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# Tyrosine-Based Monitoring of Glucocorticoid Therapy of Systemic Lupus Erythematosus

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## 1. Introduction

The present chapter considers only one aspect of glucocorticoid therapy of patients with systemic lupus erythematosus (SLE): a possibility of using blood level of tyrosine for monitoring glucocorticoid therapy. Thus, problems of SLE etiology and pathogenesis, as well as numerous schemes of SLE therapy are beyond the limits of this chapter. In the chapter normal catabolism of tyrosine and some congenital disturbances in catabolism of this amino acid are considered. But in the great majority of cases, specific features of tyrosine catabolism allow us to admit that tyrosine content in blood should be determined by the liver functional competence, in particular, its ability to synthesize an adaptive enzyme tyrosine aminotransferase and by entrance into the liver of glucocorticoids, natural hormones or glucocorticoid preparations. This chapter also presents experimental data obtained on adrenalectomized rats and observations on children with adrenogenital syndrome which clearly demonstrate blood tyrosine dependence on glucocorticoids and support the idea of using blood tyrosine content as a promising laboratory parameter for monitoring glucocorticoid therapy, similar to blood glucose for insulin. Some observations on glucocorticoid therapy in patients with SLE compared with changes in their blood tyrosine level which were earlier published only in Russian are presented, as well as the imaginary tyrosine-based monitoring of these cases.

## 2. Approaches to treatment of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) seems to be the most striking example of using corticosteroid, or glucocorticoid, preparations in non-endocrine diseases as the most powerful anti-inflammatory, immunosuppressive, anti-allergic, antitoxic, etc. agents. Sixty years ago glucocorticoids allowed clinicians to radically change the fate of patients with SLE – this collagen disease stopped to be virtually lethal (Dubois, 1974; Schroeder & Euler, 1997; Ioannou & Isenberg, 2002; Goldblatt & Isenberg, 2005; Nived et al., 2008). In modern schemes of SLE treatment glucocorticoids are usually combined with various other preparations: cyclophosphamide, mycophenolate mofettil, rituximab, cyclosporine, azathioprine, etc. (Ntali et al., 2009; Ponticelli et al., 2010). In addition to their specific effects, all these preparations are given, in particular, in order to lower the dose of steroids, however, up to now glucocorticoids remain the cornerstone in the schemes of SLE treatment. Therefore, in SLE all problems associated with using glucocorticoid preparations

in non-endocrine diseases are clearly pronounced and still urgent: the unpredictability of efficiency of glucocorticoids and nearly inevitable serious side effects, difficulties and sometimes even the impossibility to abolish glucocorticoids, and glucocorticoid resistance of some patients – such was the situation at the beginning of the "steroid era" and it is nearly the same nowadays, and the same problems are still urgent.

Since 1966, life-threatening exacerbations of SLE are sometimes treated by pulse-therapy – intravenous injection of very high doses of glucocorticoid preparations – up to 1 mg methylprednisolone daily for three days. However, the rapid immunosuppressive effect is often accompanied by various infections. But this regimen of pulse-therapy has been formed historically, although it is not excluded that lower doses of glucocorticoids would be similarly effective (Badscha & Edwards, 2003; Franchin & Diamond, 2006).

It is obvious that the existent schemes of using glucocorticoids in SLE are far from optimal, and to specify and refine therapeutical approaches there are some attempts to compare the glucocorticoid efficiency in SLE with different individual characteristics of the patients, such as the number and type of glucocorticoid receptors (Li et al., 2010; Deng & Tsao, 2010; Oakley & Cidlowski, 2011), titers of antibodies to double-stranded DNA (Rahman & Isenberg, 2008), specific features of T- and B-cells, etc. It seems clear that responsiveness to glucocorticoids should be associated with some individual specific features of the patients. Moreover, glucocorticoid sensitivity is not steady in the same patient, but can vary from time to time and can be much more changeable than it has been believed earlier (De Rijk & Sternberg, 1997).

It is rather strange but a very essential aspect of action of glucocorticoid preparations has been neglected during the whole period of using glucocorticoids in clinical medicine. It is extremely important that glucocorticoid preparations, as discriminated from all other pharmaceuticals used in the treatment of SLE, are synthetic copies of *natural products* of the organism – of glucocorticoid hormones synthesized in the adrenal cortex. Glucocorticoid preparations possessing the unique combination of therapeutic properties also inevitably retain the features of their natural prototypes, i.e. they are directly or indirectly involved in regulation of many if not all physiological processes and metabolic reactions and their using interferes the negative feedback regulation in the hypothalamus–pituitary–adrenocortical system. Therefore, it should be noted and emphasized that the inevitable complications of glucocorticoid therapy really are not "side effects", on the contrary, they are natural manifestations of just hormonal properties of glucocorticoid preparations, either of their excess or of induced disorders in the feedback regulation of the hypothalamus–pituitary–adrenocortical system. Possibly, this neglecting was reasoned by a surprising and somewhat discouraging discovery in the beginning of "the glucocorticoid era" that the therapeutical effect of glucocorticoid preparations did not depend on the level of a patient's own hormones?

However, not the level of glucocorticoid hormones should be important, but the tissue provision with these hormones, especially on taking into account that glucocorticoids are hormones of virtually total action. Nevertheless, for glucocorticoids there is no parameter to characterize the tissue provision with these hormones (or with glucocorticoid preparations) and to determine the real need in them of a subject under various circumstances, in particular, under stress situations or in disease. This is especially important because glucocorticoids play a determinative role in stress situations. For glucocorticoids an indirect parameter is required *which would be similar to blood glucose for insulin.*

Naturally, this parameter must be easily determinable in blood, have rather narrow normal limits in healthy persons, and clearly depend on glucocorticoids, natural hormones or

preparations. In particular, the glucocorticoid-dependent hepatic enzyme tyrosine aminotransferase and the resulting tyrosine level in blood which is directly determined by the activity of this enzyme deserve a special attention.

## 3. Blood tyrosine levels in some non-endocrine diseases

In the late 1950s Japanese researchers of the Nishimura group found increased levels of tyrosine in blood and urine of patients with collagen diseases (Nishimura et al., 1958; Nishimura et al., 1961) and supposed that disorders in tyrosine catabolism could be a biochemical basis of these diseases. These reports stimulated intensive studies on tyrosine catabolism in collagenoses and some other diseases, especially in Russia. As it was reasonably to expect, tyrosine catabolism was disturbed in patients with liver disorders, such as infectious hepatitis, chronic hepatitis, and liver cirrhosis, and blood tyrosine level was two-threefold increased in them (Levine & Kohn, 1967; Powell & Axelsen, 1972; Nordlinger et al., 1979).

