Determination of tolerance level of impaired growth hormone secretion of humans

S.Lakshmi [*] and A. Manickam [**]

[*] Associate Prof. of Mathematics, K.N. Govt. Arts College for Women, Thanjavur, Tamilnadu,
[**] Assistant Prof.of Mathematics, Kings College of Engineering, Punalkulam, Pudhukkottai Dist., Tamilnadu.

Abstract

In this model it is supposed that shocks contributing additively to the amount of damage occur at random points of time. Common assumptions are that the sequence of shock amounts and the process N (t), say counting their number are stochastically independent and that the shock amounts ε_1 , ε_2…(Where ε_i is the increment of the damage caused by the i-th shock) are independent and identically distributed non-negative random variables. The tolerance level is given by some constant β > 0 fixed on advance. The objective is to stop the cumulative damage process $S_n = \varepsilon_1 + \varepsilon_2 + \dots\dots\varepsilon_n$ before it exceeds the level β, but such that S_n is not too far apart from β. In our medical Application we have taken impaired growth hormone secretions as shocks so that the occurrence times of the "shocks" should be modeled as random.

Keywords: cumulative damage, tolerance level, GH

Mathematical subject classification: 60 G_{xx}, 62H_{xx}, 62$P_{xx.}$

I. Mathematical model

Introduction

Imagine a person who is, from time to time, exposed to virtually injurious substances. One may think of a cancer patient whose therapy consists of (or includes) the administration of treatments (e.g., radiations)which have the side-effect of damaging not only the target tissues, but also not attacked parts of the organism. The amount of damage is assumed to vary in a random manner from person to person and from treatment to treatment, but after having taken place it is observable and can be measured in terms of a non-negative real number. Further we suppose that a certain level of damage can be fixed which can be maximally tolerated. On the other hand, in particular in the medical example, it may be advantageous to approach this threshold level as closely as possible in order to maximize the therapeutic effect of the treatment. To reach this goal the risk of passing over the threshold is needed. Here one is interested in maintaining the device as long as the amount of damage (and therefore the risk of failure) remains below a prescribed tolerance level. If damaging occurs in shocks, the problem is to decide at which distance of the current damage level from the threshold one should withdraw the device from the service.

One of the standard mathematical tools to address questions of this kind is the cumulative damage model [8].In this model it is supposed that shocks contributing additively to the amount of damage occur at random points of time. Common assumptions are that the sequence of shock amounts and the process N(t),say counting their number are stochastically independent and that the shock amounts ε_1 , ε_2 ….. (Where ε_i is the increment of the damage caused by the i-th shock) are independent and identically distributed non-negative random variables. The tolerance level is given by some constant β > 0 fixed in advance. In medical treatments the "shocks" are caused by administered dosages so that the process N(t) can usually be considered as deterministic or stochastic.However,this difference is of no importance for the problem at hand: The objective is to stop the cumulative damage process $S_n = \varepsilon_1 + \varepsilon_2 \dots + \varepsilon_n$ before its exceeds the level β ,but such that S_n is not too far apart from β.We formalize these requirements as follows. Let F_n be the σ - field generated by ε_1 , ε_2 …..ε_n and let F_n be the trivial σ- field. Then consider the set F of all stopping times relative to $(F_n)_{n\geq0}$,that is all random variables τ such that $\{\tau = n\}\epsilon F_n$ for all n≥0 and $P(\tau < \infty) = 1$ we fix some $\epsilon \epsilon [0,1)$ and the set $F_\varepsilon = \{\tau\epsilon\ F_n\ /\ \ P(S_\tau > β) \leq \tau \}$ then the aim is to find a stopping time in which maximizes $E(S_\tau / S_\tau \leq \beta)$.Let F be the common distribution function of the X_i and assume that F is continuous and F(β) > 0. Our main result is that for $\varepsilon\epsilon (1- F(β),1)$ a control limit policy is optimal .That is, there is an S=S(ε) ϵ (0,β) such that σ - inf{n≥1/$S_{n \geq S(\varepsilon)}$ } is optimal.The control limit S(ε) can be determined as solution of the equation

$$1 - F(β) + \int_0^x \left(1 - F(\beta - t)\right) dU(t) = \varepsilon \dots\dots (1.1)$$

Where U is the renewal measure associated to F.As examples, exponential and uniform shock amount variables are treated.

The problem of approaching a goal value β as closely as possible can also be formalized in another way. If any exceedance of β is to be avoided.

