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HOMEOSTATIC MECHANISMS IN THE REGULATION
OF SERUM ALBUMIN LEVELS

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The relative constancy of the plasma albumin concentration in health suggests the existence of some sort of regulating mechanism. Control could be effected through variations in synthesis or catabolism of the protein, or through alterations in its distribution between intra- and extra-vascular pools. Although there is evidence of increased transfer of extravascular albumin to plasma in states of protein malnutrition (4, 12), such measurements are usually based on isotopic tracer data which are difficult to interpret in the unsteady states that might be expected to exist in disease or after acute experimental procedures. In any event, this type of exchange must be regarded as a temporary expedient to meet acute changes; alterations in synthesis and/or catabolism would be anticipated in more chronic disturbances. These adaptive changes have been studied in vivo in human subjects suffering from malnutrition and in animals experimentally deprived of dietary protein, and attempts have been made to correlate the findings with the in vitro behaviour of the isolated perfused liver and of cell-free systems.

Catabolism of albumin and protein malnutrition

In healthy adult men the amount of albumin catabolised per day is variously reported to be between 150 - 250 mg

kilogram⁻¹ day⁻¹ (12, 27, 29 36). This is equivalent to a fractional rate of 8 - 12% of the intravascular pool catabolised per day. Both figures (absolute amounts and fractional rates) are slightly higher in healthy children (29). A limited study of apparently healthy male Africans (5) revealed a smaller intravascular albumin pool and a lower absolute rate of catabolism, a hint that the nutritional status of the individual might affect the turnover of albumin.

When dietary protein is limited, the plasma albumin level falls and its catabolism is slowed down. This has been demonstrated in kwashiorkor and in experimentally-induced protein depletion (4, 8, 12, 15, 19, 20, 26). Initially the fractional catabolic rate is unchanged and the absolute rate falls in parallel with the plasma albumin concentration and pool size. By adaptation of the catabolic rate to the synthesis rate, a simple but effective method of compensating for reduced synthesis is thus provided (Fig. 1), and a new equilibrium is reached.

It should be stressed that this fall in the rate of albumin catabolism follows reduction of the intravascular pool and is not primarily determined by the reduction in dietary protein (12, 15, 20). Further, it is not specific to the hypoalbuminaemia of protein malnutrition, but is

Figure 1

seen in cirrhosis of the liver (7, 30, 37) and after plasma pheresis (1, 11, 23). Exceptions are seen in the nephrotic syndrome and protein-losing enteropathy where local hypercatabolism may play a part (11, 17, 42). In kwashiorkor (4, 15) and in experimental protein depletion (12) a fall in the fractional rate of albumin catabolism may also be observed.

On refeeding, a reverse sequence of events is found. A return to a normal or supranormal (see later) synthesis rate rapidly restores the plasma albumin pool, and catabolism gradually returns to its normal rate, adapting once again to the altered rate of synthesis to reach a new equilibrium (20).

The site of albumin catabolism in the body is still not known and no specific organ has been shown to play a predominant role. Studies using the isolated perfused rat liver have led to the belief that this organ normally accounts for 10 - 15% of the total amount of albumin broken down in vivo (3, 10). There is good justification for the use of this system as a model for studying adaptive changes in catabolism under experimental conditions, and for the assumption that its behaviour is representative of that of the intact live animal (13). Fig 2 shows the response of the perfused rat liver to a drastic increase

Figure 2

in perfusate albumin concentration. A constant fractional rate of breakdown is maintained, resulting in increased absolute degradation. If a liver taken from a rat which has been fed a non-protein diet for 15 - 20 days is perfused with blood taken from similarly deprived animals, a slower fractional catabolic rate is found, analagous to the observations in human subjects and experimental animals referred to earlier. It is interesting that this slow rate of catabolism can be accelerated by the addition of albumin to the perfusate pool or by perfusion with blood taken from rats fed a normal diet (Fig. 3).