The hypothesis about the role of tyrosine catabolism disorders in pathogenesis of collagen diseases was not confirmed, but very interesting observations were described, in particular, by A.S. Kainova (Kainova, 1974): tyrosine levels in blood of patients with rheumatism decreased to normal values on successful hormonal and/or medicamentous therapy, and abolishment of glucocorticoid preparations in some cases was accompanied by an increase in the blood tyrosine level.

## 4. Observations on blood tyrosine levels and glucocorticoid treatment in patients with SLE

Systemic Lupus Erythematosus (SLE) was a problem for the Clinics of Therapy and Occupational Diseases, I Moscow Medical Institute, where I entered as a biochemist in 1968 and had been working until 1978. Naturally, the disorders in tyrosine metabolism observed by Nishimura et al. in patients with collagen diseases and observations by Kainova on blood tyrosine changes in patients with rheumatism seemed to me a possible biochemical approach to start my study on SLE.

Sixteen healthy donors (14 women and 2 men in the age from 20 to 40 years old) were used for determination the normal level of blood tyrosine, and it was found to be 16.2 ± 0.9 μg/ml. Note, that the repeated measurements of blood tyrosine levels in the same donors gave virtually the same values, i.e. it occurred to be rather a stable parameter.

Altogether 80 patients with SLE, 70 women and 10 men in the age range from 16 to 53 years old, were observed at 134 hospitalizations over the period of 1973–1976. Some patients were under observation repeatedly. The patients were not selected previously basing on their case history and severity and character of the disease. Tyrosine was determined in the serum from blood samples taken from patients with SLE at 8.00–8.30 a.m. on the empty stomach, usually once during 7-14 days over the period of hospitalization. The work was not a part of a previously approved plan of investigations, therefore, no blood samples were taken specially to determine the tyrosine content. Initially, levels of tyrosine and of its transamination product *p*-oxyphenylpyruvic acid were determined in parallel samples of blood and 24-h urine. The determination of tyrosine was performed spectrophotometrically by the method of Udenfriend & Cooper (1952), *p*-oxyphenylpyruvic acid was determined as described in the work (Knox & Pitt , 1957). It was shown that the increase in blood tyrosine

level was caused by disturbance in transamination (Rass, 1976), whereas the further stages of tyrosine oxidation in the patients under study were virtually unaffected.

Changes in blood tyrosine in every patient were compared with the clinical and laboratory data recorded in their case histories after the patients' discharge from the hospital, with a special attention to using glucocorticoid preparations, i.e. a kind of the retrospective experiment was performed. The results were published in Russian in the work (Rass et al., 1977). Thirty-six patients were observed in the state of clinical remission; blood tyrosine was in normal limits in 23 of them and was steadily elevated in three patients (two of them had the affected liver); 28 patients obtained a supporting dose of glucocorticoids (not more than 15 mg prednisolone per day).

In 44 patients with SLE short-term "splashes" in blood tyrosine level were observed, and the retrospective analysis revealed that these "splashes" occurred simultaneously with some extraordinary events, such as a concurrent infection, aggravation of symptoms, or on the other day of a severe diagnostic procedure (e.g. the kidney biopsy), during the reaction to a new preparation, etc. Thus, these "splashes" were associated with a "stress-situation" when the need in glucocorticoid hormones was increased and in healthy subjects the synthesis of glucocorticoid hormones should increase. Thus, in a patient with chronic SLE who obtained 5 mg/day prednisolone as a supporting dose over the period of 50 days of hospitalization blood tyrosine values were 25, 20, 22 μg/ml, and a "splash" to **53** μg/ml was recorded on the day after the diagnostic intravenous urography. At the other hospitalization two years later this patient obtained the daily dose of 10 mg prednisolone and had blood tyrosine level of 8 μg/ml (possibly, the supporting dose of 10 mg prednisolone/day was too high – the previous supporting dose of 5 mg/day seemed sufficient to maintain the level of blood tyrosine in normal limits of 20-25 μg/ml). Similar "splashes" in blood tyrosine level were also observed in patients with glomerulonephritis under similar situations.

A very demonstrative was an attempt to even slightly lower the dose of glucocorticoid preparations in a clinically steroid-dependent patient with subacute SLE (Fig. 1). This "splash" in blood tyrosine was observed concurrently with the aggravation of her condition. In this patient the high background content of tyrosine was thought to be associated with the liver affection.

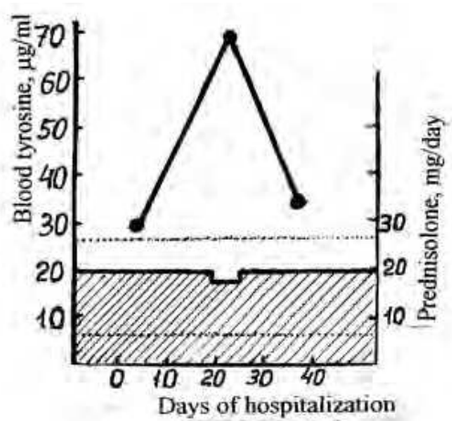


Fig. 1. Changes in the blood tyrosine content in a clinically steroid-dependent 40-year-old patient with subacute SLE. The attempt to decrease the dose of prednisolone was associated with an aggravation of the patient's condition. Dotted lines here and in the further Figures show normal limits of blood tyrosine contents.

"Splashes" in blood tyrosine were also observed in some patients with SLE at the alternate-day scheme of hormonal treatment on the next morning after glucocorticoid-free day.

But comparing results of glucocorticoid therapy with the initial level and behavior of blood tyrosine in patients with SLE seems to be the most interesting and informative. Changes in blood tyrosine upon prescribing or increasing the dose of glucocorticoids (40-60 mg/day calculated per prednisolone) because of SLE exacerbation were followed in 32 patients. Glucocorticoid preparations were prescribed according to the conventional schemes. The post-discharge analysis of the case histories revealed that to 20 patients glucocorticoids were prescribed at the significantly increased level of blood tyrosine (49.1 ± 0.8 μg/ml as compared to 16.2 ± 0.9 μg/ml in 16 healthy donors) and an essential improvement of clinical and laboratory parameters was recorded in 17 of them. In 13 patients this improvement was accompanied by a decrease in blood tyrosine, and this decrease was recorded before appearance of signs of Cushing's syndrome; in four patients with markedly affected liver functions the level of blood tyrosine remained elevated although their general condition became somewhat better. It should be noted that the "improvement" in all cases concerned only parameters of SLE activity, and side effects were considered as inevitable.