One can reward the reached degree of closeness of S_n to β from below by a function f(S_n) as long as $S_n \leq \beta$ .We shall assume that   f:[0,β] → [0, ∞) is monotone non decreasing and concave. Usually the penalty α will be negative but we shall even solve the optimal stopping problem for any α < f(β).Incidentally,the case f(S_n) → S_n will be the starting point for the solution of our main problem formulated above. If it is only the closeness of S_n to β which matters, one may measure the distance to the goal by some "loss function"g(| $S_n - \beta$ |),where g:[0,∞)→ [0. ∞) is non decreasing and satisfies g(0) = 0 .If g is additionally assumed to be convex, an optimal stopping time for the corresponding minimization problem.

Optimal stopping in deteriorating stochastic systems has been mainly studied in the context of replacement policies. For example, [10] derived an optimal replacement policy for the case in which the damage process is compound poisson. Considered a similar model with a more general structure, where the shocks appear at discrete points in time. In [13] replacement is also allowed between the occurrence times of shocks. However, this paper is not concerned with replacements of deteriorating "items" but with **trying to exploit the tolerance of one item at a maximal degree subject to a bound for the probability of failure**. Continuous time problems related to the optimal stopping problems of below have been studied by [1, 13] for Markov and semi Markov processes.

2. Two problems of optimal stopping

Let S_n =0 and denoted by I_A the indicator function of the event A. In this section the following two optimal stopping problems are solved.

(a) Maximize E(f(S_τ) $I_{[S_\tau \leq \beta]}$ +α $I_{[S_\tau > \beta]}$) with respect to all stopping times $\tau \epsilon F$
Here f:[0,β] → [0, ∞) is assumed to be a concave,nondecreasing function and αϵR is a constant satisfying α<f(β).

(b) Minimize E(g(|$S_n - \beta$ |)) with respect to all stopping time $\tau \epsilon F$ f:[0,β] → [0, ∞) is assumed to be a convex function for which g(0)=0 and g(S_n) is integral for all n≥ 1.
Observe that g attains its minimum at 0 is monotone non-decreasing.for sϵR we define $\sigma(s) \epsilon F$ by $\sigma(s) = \inf\{n \geq 1/S_n \geq S\}$.

Theorem2.1:

(a). If f(0)≥$\int_0^\beta f(x)dF(x) + \alpha\left(1 - F(\beta)\right)$......(2.1)

The stopping time $\sigma = 0$ is optimal for problem (a).If (2.1) doesnot hold.there is an

s$\epsilon (0,\beta)$ satisfying

f(s) = $\int_0^{\beta-s} f(s + x)dF(x) + \alpha\left(1 - F(\beta - s)\right)$.....(2.2)

In this case $\sigma(s)$is optimal for problem (a).

(b). If g(β)≤$\int_\beta^\infty g(x - \beta)dF(x) + \alpha(1 - F(\beta - x)dF(x))$...(2.3)

$\sigma = 0$ is optimal. Otherwise there is an u $\epsilon (0,\beta)$

such that $g(u) = \int_u^\infty g(x - u)dF(x) + \int_0^\infty g(u - x)dF$.(2.4)

and $\sigma(\beta - u)$ is optimal.

Proof: Let Xn =f(S_n) I $_{[S_\tau \leq \beta]}$ +α I$_{[S_\tau > \beta]}$. We shall show that, for any n≥0,

{$X_n \geq E(X_{n+1}/F_n)$ C $X_{n+1} \geq E(X_{n+2}/F_{n+1})$ }… .(2.5)

To prove (2.5) note that on {$S_{n+1} > \beta$} we have X_{n+1} = x_{n+2}=….=α so that

{$S_{n+1} > \beta$}C $X_{n+1} \geq E(X_{n+2}/F_{n+1})$.Thus it suffices to prove that

{$S_{n+1} \leq \beta$, $X_n \geq E(x_{n+1}/F_n)$} C { $S_{n+1} \leq \beta, X_{n+1} \geq E(x_{n+2}/F_{n+1})$}..(2.6)

3. Application

Introduction

Growth hormone (GH) release was studied in adults of normal stature, ages $21 - 86$ year. The subjects were $85 - 115$ % of ideal body weight, between the 5th and 95th percentiles in height, and free of active or progressive disease 9 to 12 individuals in each decade from third to ninth were evaluated. The following criteria of GH status were measured; serum GH concentration, analyzed by radioimmunoassay at half hour intervals for 4h after onset of sleep, and at 1-h intervals from 8 a.m to 4 p.m in 52 subjects; daily retention of N,P and K in response to 0.168 U human (h)GH/kg body wt3/4/day in 18 subjects. All 10 individuals,$20 - 29$ year old, released substantial amounts of endogenous GH obtained during both day and night (average peak serum GH obtained during day and night was 7.3 and 20.3 ng/ml,respectively.