Fig. 3

The observed constancy of fractional albumin breakdown rate by the perfused liver may be explained by the theory of fluid endocytosis, in terms of which hepatic cells engulf a fixed volume of ambient fluid per unit time (14). The number of albumin molecules introduced into the cell and therefore available for lysosomal proteolysis, will be proportional to the concentration of the protein in the engulfed fluid, i.e. in the extracellular milieu, provided selective adsorption of molecules at the cell membrane does not occur. This would explain the maintenance of first-order kinetics for albumin breakdown observed in vivo and in vitro.

In order to interpret the lower fractional rate found with livers from protein-deprived rats, one might postulate a reduced rate of endocytosis and/or lysosomal activity. Protein starvation has been shown to produce structural changes in liver lysosomes as well as alterations in proteolytic enzyme activity (25), but the relationship to the functional changes mentioned above is not clear.

Synthesis of albumin and protein malnutrition

Aminoacids for plasma protein synthesis are derived mainly from dietary sources. It is not surprising that one finds a close correlation between plasma albumin concentrations and the level of protein in the diet (19). With prolonged restriction of available protein, albumin synthesis is progressively reduced leading to gradual diminution in the size of the body albumin stores (12, 15, 20). Refeeding with a diet of normal protein composition causes a dramatic increase in albumin synthesis rate, which is apparent within 24 hours and which appears to be increased above the normal range. This leads to rapid restoration of body albumin.

Perfusion of the isolated liver provides a better model for studying albumin synthesis than it does for catabolism, since production of this protein is confined

to the liver (24). Yet, under ordinary conditions livers taken from normal rats appear to synthesize only half the amount of albumin produced by the intact animal. Despite this, the system has proved most valuable for comparative studies.

Rothschild et al (28) have perfused rabbit livers with blood diluted with a solution containing glucose and aminoacids. They found reduced rates of albumin synthesis when the donor rabbit had been fasted for 18 - 36 hours prior to extirpation of the liver. In a study of protein deprivation, as opposed to starvation, we have found similar lowering of albumin synthesis (Hoffenberg, Gordon and Black, unpublished observations). Because of difficulties in interpretation when synthesis rates of urea and protein are low, we abandoned the $^{14}\text{CO}_2$ method of McFarlane (21) in favour of direct measurement of rat albumin production by an immunodiffusion technique (22) using a system of heterologous (rabbit) plasma with homologous red blood cells. Livers taken from rats previously fed non-protein diets for 15 - 20 days showed significant depression of albumin synthesis (Table 1). Yet these differences were abolished if liver size was taken into account and, weight for weight, livers of protein-deprived rats seemed competent to manufacture

Table 1

albumin. The extent to which total albumin production is impaired in these livers is comparable to that seen in vivo after exposure to a non-protein diet (19), although, as mentioned, the performance of the isolated liver does not match that found in the intact animal. With livers taken from refed animals the findings are again similar to those in the intact rat. If the donor animal is fed a normal diet for 48 hours after 15 - 20 days of protein-deprivation, high albumin synthesis rates are found (Table 1). These are within the normal range in absolute terms, but are considerably raised when related to liver weight.

These responses of the isolated liver must be considered in the light of structural changes known to affect the hepatic albumin-synthesizing apparatus in protein-deprivation. Starvation and aminoacid or protein restriction are attended by prompt alterations in polysome profile with a breakdown of membrane-bound polysomes and the appearance of more free monosomes and disomes (2, 9, 16, 33, 34, 38).

The shift of polysome particles from heavy to light is generally assumed to reflect a reduced capacity for protein synthesis. Reaggregation and a restoration of ability to incorporate aminoacids into protein rapidly follows the introduction of aminoacids into the system.

Tryptophan, in particular, seems to exert a unique and powerful influence on polysome structure and function.