Twelve patients were given glucocorticoids on the background of normal blood tyrosine (≤ 26.5 μg/ml); glucocorticoids were inefficient in nine of them, and in four patients signs of Cushing's syndrome appeared very rapidly. Some improvement was recorded in three patients but this improvement could be due to other preparations given to them concurrently with glucocorticoids: azathioprine, heparin, cyclophosphamide, etc.

Let us consider some real cases.

Patient M., 27 years old, suffering from SLE for nine years was hospitalized because of aggravation of chronic SLE. Blood tyrosine at the first determination was 47.5 μg/ml. She was given prednisolone (30 mg/day) and antibiotics because of catarrhal state, however, 20 days later the immunologic activity was still present, as well as arthralgia and myalgia, blood tyrosine remains increased - 40 μg/ml; because of a continued aggravation of her condition 15 days later the prednisolone dose was increased to 40 mg/day, and *in a week a pronounced clinical improvement was recorded, together with a decrease in the blood tyrosine level to normal (25 μg/ml)*. She received 40 mg/day prednisolone for 20 days, and then the lowering prednisolone dose was started – and blood tyrosine slightly increased. The patient was discharged with the improved clinical and laboratory data (Fig. 2).

The following case (Fig. 3) presents a 21-year-old patient Zh., suffering of SLE during five years. She received long-term courses of prednisolone earlier in the maximal dose of 30 mg/day. A progressing osteonecrosis was observed. This time she was hospitalized because of an acute flare. At the first determination blood tyrosine level was somewhat increased (34.0 μg/ml), on the next day she was prescribed with prednisolone – 45 mg/day, and this dose was maintained *during 20 days. Five days* after the beginning of glucocorticoid therapy blood tyrosine decreased to 20.0 μg/ml, and *two days later a moon-like face appeared and elevations of arterial pressure up to 170/100 mm Hg* were recorded. GG therapy for 1.5 months was considered to be unfavorable; moreover, pains in femoral joints increased. Clinical improvement in this patient was obtained on prescribing heparin.

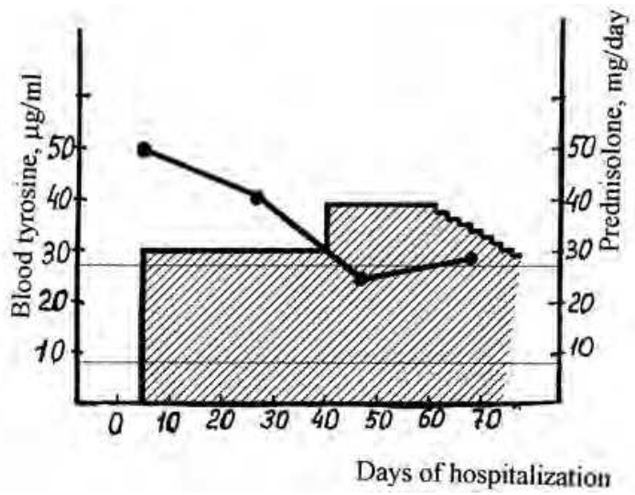


Fig. 2. Changes in the blood tyrosine content and regimen of glucocorticoid therapy (hatched) in a 27-year-old patient with chronic SLE.

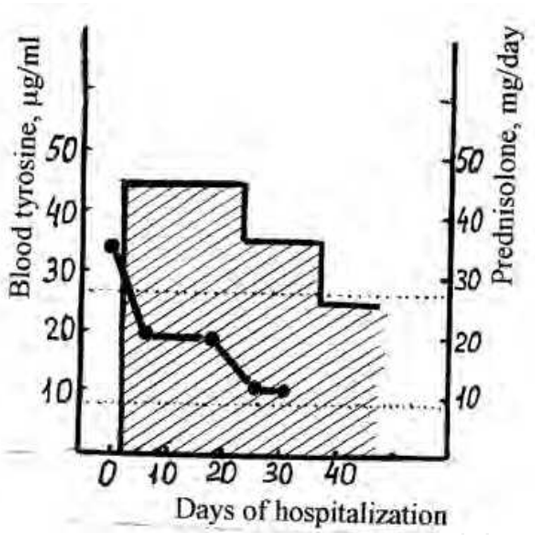


Fig. 3. Changes in the blood tyrosine content and regimen of glucocorticoid therapy (hatched) in a 21-year-old patient with chronic SLE.

Figure 4 shows changes in blood tyrosine level observed at withdrawal syndrome in a 22-year-old patient P. with subacute SLE (Fig. 4). The patient was in the state of a relative clinical and laboratory remission at the supporting dose of prednisolone (15 mg/day) for rather a long time. Such a rapid abolishment of prednisolone at the hospitalization in 1974 was forced by development of a pronounced aseptic osteonecrosis of femoral heads, and this abolishment was associated with a sharp aggravation of SLE symptoms associated with a sharp increase in blood tyrosine level.

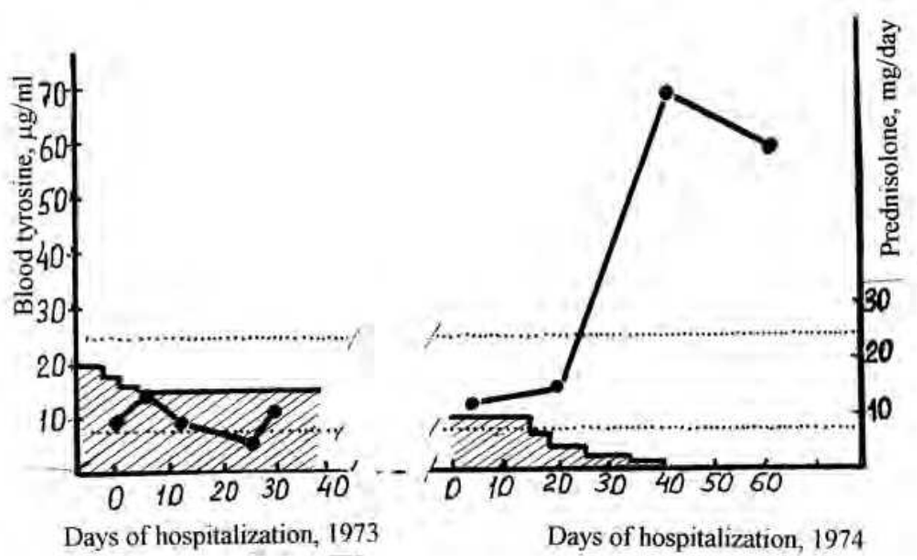


Fig. 4. Blood tyrosine levels and regimen of glucocorticoid therapy in a patient with subacute SLE during two hospitalizations, at the state of relative remission in 1973, and at withdrawal syndrome in 1974.