In children and adolescents, serum growth hormone (GH)l levels rise to peak values of 20-50 ng/ml during the first 4 h of sleep (1-3). In adulthood, the nocturnal peaks of serum GH are less pronounced (4-7). Some individuals over age 40 release little GH during sleep. Two easily measured consequences of impaired secretion are subnormal levels of circulating somatomedins [6], and hyper responsiveness to the anabolic effects of exogenous human (h)GH, reflected by retention of abnormally large amounts of N, P, and K during treatment with a standard dose of hGH (10- 12).The object of this study was to investigate the prevalence of impaired GH release in the adult population of normal stature

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by measuring waking and sleeping release of endogenous GH, and anabolic responsiveness to exogenous hGH. Because endogenous GH release is influenced by nutritional state (13-19) and by disease (20-23), we confined the study to ambulatory adults who were within 15% of ideal body weight and free of progressive or active disease.
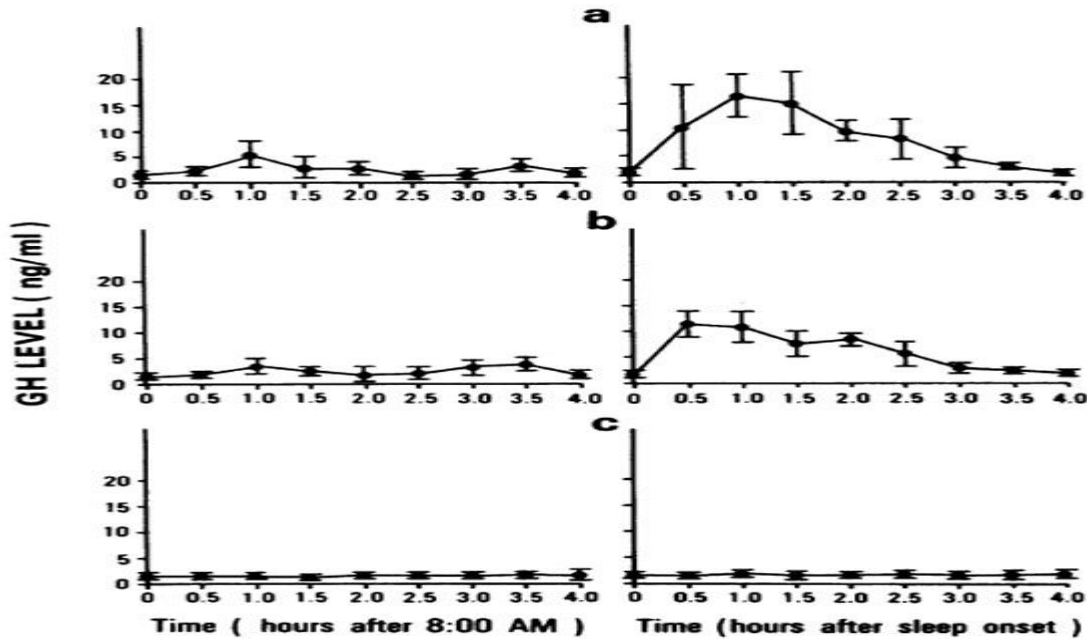

FIGURE -1 (a) Average serum GH concentration curves for six subjects ages 20-29 in both the waking (left) and sleeping (right) state. (b) Average serum GH concentration curves for six subjects ages 60-79 with SmC≤0.64 U/ml in both the waking (diurnal) and sleeping (nocturnal)state.(c) Average serum GH concentration curves for six subjects ages 60 – 79 with SmC >0.64U/ml in both the waking (diurnal) and sleeping (nocturnal)state.

Phase A: 20-29 year olds. Average serum GH concentration curves for these six subjects in both the waking and sleeping state are shown in Fig-1(a).For patients in the third decade, the peaks of serum averaged 7.3 (day) and 20.4ng/ml (night);the average areas per hour were 2.84 (day) and 8.64 ng/ml (night).The average level of plasma SmC concentration was 1.38 U/ml.

