

the upper limit of normal in subjects up to 50 years old and those older. However, the number of subjects older than 50 years in their sample was too small to reach any definite conclusions. I therefore measured glucose in the urine of 100 healthy subjects (58 men, 42 women; age range 51 to 72 years). There were no pregnant or lactating women or galactosemic subjects in the sample. Urine specimens, regardless of prandial status, were obtained in sterile vials from all subjects. Urinary glucose was measured in each specimen by the *o*-toluidine method (5).

The mean values for male and female subjects did not differ significantly, so I included all the subjects in a single group. The mean (and SD) value was 119 (85) mg/L, or 0.66 (0.47) mmol/L. As the distribution was non-gaussian, a nonparametric method was used to calculate the reference interval. The 95% range (2.5th–97.5th percentile) was 11–400 mg/L (0.06–2.22 mmol/L).

This range is somewhat wider than that reported by Gupta et al. (4), but because of the larger sample size in the present investigation I believe the reference interval reported here to be more representative of a normal population. However, I endorse the suggestion of Gupta et al. (4) that qualitative tests for urinary glucose are not sensitive enough to detect mild diabetes in subjects older than 50 years because the upper normal limit for urinary glucose in this age group is much lower than in younger subjects.

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#### *In Situ* Monitoring by Reflectance Spectrophotometry

##### *To the Editor:*

Reflectance spectrophotometry is increasingly used as a noninvasive technique to measure, *in situ*, the relative amounts of an absorber—in particular, bilirubin (1–4)—present in tissues. Invariably, results of these studies have been less than satisfactory, with the consequence that monitoring of bilirubin by the reflectance technique is rarely used clinically. This outcome, however, is predictable in view of our current understanding of those factors that determine the intensity of light back-scattered from a turbid medium such as skin. Implicit in all these studies is that the light-scattering properties of skin are identical among individuals and that the tissue is homogeneous with respect to the size and distribution of scattering particles and with respect to the distribution of the various absorbers. Such simplifying assumptions, besides being clearly invalid, are ultimately undesirable because they inherently obscure a wealth of information that might be obtained from a reflectance measurement.

Reflectance measurements yield two basic types of information: the light scattering and absorptive properties of the medium. Evaluation of the former is a complex task, being affected by various physical variables, including the size of the scattering particles, their shape, their packing density (number per unit volume), and their index of refraction. This analysis is further complicated by any degree of heterogeneity of these variables, especially with depth in the medium. Consideration of such heterogeneity is important because the contribution by an absorber to the overall reflectance spectrum depends on its depth within the medium. This is true because the scattering of light generates a nonlinear dependence of pathlength on wavelength such that shorter pathlengths occur at shorter wavelengths. For absorbing compounds distributed nonhomogeneously in a turbid medium, this effect has some rather unexpected consequences.

For example, in tissue, the detection of a compound such as deoxyhemoglobin that absorbs maximally in the visible and near-infrared regions, situated beneath a layer of oxyhemoglobin, will be limited to the near-infrared region. This is true because the shorter wavelengths of light are never able to reach the lower layer, owing to the greater degree of light scattering at the shorter

wavelengths. As the thickness of the overlying layer is decreased, the absorption spectrum of deoxyhemoglobin will become increasingly detectable at the shorter wavelengths. The relative contribution to a reflectance spectrum by absorbers that are present at various depths within tissue can be determined if the light-scattering properties of the tissue are known. Viewed in another fashion, if the light-scattering properties of the tissue can be measured, then the depth of the absorbers that are present in the tissue can be determined. This conclusion means that reflectance spectrophotometry is inherently an imaging technique. The image generated would be a three-dimensional representation of the light scattering and absorptive properties of the tissue. In addition, in contrast to other noninvasive imaging techniques (e.g., x-ray computed tomography, proton nuclear magnetic resonance, imaging, and ultrasound) that yield anatomical information, reflectance imaging would yield metabolic information.

Clearly, the maximum depth from which measurable changes can be detected is important. Fortunately, light in the near-infrared region (<700 nm) is capable of significant penetration into tissues. Jobsis et al. (5) demonstrated that it is possible to monitor, simultaneously and continuously, changes in the tissue blood volume, relative concentrations of oxyhemoglobin, and the redox state of cytochrome oxidase in brain, *in situ*, by directing near-infrared light to the scalp and measuring the intensity of reflected light that penetrated through the skull and into the brain. In a transmittance mode, Jobsis (6) showed that similar measurements could be made through the head of a cat. Thus, it is possible to measure the penetration of near-infrared light on the order of a few centimeters in depth.