Thus, a certain association obviously occurred between the therapeutic effect of glucocorticoid preparations and their regulatory effect manifested by changes in the blood level of tyrosine. Moreover, such association cannot be occasional, exclusive, or SLE-specific, because the dependence of tyrosine catabolism on glucocorticoids is fundamentally the same in humans and in other mammals. Such an association must be significantly most common. In particular, blood tyrosine level was also increased in patients with bronchial asthma (not receiving glucocorticoids) during the period of attacks and was normal during the state of remission (Rass et al., 1978).

If so, may be blood tyrosine content can be used as a representative index of action of glucocorticoid hormones on metabolism, as an index of tissue provision with these hormones, and of real need of a subject in these hormones? May be blood tyrosine level can be used as a parameter (index) of glucocorticoid action, similarly to blood glucose which is a parameter of insulin action?

## 5. Tyrosine catabolism and blood tyrosine level as an index of glucocorticoid hormone action

This idea induced by observations on changes in blood tyrosine levels and regimens of glucocorticoid therapy in patients with SLE was for the first time published in the above-mentioned work (Rass et al., 1977) and was theoretically considered in the paper (Rass, 1978); then this idea was confirmed by experimental studies on adrenalectomized rats (Rass, 1980; Rass, 1983) and by observations on children with adrenogenital syndrome receiving long-life substitutive glucocorticoid therapy (Rass et al., 1979). In 1991 the hazard of glucocorticoid hormone application in non-endocrine diseases was considered to be mainly due to the absence of a test for sufficiency and real need in these hormones, and introduction of blood tyrosine as such a test was proposed as a safety basis for the individualized strategy of glucocorticoid therapy (Piruzian & Rass, 1991). However, all

these works were published only in Russian, and this apparently promising idea remained virtually not called for until the review (Rass, 2010) was published in English.

Let us consider some specific features of tyrosine catabolism, especially those which allow us to consider the blood level of this amino acid as a promising laboratory parameter for monitoring glucocorticoid therapy.

Tyrosine is produced in the organism as a result of hydrolysis of food protein immediately or after hydrolysis of phenylalanine. About 30% of produced tyrosine is used for synthesis of catecholamines, melanin, and thyroid hormones, a portion is used for renewal of tissue proteins, and more than 60% is oxidized in the liver (Knox, 1955). And the first reaction in the major oxidation pathway of tyrosine is its transamination with alpha-ketoglutaric acid under the influence of tyrosine aminotransferase with production of *p*-oxyphenylpyruvic acid. Then *p*-oxyphenylpyruvic acid is oxidized under the influence of the appropriate oxidase in the presence of ascorbic acid with production of 2,5-dioxyphenylpyruvic, or homogentisic acid. The terminal products of the major pathway of tyrosine oxidation are acetoacetic and fumaric acids (Fig. 5).

Most frequently, tyrosine content in blood is determined using its reaction with alpha-nitroso-beta-naphthol with a subsequent recording by spectrophotometry (Udenfriend & Cooper, 1952) or by fluorimetry (Grenier & Laberge, 1974; Gavrilov et al., 1998). In some works HPLC (Kand'ar & Zakova, 2009), ion-exchange chromatography (Allard et al., 2004), and gas chromatography – mass-spectrometry (Deng et al., 2002) are also used. In some of the above-listed works tyrosine was determined in blood samples dried on filter paper discs.

The interest for determination of tyrosine level in blood is caused by necessity of early diagnosis of congenital disturbances of phenylalanine–tyrosine catabolism which result in severe disorders in the mental and physical development of the affected children. Phenylketonuria is caused by deficiency of the enzyme phenylalanine hydroxylase and is characterized by an extremely low level of blood tyrosine (< 0.05 μg/ml), tyrosinosis which is caused by an insufficient elimination of *p*-oxyphenylpyruvate acid due to deficiency of the appropriate oxidase (Scriver, 1967; Cerone at al., 1997) is manifested by a stable hypertyrosinemia up to 100 μg/ml, and in Richner–Hanhart syndrome caused by an inborn insufficiency of tyrosine aminotransferase blood tyrosine level can reach 600 μg/ml (Goldsmith, 1978; Natt et al., 1992). Incidence of phenylketonuria throughout the world is, on average, 1 : 15'000, and of the two other disorders in tyrosine catabolism are, respectively, 1 : 100'000 and 1 : 250'000, but in Canada they are recorded more frequently.

Tyrosine aminotransferase is an adaptive enzyme synthesized by the liver cells in response to entrance of the substrate – tyrosine, but for the substrate induction of this enzyme the entrance of glucocorticoids in the liver is necessary (Rosen and Nichol, 1963; Gelehrter, 1973; Thompson, 1979). Synthesis of hepatic tyrosine aminotransferase is a well-known example of the so-called gene-mediated action of glucocorticoids, and this enzyme is the most demonstrative and beloved object for studies of such effects of glucocorticoids (Sun at al., 1998; Grange et al., 2001; Hazra et al., 2007). Tyrosine aminotransferase is also used for testing on cell cultures and on intact and adrenalectomized animals of newly synthesized preparations which are expected to have less adverse effects than "classic" glucocorticoid preparations (Schacke et al., 2004; Zimmermann et al., 2009). The synthesis of tyrosine aminotransferase quantitatively depends on glucocorticoids, but being a hepatic enzyme, it cannot be determined in blood. However, tyrosine aminotransferase is a key enzyme in the major pathway of tyrosine catabolism and its activity determines the level of free tyrosine in

blood. As a result, blood tyrosine level also depends on glucocorticoids (and, naturally, also on the functional competence of the liver cells).