Phase A: 60 – 79 Year olds. Average SmC level was significantly lower than in the 20 – 29 years olds (P< 0.001).In 6 of 12 subjects,SmC level was below the lower 2.5 % tolerance limit for the third decade (<0.64 U/ml).The 60 – 79 year group was now divided into two subgroups based on whether SmC was greater or less than 0.64U/ml Subjects with SmC >0.64 U/ml resembled the 20 -29 year olds in that they had substantial release of GH during the day and night, and an unresponsiveness of elemental balances and SmC to exogenous hGH.Fig-1(b) displays the average serum GH concentration curves for these subjects in both the waking and sleeping state. their average peak day and night serum GH levels were 5.4 and 14.1 ng/ml.

Fig-1 (c) displays the average serum GH concentration curves for these six subjects in both the waking and sleeping state. Average day and night peak serum GH levels were only 3.3 and 3.2 ng/ml. Treatment with hGH raised the plasma SmC concentration from the initial average value of 0.27 U/ml to the post-treatment average value of 0.92 U/ml, which was within the normal range for the third decade.

4. Mathematical Results
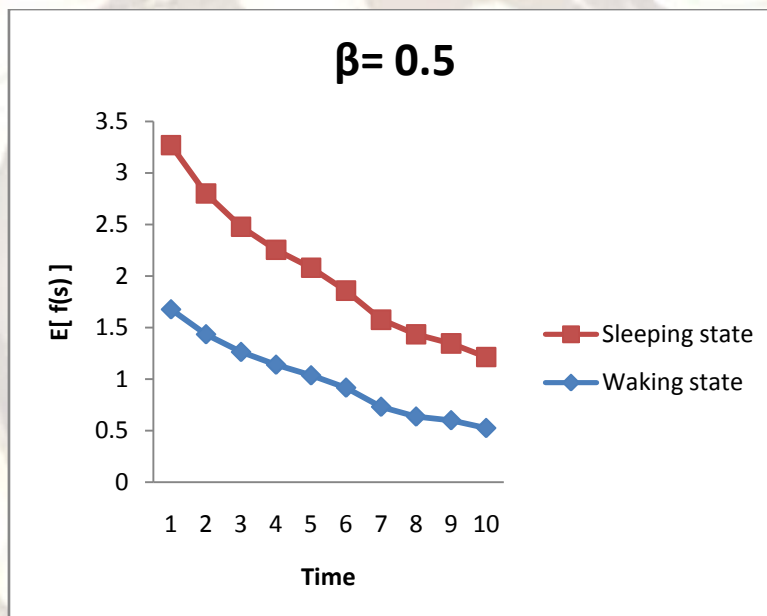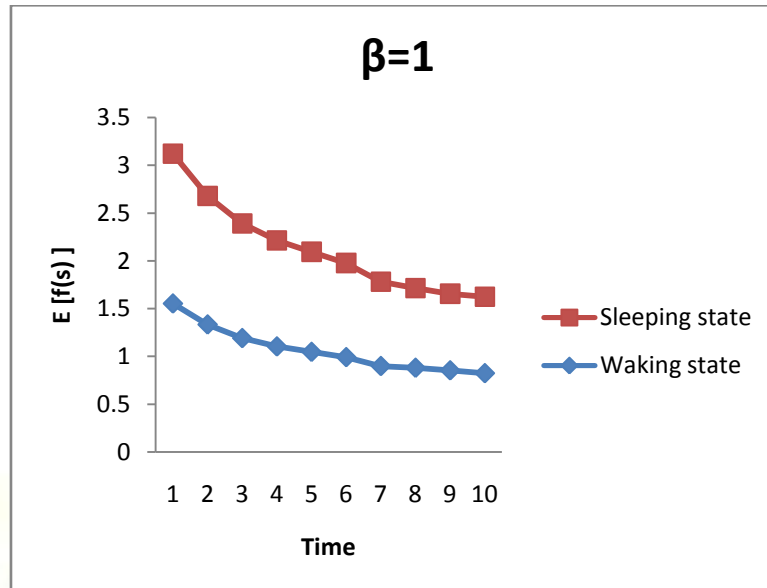
5. Discussion

The data show a progressive decline in GH secretion and plasma SmC level from the third to the ninth decade. Within each decade, however, endogenous GH status showed considerable variability. For example, in 55% of the subjects over 69, little day or night release of GH (<4 ng/ml in any serum sample), is measured, whereas in the remainder hormone release was readily detected. Associated with the failure to release GH was a Hyper responsiveness to the anabolic action of exogenous hGH, and a subnormal plasma level of SmC, in comparison with the corresponding features in adults of the third decade. Because of the strong correlation between GH release and plasma SmC concentration in the adult population studied, the latter level could be used as an indicator of endogenous GH status in these individuals. In subjects with under nutrition (13-19), liver disease [5, 9] renal insufficiency or hypothyroidism [7], however, SmC is not a reliable indicator of GH release.