The interpretation of polysome profiles in relation to dietary protein intake and aminoacid incorporating ability must be adopted with caution, as aggregation may be restored when animals are refed a non-protein diet after a period of fasting, i.e. exogenous protein is not mandatory for their restoration (39, 41). Wilson and Hoagland (40) have shown that 36% of liver polysomes are stable after fasting, i.e. not subject to these structural changes, and a majority of these can synthesize albumin. Selective disaggregation of polysomes not committed to albumin synthesis could confuse the picture outlined above.

A final word to try to relate these findings to changes in liver enzymes that have been described. In classical studies, Schinke (31, 32) and, more recently, Deosthale and Tulpule (6) have shown reduction in all hepatic urea cycle enzymes after protein deprivation. Reduced urea synthesis is reflected in low blood urea and urine excretion levels in protein malnutrition and was encountered in our perfusion studies on livers from protein-deprived rats. It is interesting that aminoacid activating enzymes have been shown to be increased in

depletion studies (35), suggesting that aminoacids would preferentially be diverted into protein synthesis rather than urea formation. The liver might be thought of as "primed" to synthesize protein as soon as adequate aminoacids are supplied. This concept would fit very well with the prompt, even exaggerated, response to refeeding, which has been found in vivo and with the perfused liver system.

In conclusion, one should emphasize that body responses cannot be contemplated in vacuo. In particular, the role of hormones needs to be considered, as John and Miller (18) have recently demonstrated: in their studies maximum albumin synthesis by the perfused liver required insulin and cortisol as well as aminoacid supplementation. Any attempt to ignore these factors must lead to an oversimplified view.

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TABLE 1

Albumin Synthesis rates: Livers taken from rats fed diets of different protein composition

	mg/h		mg h ⁻¹ 100 g rat ⁻¹	
	¹⁴ CO ₂	Imm-diff.	¹⁴ CO ₂	Imm-diff.
N.L. (n=6)	5.0 (2.7-8.3)	4.0 (2.6-4.6)	1.50 (0.68-2.85)	1.13 (0.76-1.28)
O.P.L. (n=5)	—	1.4 (0.9-1.7)	—	0.92 (0.55-1.13)
Refed L. (n=3)	3.4 (2.2-4.1)	4.4 (3.5-5.0)	1.77 (1.24-2.16)	2.32 (1.73-2.65)

LEGEND

Table 1 : Albumin synthesis rates (mean and range)
by isolated perfused rat livers. NL = livers
from rats fed normal diet; OPL = livers from
rats fed protein-free diet for 15 - 20 days;
refed L = rats refed normal diet for 48 ~~h~~
after protein-free diet for 15 - 20 days.

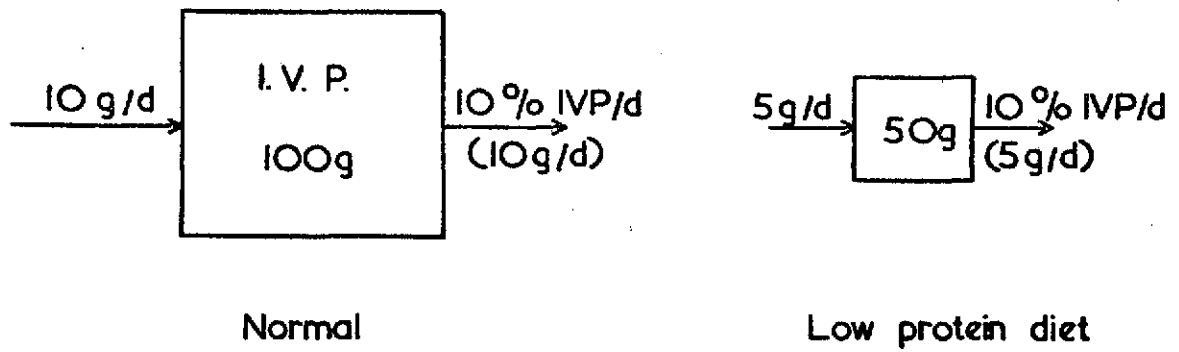


Figure 1. Diagrammatic representation of effects of diminished synthesis on albumin pool size. Maintenance of a constant fractional breakdown rate establishes a new equilibrium.