The ability to identify the light scattering and absorptive properties of tissues at various depths potentially creates a broad spectrum of new diagnostic applications. Previous studies have shown that a decrease in the oxygenation of tissues—ischemia (5)—or a decrease in their capacity to utilize oxygen—cyanide poisoning (7)—is measurable by reflectance spectrophotometry. Clearly, detection of these conditions at specific depths within the tissue would be valuable, especially when one is dealing with cerebral pathology. It is important to recognize that changes in the light-scattering properties of tissues could occur independent of a change in its absorptive properties, with each being measur-

able. Thus, variations in light scattering owing to a specific change in the shape of the erythrocyte (e.g., sickle cell anemia) or to the formation of immune complexes in tissues should also be identifiable.

Measurement of the light scattering and absorptive properties of tissues, *in situ*, and the reconstruction of three-dimensional images are complex but solvable problems. Our needs for simplicity should not be allowed to obscure our understanding of the complexities of nature, which often proves more rewarding.

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### Significance of Low Creatine Kinase in Intensive-Care Patients

#### To the Editor:

Barnert and Behr (1) reported on low creatine kinase (CK; EC 2.7.3.2) activity in serum of patients with acute viral hepatitis. They supposed that the patients' physical inactivity was the reason for these low CK values. Earlier, low CK activities have been associated with intake of several drugs: oral contraceptives (2), glucocorticoids (3), chemotherapy (4), and captopril (5).

We have observed 60 (9.5%) of 630 intensive-care patients with this phenomenon (<5 U/L at 37 °C). By comparison, of 2000 patients from other departments, only four (0.2%) had low CK values.

Of the 60 patients with low CK activity, severe infections were present in 36 (67%), nearly half of them presenting with septicemia. In this subgroup, Gram-negative ( $n = 31$ ) and Gram-positive bacteria ( $n = 18$ ), as well as yeasts ( $n = 7$ ), were isolated from the blood. These patients were receiving intensive antibiotic treatment, but antibiotics per se were not involved, because the *in vitro* addition of cephalosporins, aminoglycosides, imidazoles, or ampicillin derivatives to normal serum caused no significant depression of CK activity. Neither did the addition of suspensions of the isolated bacteria or yeasts.

In our study, low values for CK activity were measured by systems based on activation with either *N*-acetylcysteine (6) or dithiothreitol (7). Dilution experiments with sera having normal or high CK activity gave no indication of the presence of an inhibitor in the low-CK serum samples.

The low activities corresponded well with the most critical period of these patients' illness and were preceded by a three- to five-day gradual decrease of total CK activity. With clinical improvement the phenomenon reversed, with a concomitant return of CK activity to normal values, but without any notable increase in the patients' muscle activity.

The rate of diffusion of cytoplasmic enzymes into plasma is determined by their molecular size (8). When we measured the activities of some other cytoplasmic enzymes [lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] (9) in the low-CK serum samples, we observed a decrease of CK activity but only slight variations in the other cytoplasmic enzymes. The variations in day-to-day enzyme activity were fitted into a first-order equation:  $A_t = A_0 \exp(-kt)$ , where  $A_0$  is the initial activity,  $A_t$  the activity at time

$t$ ,  $t$  is the time (days), and  $k$  is the fractional rate constant of turnover (10). Table 1 summarizes the mean values of the fractional rate constant of turnover for LDH, ALT, AST, and CK in 10 patients without liver disease but with low CK activity in serum, calculated over the week preceding the lowest CK activity. Evidently the decrease of serum CK activity cannot be explained by a decrease in cell-permeability, as had been postulated in corticosteroid-treated patients (3).

Moreover, the mean concentration of creatine in the serum of our patients with low CK values was 89 (SD 24) mg/L (reference range, 2-10 mg/L), as can be observed in severe muscle pathology, which suggests an impaired metabolism of creatine, the substrate for CK.

We observed transient low-CK values in intensive-care patients, accompanied by extremely high concentrations of serum creatine. Our results suggest that the low serum CK values in intensive-care patients may form a particular entity, which cannot be explained by simple changes in membrane permeability.

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Table 1. Fractional Rate Constant of Turnover of Various Muscle Enzymes in Patients with Low CK Activities in Serum<sup>a</sup>

Enzyme	Fractional rate constant ( $k$ ) of turnover, day <sup>-1</sup>	$M_t$	Initial enzyme activity, U/L
Lactate dehydrogenase	-0.080 ± 0.110 <sup>b</sup>	135 000	274 ± 85 <sup>b,c</sup>
Alanine aminotransferase	0.180 ± 0.250	120 000	24 ± 16
Aspartate aminotransferase	-0.036 ± 0.100	93 000	60 ± 31
Creatine kinase	0.753 ± 0.200 <sup>d</sup>	85 000	190 ± 54

<sup>a</sup>Ten patients with low CK activity, but without liver disease. <sup>b</sup>Mean ± SD. <sup>c</sup>Mean value (37 °C) at the beginning of the one-week period preceding the lowest CK activity. <sup>d</sup> $p < 0.01$ .