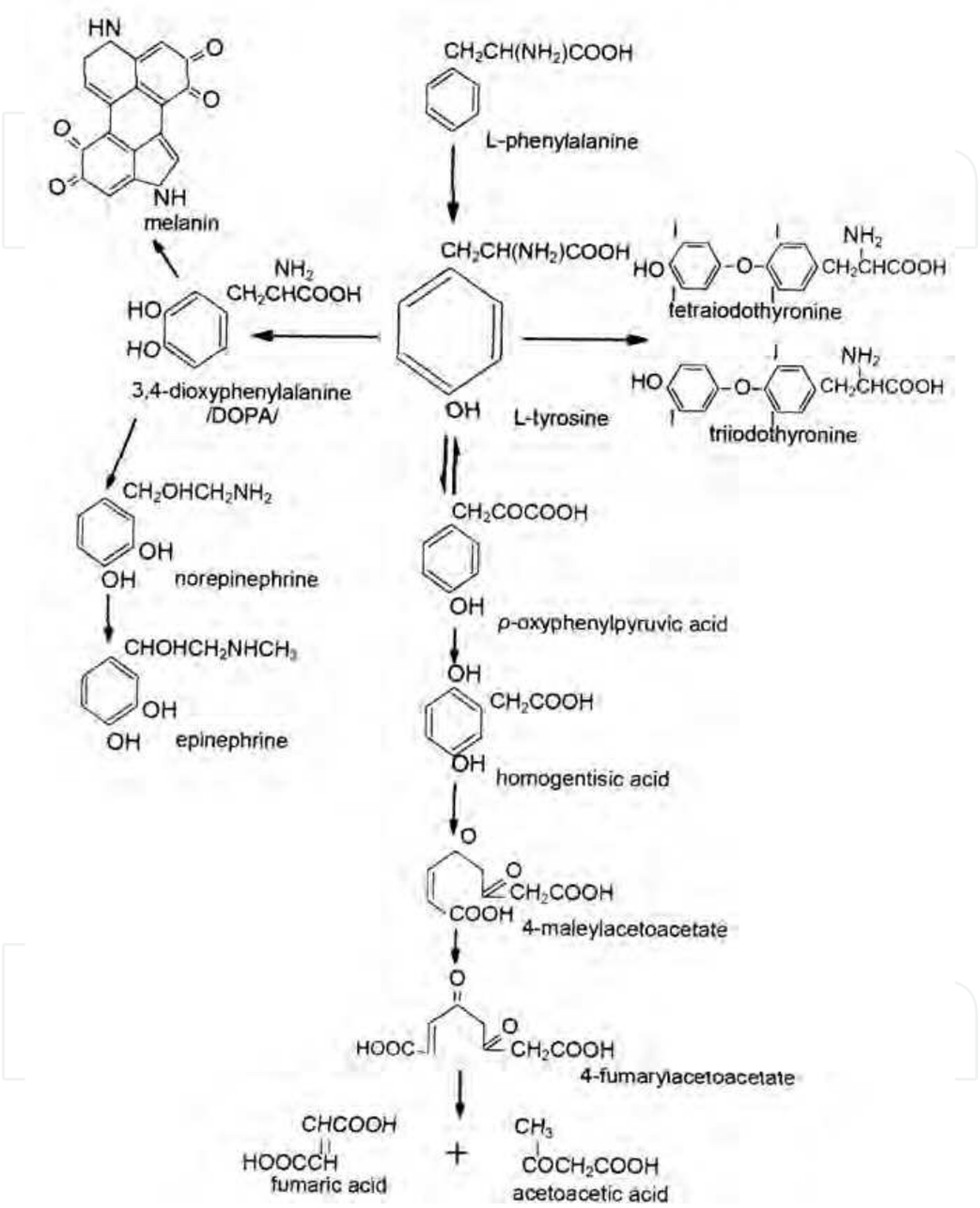


Fig. 5. Tyrosine catabolism (Scheme).

Due to substrate induction of tyrosine aminotransferase, even on tenfold increase in protein amount in the diet the blood content of tyrosine increases no more than by 50% above the basal level (Scriver et al., 1971), whereas circadian variations in blood tyrosine level mainly depending on circadian variations in production of natural glucocorticoids are in the limit of ± 25% (Wurtman et al., 1968).

But in the majority of cases and under real conditions an increase in blood tyrosine can be mainly determined by two factors: 1) a functional inferiority of the liver leading to a disturbed reception of glucocorticoids and inability of the liver cells to synthesize some enzymes including tyrosine aminotransferase, and 2) an insufficient entrance of glucocorticoids in the liver. As a result, under conditions of physiological rest, in the absence of extreme fluctuations in the diet, and on determination on the empty stomach in the morning the levels of free tyrosine in blood are similar in healthy animals and humans and do not depend on age and sex (Table 1).

| Subjects under study | The number of subjects | μg/ml |
|---|---|---|
| **Men** | 91 | **13.0 ±** 2.7 |
| **Women** | 103 | **12.3** ± 2.4 |
| **Boys** 6-18 yr | 75 | **12.3** ± 1.8 |
| **Girls** 6-18 yr | 65 | **11.4** ± 2.0 |

Table 1. Blood tyrosine levels in humans, after (Armstrong & Stave, 1973a)

Moreover, it should be noted that blood samples taken from the same subjects (35 boys and 26 girls) four times over the period of 3–3½ years displayed characteristic individual patterns for the most of plasma amino acids, in particular, the content of blood tyrosine was virtually constant in the same subject (Armstrong & Stave, 1973b). We have also observed virtually the same values of blood tyrosine level in the samples taken repeatedly from the same healthy donors, as well as in blood samples from patients with SLE on supporting dose of glucocorticoids in the state of remission.

Injection of glucocorticoid preparations induced a 20–40% dose-dependent decrease in blood tyrosine in both animals and humans (Rivlin & Melmon, 1965; Betheil et al., 1965), and this decrease was the most pronounced 4-5 h after the injection, i.e. at the maximum of the glucocorticoid-induced synthesis of tyrosine aminotransferase. A decrease in the content of blood tyrosine was also recorded under stress conditions (Nemeth, 1978), obviously, due to a well-known increase in the glucocorticoid production by the adrenal cortex. Effects of hydrocortisone injection to healthy volunteers recorded by changes in the blood tyrosine levels and in the peripheral lymphocyte counts were considered as manifestations of genomic and nongenomic effects of glucocorticoids, respectively (Derks et al., 1999).

It is interesting to note that injections of hepatotoxins caused in rats an increase in the level of blood tyrosine, and the more pronounced was the liver necrosis the higher was this increase (Clayton et al., 2007).

## 6. Blood tyrosine content is an index of tissue provision with glucocorticoids: Confirmation on the experimental and clinical models

The dependence of blood tyrosine content on glucocorticoids was demonstrated experimentally on adrenalectomized rats (Rass, 1980; Rass, 2010). In intact rats blood tyrosine level was 15.0 ± 1.4 μg/ml. After bilateral adrenalectomy the blood level of tyrosine began to increase and reached, on average, 37.9 ± 6.4 μg/ml on the 5$^{th}$ day concurrently with the worst condition of the animals; then blood tyrosine level began to decrease most likely

due to synthesis of corticosterone in the brown fat tissue in response to the increased synthesis of ACTH after adrenalectomy; on the 10th day blood tyrosine level was the same as initially (under conditions of physiological rest!). Thus, the tyrosine level in blood manifested a pronounced dependence on production of natural glucocorticoids.
Starting from the 7th day after the operation, adrenalectomized rats were injected daily intraperitoneously with hydrocortisone in the dose of 2 mg per kg body weight (this dose approximately corresponded to the supporting dose 15 mg/day of prednisolone). Daily injections of hydrocortisone during 20 days resulted in a decrease in the tyrosine level in blood to undeterminable level, the abolishment of the injections and their absence during 5 days caused an increase in blood tyrosine, and the recommencement of hydrocortisone injections (5 mg per kg body weight) was accompanied by a decrease in blood tyrosine (Fig. 6).