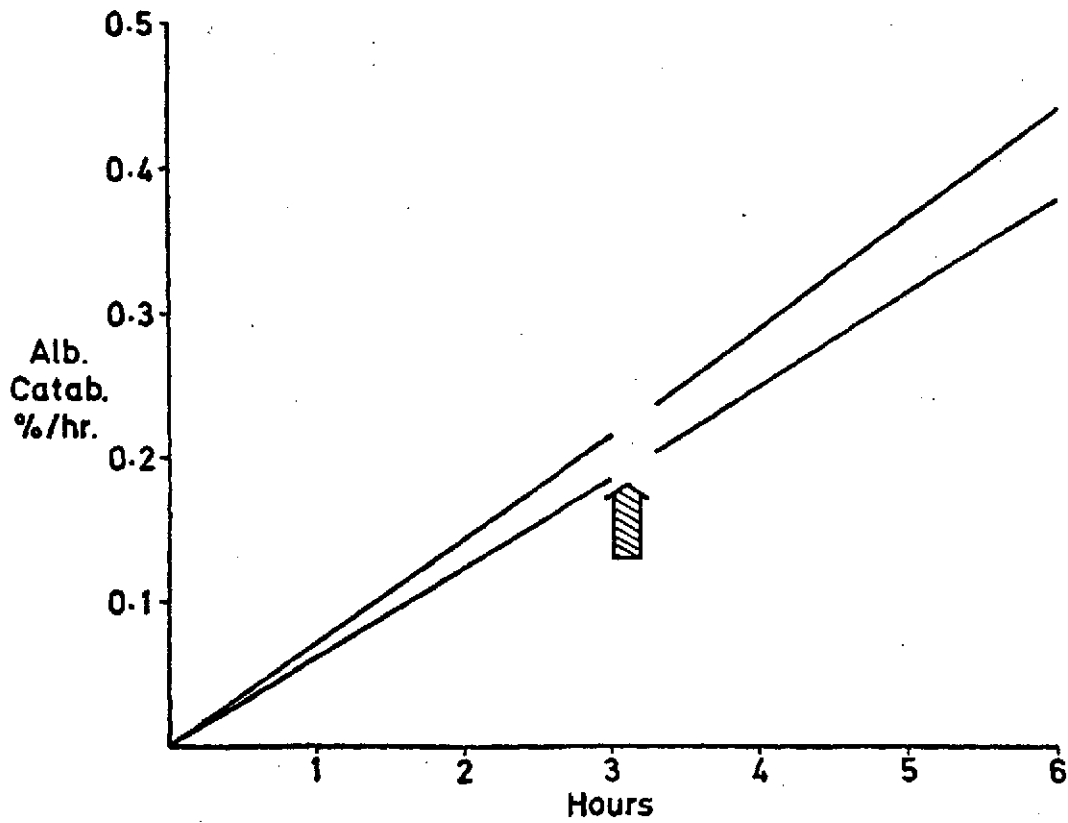


Figure 2. Effect of increased concentration on the fractional breakdown rate of albumin by the perfused rat liver. Additional albumin raised the plasma concentration of the perfusate from 21.8 to 38.9 mg/ml and 24.6 to 37.6 mg/ml in the two experiments. Catabolic rate measured from non-protein-bound/protein-bound iodide ratios.

