence, while not a statistically significant result, is suggestive of a therapeutic effect.

Summary

In order to determine the influence of intrascrotal hyperthermia on testicular function, studies were carried out on human males with the following results:

1. The mean scrotal-rectal temperature differential (S-R differential) of 36 normal men in the supine position at room temperature was 2.38° C. Changes in posture affected this gradient to some extent. Age apparently had no effect.

2. The mean S-R differential of 1.75° C. in 21 euspermic individuals, 1.93° C. in 37 oligospermics, and 2.0° C. in 8 men with varicoceles must await interpretation pending the accumulation of sufficient data to warrant statistical evaluation.

3. Infraclavicular immersion of 8 euspermic subjects in hot baths (38 to 43° C.) resulted in a shift of the median S-R differential from −1.6° C. to +1.2° C., i.e., an inversion of the S-R ratio from 36.1:37.7 to 40.5:39.3, or from 0.96 to 1.03.

4. In 6 euspermic individuals wearing insulating underwear almost constantly for about 6 weeks, and in a seventh subject who wore the insulating clothing for approximately 14 weeks, the sperm count began to decrease at about the third week after the start of insulation, reaching its lowest point between the fifth to the ninth week. With one exception, the men remained oligospermic for 3 to 8 weeks after omitting insulation and then gradually returned to their characteristic preinsulation sperm output. This was reached, at the latest, by the twelfth postinsulation week in all subjects.

No effect on volume of semen was observed. Nor was there any change in the morphology of spermatozoa, with the single exception of the subject who wore the insulation for as long as 14 weeks.

A lowering of the mean S-R temperature differential by 1° C. accompanied the suppression of spermatogenesis.

5. In 20 oligospermic individuals, application of wet heat (43 to 45° C.) to the scrotum for half an hour on 6 alternate days resulted in a decrease in sperm count within 11 to 112 days. In 9 of the men, the drop was followed later by a rebound to levels higher than had prevailed prior to treatment. The wives of 6 of the men conceived within 5 months of start of therapy. All pregnancies were normal.

Modification of spermatogenesis by induced intrascrotal hyperthermia may have practical application not only as a means of controlling fertility, but also as a therapeutic tool in certain cases of oligospermia. These studies are being continued with the aim of elucidating the exact mechanism whereby heat effects such changes in testicular function.

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Discussion

DR. WILLARD M. ALLEN, St. Louis, Missouri. It is a difficult task to discuss a paper by a man who is probably closer to immortality than most mortals ever get for reasons which all of you fully appreciate. Dr. Rock has shown remarkable courage and great wisdom in his advocacy of greater understanding and tolerance in the delicate area where religious beliefs and the sanctity of family planning seem to be in conflict.

In this particular paper he has delved into the relationship between scrotal temperature and the sperm count in man. He has, in fact, shown that man does not differ from other animals. It is well known in animals that sterility occurs within a few days when the testes are moved from their normal location in the scrotum to the abdominal cavity. The loss of fertility is presumed to be due to the increased temperature within the abdominal cavity. In animals, recovery of fertility is delayed for a few weeks after return of the testes to the scrotal sac.

The present study shows rather convincingly that suitable wrapping of the human scrotum elevates the intrascrotal temperature and also that there is a remarkable reduction of the sperm in the ejaculate to levels that usually represent infertility. In his subjects, as in animals, there is considerable delay in recovery of a normal sperm count after removing the scrotal covering.

This careful study, of course, lends substantial weight to the contention of the "infertility experts" that the apparel and sleeping habits may be responsible for male infertility in occasional instances.

I recall discussing this very problem with our medical students during World War II on an especially hot summer day. I mentioned to them that the number of births 9 months after the hot summer was considerably less than 9 months after the cold winter, and indicated that the high temperatures of summer might lead to enough increase in scrotal temperature to appreciably reduce fertility. One of the students

disagreed with this speculation and said, "I have another explanation. In a hot St. Louis summer it is just too hot to do anything."

DR. S. LEON ISRAEL, Philadelphia, Pennsylvania. It is important to place in the discussion the fact that the kind of spermatogenic depression that Dr. Rock observed with increased scrotal heat and the sort of rebound that follows constitute a familiar phenomenon in testicular physiology. This same sort of reaction has been shown by the work of Hotchkiss, Charny, and others. When you depress spermatogenic activity by testosterone, after an interval the rebound is of the same order of magnitude and it takes about the same time to appear.

DR. ROCK (Closing). In this study carried out in our clinic, we gave large doses of testosterone to some 40 men, three injections a week usually for 6 to 16 weeks, each injection being 50 mg. Three weeks after we started, sperm production had decreased and continued to fall. Of the whole group only one had a significant rebound. His wife became pregnant for the first time, and then proceeded to have 2 more children. This was the only case in which we were able to demonstrate the rebound. If it occurs, I think it is of very short duration.

Some 14 years ago, Dr. Bartelmez showed clearly in the monkey that there was no significant secretion that entered the uterine cavity in the postovulatory phase. The secretion from the glands comes before ovulation. This is of significance to the migration of spermatozoa, perhaps, and for the sustenance of the morula when it arrives. In the postovulatory phase, the secretion accumulates in the glands and cannot enter the uterine cavity. Since secretory activity is not limited to the postovulatory phase, we should not designate this phase as "secretory," but rather as "progestational."