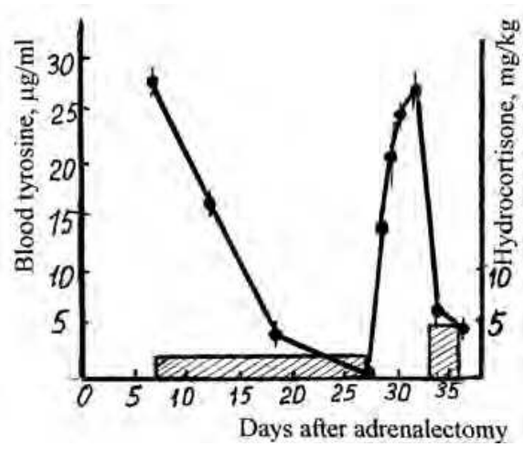


Fig. 6. Changes in tyrosine content in blood of adrenalectomized rats subjected to daily injections of hydrocortisone (hatched), upon abolishment of the injections, and on their recommencement.

And it seems that the only clinical situation exists (the model was recommended by Prof. M.A. Zhukovsky) which allows a physician (endocrinologist) to control the entrance of glucocorticoids in the organism and to some degree assess the adequacy of tissue provision with glucocorticoids to real needs of just this patient. This unique situation is presented by adrenogenital syndrome (synonyms: congenital adrenal hyperplasia, congenital virilizing adrenal cortex dysfunction) in children. The disease is caused by a genetically determined deficiency of glucocorticoid biosynthesis enzymes in the adrenal cortex, most frequently of 21-beta-hydroxylase, and a resulting shift to synthesis of androgens, mainly of dehydroepiandrosterone. The decreased production of glucocorticoids induces an increased synthesis of ACTH in the adenohypophysis that permanently stimulates the adrenal cortex with a resulting surplus synthesis of androgens (Brooks, 1979). The excess of androgens is displayed by a characteristic clinical picture: an abnormal structure of external sex organs, an accelerated body growth with an overdevelopment of masculine type muscles during the first years of life, the early arresting of growth because of premature ossification of tubular bones, etc. In the affected girls a picture of pseudohermaphroditism is developed.

The lifelong substitutive glucocorticoid therapy is the only pathogenetically reasonable treatment of this disease (Lo et al., 1999; Stikkelbroeck et al., 2003; Hughes, 2007). Glucocorticoid preparations break the vicious circle: recompensing the shortage of endogenous glucocorticoids they inhibit synthesis of ACTH responsible for overproduction of androgens. Glucocorticoid therapy started as early as possible after the birth and the appropriate dose can provide the normal physical and sexual maturation of the affected children according to their genetic sex, with a possibility of normal pregnancy and labor in females. The dose of glucocorticoids must be strictly individualized, and it can vary from 2.5 to 15 mg prednisolone per day.

On the other hand, changes in the clinical picture observed in children with adrenogenital syndrome – the rate of growth, ossification, and sexual maturation – allow a physician to relatively objectively and faultlessly estimate the correctness of the dose. In adult patients with this syndrome and in other conditions which obviously require the substitutive glucocorticoid therapy, after bilateral adrenalectomy or in chronic hypocorticism of various etiology, the dose of glucocorticoids can be prescribed only "according to the patient's self-feeling". According to B. Lukert (Lukert, 2006), "The problem for the clinician is the lack of objective criteria for determining adequate, but not excessive doses of glucocorticoids… In current practice, the clinician must rely on surrogate markers of glucocorticoid excess (early changes of Cushing's syndrome) rather than definitive end points".

Our study was performed with participation of 38 children with virilizing adrenogenital syndrome (33 girls and five boys of 3–18 years old hospitalized in the Pediatric Department of the Institute of Experimental Endocrinology and Chemistry of Hormones, the USSR Academy of Medical Sciences). Tyrosine levels were determined in blood samples taken in the morning on empty stomach and compared with clinical picture which characterized the degree of compensation of the genetic defect. The results were published in Russian (Rass et al., 1979) and republished in English in the review (Rass, 2010). The main results are presented in Fig. 7.

Figure 7 shows that in 17 children with adrenogenital syndrome at the complete clinical compensation blood contents of tyrosine were the same as in healthy donors (16 adults and seven children of 7–13 years old). In a girl with signs of Cushing's syndrome blood tyrosine was below the normal level. In untreated patients and in non-compensated patients because of irregular treatment blood tyrosine was significantly increased. In three non-compensated patients a pronounced melanodermia was observed along with the normal level of blood tyrosine, i.e. a part of excessive tyrosine was not oxidized through the major pathway but was converted into melanin (compare with the Scheme in Fig. 5!). Prescribing glucocorticoids resulted in "whitening" of such patients. Normalization of skin color in patients with hypocorticism upon taking glucocorticoids was also described in the literature (Snell, 1967).

In two compensated patients who initially displayed normal levels of blood tyrosine, transient increases to 29.0 and 45.0 μg/ml were recorded in association with a concurrent acute respiratory disease. Obviously, these increases are very alike "splashes" observed in patients with SLE, and can be explained by increased requirements for glucocorticoid hormones under conditions of stress or concurrent disease. Such observations justify the empirical recommendation to increase the dose of glucocorticoid preparations in the case of stress situations.

Two previously untreated girls were prescribed with glucocorticoids, and the determinations of blood tyrosine levels were helpful for choosing the optimal dose. Note that in patients with hypocorticism an acute withdrawal of the substitutive hydrocortisone injections resulted on the next day in a 25-30% increase in the level of blood tyrosine, whereas the levels of other amino acids remained virtually unchanged (Christiansen et al., 2007). The data presented in this section show that the normal level of blood tyrosine seems to indicate a sufficient provision of tissues and glucocorticoid-dependent reactions and processes with these hormones, whereas an increased level of blood tyrosine seems to be due to insufficient level of glucocorticoids. This seems rather clear for endocrine diseases.