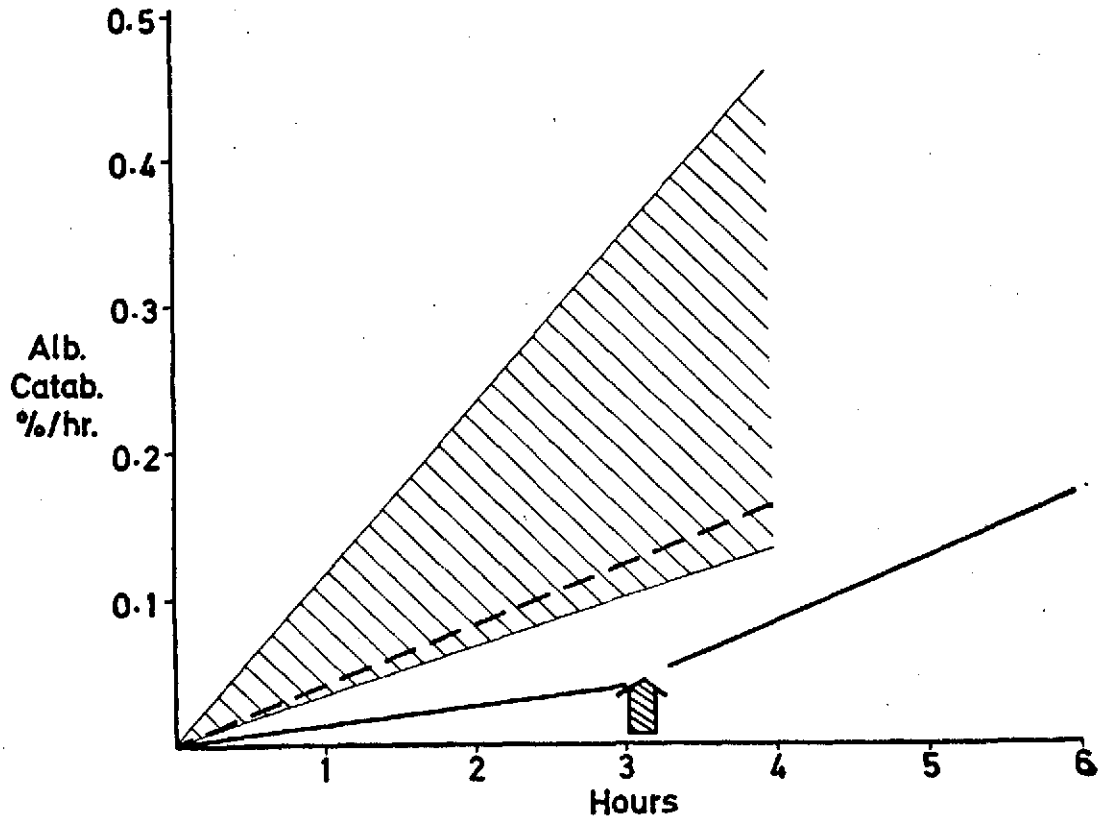


Figure 3. Albumin catabolism by livers taken from rats fed a protein-free diet. Note slow rate when perfused with blood from similarly deprived animals and attainment of normal rate when albumin is added to increase the concentration from 18.7 to 21.6 mg/ml (solid line), or when perfused with normal blood (broken line). Normal range of catabolic rate shown by hatched area.

INTRODUCTORY REMARKS

PANEL ON RESEARCH IN MEDICAL EDUCATION
NINTH MEETING OF THE ADVISORY COMMITTEE ON MEDICAL RESEARCH

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The development of efforts to the maximum degree, activated by a high order of interest in matters pertaining to health protection and promotion, are universally regarded as the prime responsibility of both governments and society, not only to preserve the inalienable birthright of all men to health, but also because health is a fundamental factor in the socioeconomic evolution of the people. Among the multiple aspects which this subject embraces, of singular significance is that which relates to the human resources available for health promotion, and within these latter, of notable importance, the medical profession. This, in its true and trascendental value, has been recognized by the Pan American Health Organization, inducing it to make a study of the problem, particularly insofar as affects Latin America, where the problem is of major importance.