GH release must have been adequate during the growing years, because the study population was of normal height (within 5-95 percentiles). Secretion of GH continued at a substantial rate until age 30, and then began to diminish. Impairment of GH secretion begins to appear in the fourth decade and thereafter becomes more common with advancing age. The mechanisms responsible could be operating at the (a) suprahypothalamic, (b) hypothalamic, (c) hypophyseal, or (d) peripheral level. The cessation of nocturnal GH release in old age could be related to the decline in slow wave sleep that occurs during the

same decades [7]. GH releasing mechanisms depend on α-andβ-adrenergic, dopaminergic,and serotonergic neural circuits [2].Levels of bioactive amines in some brain regions change with advancing age (37-40); such alterations could influence hypothalamic secretion of GH-releasing factor and of somatisation. The size of the pituitary gland decreased by only 20% in old age [11].The concentration of GH within the adult rat or human hypophysis does not decline with advancing age (42-45). Nevertheless, the amount of GH released in vitro by the aged rat pituitary gland in response to a hypothalamic GH-releasing factor preparation is markedly less than by the young gland [4].GH promotes bone Formation (56-59), increases renal blood flow, and stimulates protein synthesis in the lean body mass. The geriatric decline in each of these functions (63-67) could result in part from cessation of GH secretion. The present findings imply a possible new clinical use for hGH. Those older individuals who have stopped secreting endogenous GH are highly responsive to the anabolic actions of the exogenous hormone at a dose (0.168 U/kg BW314/d) similar to those used to treat GH-deficient children (0.125-0.25U/kg BW3'4/d). In such adults, whose proportion in the population increases progressively with age, hGH provides a new way of accelerating protein synthesis and stimulating positive N balance.

6. Conclusion

In the mathematical model the control limit policy is proved to be optimal, which is used for GH secretion and the expectation of the function f(s) show a progressive decline in GH secretion from third to ninth decade. Within each decade, however, endogenous GH status showed considerable variability. For example, in 55% of the subjects over 69, little day or night release of GH (<4 ng/ml in any serum sample), is measured**,** which is coincide with the medical findings.

References

[1]. Feldman RM (1976) Optimal replacement with semi-Markov shock models J Appl Probab 13:108- 117.

[2]. Krulich, L.1979.Central neurotransmitters and the secretion of prolactin, GH, LH and TSH.Annu.Rev.Physiol.41:603-615.

[3]. Othmer, E., W.R.Levine, W.B.Malarkey, J.C.Corvalan, M.P.Hayden-Otto P.M. Fishman, and W.H.Daughaday.1974.Body build and sleep-related growth hormone secretion. Horm.Res.(Basel).5:156-166

[4]. Pecile,A.,E.Muller , and G.Falconi.1965.Growth hormone releasing activity of hypothalamic extracts at different ages. Endocrinology. 77:241-246.

[5]. Phillips, L.S., A.T.Oraeski, and D.C.Belosky.1978.Somatomedin and nutrition, IV.Regulation of Somatomedin activity and growth cartilage activity by quantity and composition of diet in rats.Endocrinology.103:121-127.

[6]. Phillips, L.S., and R.Vassilopoulou-Sellin.1980. Somatomedin.Part I.n.Engl.J.Med.302:371-380.

[7]. Quabbe, H.J.1977.Chronobilogy of growth hormone secretion.Chronobiologia 4:217-246.

[8]. Saunders SG (1982) Cumulative damage models.In: Johnson S, Kotz NL (Eds) Encyclopedia of Statistical Sciences.Wiley, New York,pp 230-233

[9]. Smith, S.R., P.J.Edgar, T.Pozefsky, M.K.Chhetri, and R.E.Prout.1974.Growth hormone in adults with Protein-calorie malnutrition.J.Clin Endocrinol.Metab.39:53-62.

[10]. Taylor HM (1975) optimal replacement under additive damage and other failure models.Nav Res Logist Q 22:1-18.

[11]. Verzar,F.,and H.Spichten. 1966. The role the pituitary in the aging of collagen.Gerontologia (Basel).12:48-56.

[12]. Zuckerman D (1978) optimal stopping in a semi-Markov shock model J Appl Probab 15:629-634.

[13]. Zuckerman D (1980b) optimal stopping in terminating one-sided processes with unbounded reward functions. Z Oper Res 24:145-154.