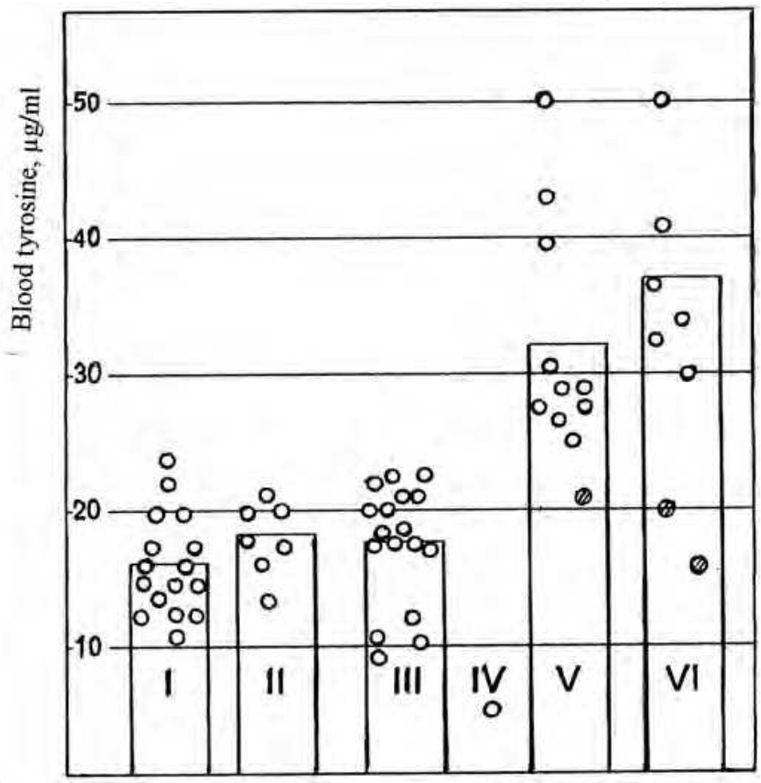


Fig. 7. Tyrosine contents in blood of healthy donors and children with adrenogenital syndrome. The columns present arithmetic means for the corresponding groups; the circles show individual values: I) healthy adults; II) healthy children; III) patients with the complete clinical compensation; IV) a girl patient with overdosed glucocorticoids; V) irregularly treated non-compensated patients; VI) untreated patients. Hatched circles in the columns V and VI show patients with a pronounced melanodermia.

However, it is also reasonable to expect that blood content of tyrosine could be a promising candidate for the role of an indirect marker for prescribing the correct dose in non-endocrine diseases. Unfortunately, for non-endocrine diseases there are no similar data, nevertheless, let us admit that blood tyrosine level could be used as an index of tissue provision and real need in glucocorticoid hormones (or glucocorticoid preparations) – in our patients with SLE described in the Section 4.

## 7. The imaginary tyrosine-based monitoring of glucocorticoid therapy in the above-presented cases of SLE (reconsideration of cases presented in Figs. 2–4)

Thus, keeping in mind the blood tyrosine as an index of the real need in glucocorticoids, let us look again at Figs. 2–4 and *imagine* the tyrosine-based monitoring of glucocorticoid treatment in these patients with SLE.

*Fig. 2 – the imaginary monitoring*. The patient M. was prescribed with 30 mg prednisolone daily on the background of a rather high initial level of blood tyrosine (47.5 μg/ml); she received this dose during 35 days without a pronounced clinical effect and on retention of the increased blood tyrosine (40.0 μg/ml). The improvement was achieved as soon as a week after increasing the prednisolone dose to 40 mg/day and this improvement was accompanied by normalization of blood tyrosine. The patient continued to receive 40 mg prednisolone for the following 15 days. Thus, in total, the patient M. received *30-40 mg prednisolone daily within two months*. But, taking into account the initial high level of blood tyrosine, as well as its retention at the second determination 20 days later, *it would have been reasonable to give her 40 mg prednisolone earlier and to start lowering the dose on normalization of blood tyrosine, i.e. the course of hormonal therapy could be much shorter.*

*Fig. 3 – the imaginary monitoring*. The increased level of blood tyrosine (34 μg/ml) at the first determination on the next day after the hospitalization could be a kind of "splash" – the reaction to hospitalization-associated procedure. The patient was prescribed 45 mg prednisolone per day and obtained this dose for 20 days. Blood tyrosine became normal very rapidly – on the 5$^{th}$ day after the hospitalization (even *earlier than the recorded in the case history appearance of the moon-like face and elevations in blood pressure*!) and continued to decrease to very low level during the treatment with glucocorticoids. After 1.5 months, glucocorticoid therapy was qualified as unfavorable. Was it a case of steroid-resistance or simply a manifestation of a sufficient provision with own hormones? In any case, *this patient did not need such a prolonged and rather intensive glucocorticoid therapy.*

*Fig. 4 – the imaginary monitoring*. Withdrawal syndrome in a 22-year-old patient with subacute SLE. The normal blood tyrosine level during the hospitalization the year before at the supporting dose of prednisolone 15 mg/day made it possible to think about at least *of decreasing the supporting dose of glucocorticoids, or even of trying to abolish hormonal preparations the year earlier!*

## 8. And the real successful course of glucocorticoid therapy *without side effects*

The next case (Fig. 8) exemplifies a successful course of glucocorticoid therapy performed by Dr. I.A. Borisov (described in detail in the work (Rass et al., 1977)) in a 48-year-old patient E. who had been suffering of SLE for 12 years. This hospitalization was because of a serious flare of SLE after an acute respiratory disease. *All previous courses of glucocorticoids in this patient resulted in a rapid development of Cushing's syndrome*. On the entrance blood tyrosine was 45–79 μg/ml. She was given prednisolone (40 mg/day) within a week and then transferred to alternate-day scheme of the dose lowering (the increase in blood tyrosine to 100 μg/ml was recorded in the morning two days after the abolishment of daily

prednisolone). The alternate-day scheme was started from daily dose of 75 mg with a stepwise decreasing to 25 mg/day (combined with methindol on prednisolone-free days). Blood tyrosine decreased to the normal level (16 μg/ml) alongside with a general improvement of all clinical and laboratory data. The increase in the blood tyrosine level to 35 μg/ml concurrently with the SLE activation was recorded when prednisolone was replaced by decortilene; then a respiratory disease was associated with blood tyrosine increases to 30–45 μg/ml; and prednisolone was prescribed again in the daily dose of 30 mg during a week followed by the alternate-day lowering the prednisolone dose starting from 55 mg. The patient was discharged with an essential improvement *without any side effect of glucocorticoid therapy*.

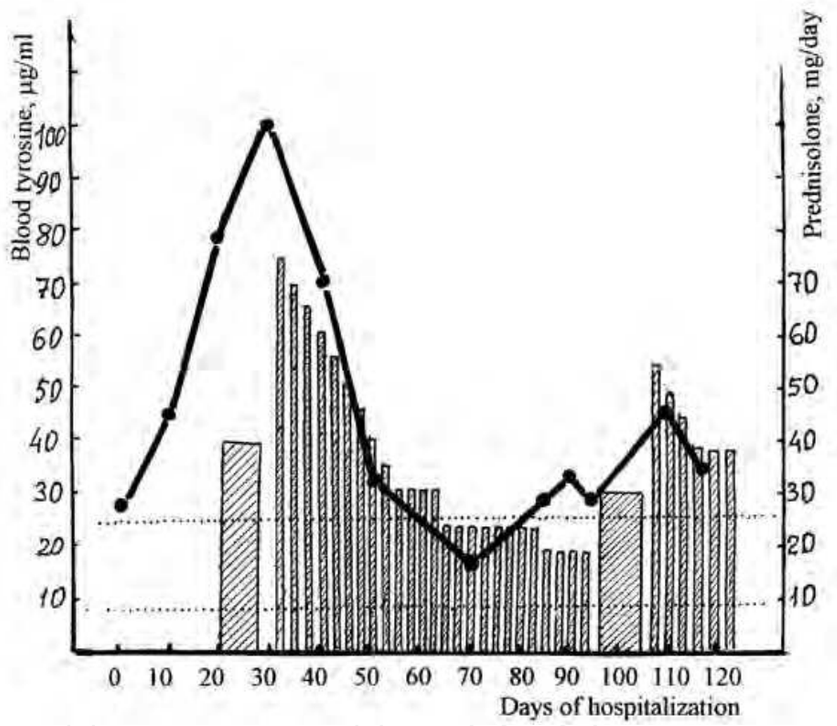


Fig. 8. Changes in the blood tyrosine content and regimen of glucocorticoid therapy (hatched) in a 48-year-old patient with SLE.

It should be underlined that in this case two specific hormonal features of the glucocorticoid preparations were taken into account: the organism's provision with glucocorticoids characterized by blood tyrosine level and using the alternate-day scheme for lowering the dose of hormonal preparation dose to promote the recovery of the negative feedback regulation in the hypothalamus-pituitary-adrenocortical system.

## 9. Conclusion

Preparations of glucocorticoid hormones for more than 60 years remain one of cornerstones of modern medicine as the most effective anti-inflammatory drugs also possessing anti-allergic, immunosuppressive, antitoxic, and anti-shock properties. Glucocorticoid

preparations are widely used in all fields of clinical medicine and are virtually indispensable, although very serious complications are associated with their application. The number of works concerning glucocorticoid treatment of various diseases is innumerable. However, despite the extreme importance and indispensability of glucocorticoid preparations, up to now there is no objective laboratory parameter, similar to blood glucose for insulin, which would allow a clinician to foresee the effect of hormonal therapy in a given patient and realize a reasonable monitoring of the dose of glucocorticoid preparations.

The problem of safety of glucocorticoid therapy arose concurrently with the first usage of glucocorticoids by Dr. P. Hench and colleagues in 1948 (Hench et al, 1949) and difficulties which should be inevitable on using glucocorticoids were predicted and described in their large publication (Hench et al., 1950). Unfortunately, multiple refined studies on glucocorticoids by biochemists, geneticists, endocrinologists, physiologists, although very informative, are not frequently intersected with real need of clinical medicine.

Just the permanent critical state of glucocorticoid therapy made me reconsider my old works published in Russian in 1976–1983 which remained unnoticed and unknown. And only the publication in English (Rass, 2010) has attracted the attention to the still urgent problem of absence of a laboratory parameter extremely required for glucocorticoid therapy of both endocrine and non-endocrine diseases.

I hope that rather an easy determination of blood tyrosine level will be at last used as a suitable laboratory parameter for many situations in clinical medicine, endocrinology, and physiology of the hypothalamus–pituitary–adrenal cortex system. In physiology blood tyrosine determination can supplement measurements of levels of the hormonal participants of this system by data on adequacy of this system functioning to the organism's needs under different situations.

And finally some speculations.

The comparison of therapeutic effect of glucocorticoid preparations in SLE with their regulatory influence on the blood tyrosine level suggests that the therapeutic action of these preparations cannot be conditioned by an exclusive combination of pharmacological properties; on the contrary, the unique combination of therapeutic properties of these preparations is caused by retention of specific hormonal properties.

Glucocorticoid hormones are essentially responsible for supporting homeostasis – they directly or indirectly participate in regulation of the majority (if not all) biochemical reactions and physiological processes. They are hormones of total action and of vital importance. But in addition to supporting homeostasis under conditions of health and physiological rest, glucocorticoid hormones play a very important and sometimes a decisive role under conditions of stress or disease when, as a rule, their secretion increases. Under stress situations or in disease glucocorticoid hormones can realize their effects acting via the evolutionary selected best pathways, and, no doubt, a certain optimum of the adrenal cortex activity must exist for every subject (a human or animal) under extraordinary conditions. However, it seems that the optimum of this individual adrenocortical response can be revealed not by determination of functions of the hypothalamus-pituitary-adrenocortical system links, but only using a result of this system activity - an indirect glucocorticoid-dependent parameter, which can indicate whether this response is sufficient or not just for the concrete subject in a specific situation.

Glucocorticoid preparations retain the fundamental features of their natural prototypes, including their physiological and regulatory functions and can act via the same pathways. Therefore, it seems very likely that glucocorticoid therapy in non-endocrine diseases must imitate the optimal hormonal response of a given patient under conditions of disease – as if his adrenals could realize such a response. Glucocorticoid therapy must compensate an insufficient response of the patient's own adrenals, it can be life-saving within these limits and dangerous beyond them. The determination of blood tyrosine level which is a manifestation of the regulatory effect of glucocorticoid can allow a clinician to assess the correspondence of the hormonal provision to real needs of the patient.

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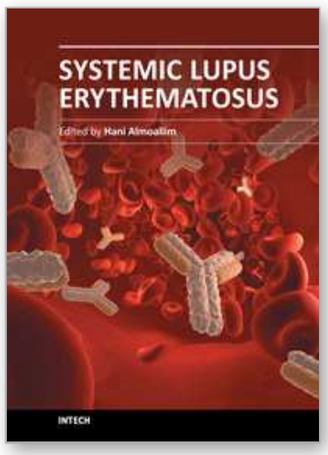


**Systemic Lupus Erythematosus**

Edited by Dr Hani Almoallim

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.



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