In August 1969 the Pan American Health Organization presented for consideration an excellent and well-documented report and survey that clearly reveals the situation prevalent in the Schools of Medicine of Latin America, and from which can be inferred the necessity of determining the measures most appropriate to providing a solution of their problems; to remedy their deficiencies; and to direct their activities to ensure an improved program of teaching tending to a better formation of these unvaluable human resources.

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Conscious of the high importance of this problem and of the imperative necessity of making a thorough study of it, it has been proposed that this session be dedicated to listening to the authorized opinions of those who have had experience in the carrying out of projects and studies, with the idea that their experience may prove of positive benefit in the formulation of a Latin American policy of medical education. We feel that the discussion of some of these experiences--not only those related to programs already defined and in course of application in some universities, such as those corresponding to pedagogic research on the process of clinical diagnosis--as also to become acquainted with those systems of evaluation of quasi-experimental character which have been applied to some aspects of medical education.

For some years back, a feeling of disquiet has been manifest in respect to the necessity of introducing radical education reforms, since the general conviction is that the present programs and systems are anachronistic and, many of them, either totally or partially, obsolete, and while useful in their time, are not so today vis-à-vis modern teaching systems; should include the scientific advances every day greater; cover more extensively the behavioral sciences and--of everincreasing importance--the principle that the medical sciences be made more applicable to the service of the community. Moreover, it is felt that the teaching of medicine should be made more flexible and, above all, have regard to the desirability of constant renewal, in order that it conform to the march of scientific programs.

The trials effected with these aims in view in some Schools of Medicine of the world have pointed out new paths to follow and undoubtedly constitute some advance which points implicitly to the need for introducing extensive

modifications in the traditional systems of teaching. Nevertheless, these trials cannot be considered as totally satisfactory, and indeed are in a period of evolution incorporating frequent changes still not sufficiently evaluated. We can await with assurance that the vigor and audacity with which these trials have been conducted, apart from revealing the expedience of necessary reform, will provide useful material for elaboration of a structure, distinct and more efficient, of the teaching systems of the Schools of Medicine.

In Latin America, the characteristics proper of each country and their limited economic capacity will undoubtedly render difficult the application of these modern systems of teaching, but not because of that must we abandon consideration of them and seek the means to bring about their application, totally or only in part.

Within this process of change, of reconstruction, of establishment of new norms and teaching systems in the Schools of Medicine, must be clearly defined the aims and objectives pursued and the philosophy of the program which it is desired to develop in the schools. In this respect, it is important to bear in mind that once the objectives are determined, they will be neither operative nor realizable unless teaching staff, capable of conduction of these programs and systems, is available; unless we can count on a teaching faculty conscious of their responsibility and equipped with the appropriate mental outlook, not only as related to the application of the new systems, but also capable of developing new approaches; a problem of such proportion that on occasions has proved a difficult obstacle to overcome in the schools which have tried to break away from the traditional pedagogic procedures. It becomes essential, therefore, that every effort

be made to build up a teaching staff with the right mental attitude, adaptable to the new ideas and systems, who will be able to contribute to attainment of the best results.

Although universally radical changes such as we are discussing are gaining force, these changes are felt to be more pressing in the Schools of Medicine of Latin America, inasmuch as in a good proportion of these rigid and out-dated teaching programs are still taught to a student population whose large numbers constitute in itself a difficult barrier to the introduction of changes, and whose motivation and aptitude for medical studies have not been duly evaluated or directed.

In many Latin American countries the Schools of Medicine do not satisfy the necessities of professionals of the medical sciences and, in general terms, the professionals graduating from them have not an adequate preparation. Moreover, their number is inferior to the ever-growing demand for their services, due above all to the demographic increase which, in some of our countries, is among the highest indices of the world. Only in few countries is seen an effort to solve this situation, where a significant number of new schools are brought into operation, and at the same time, innovations are also being introduced in the teaching systems to bring them more in keeping with the present-day scientific picture. Without doubt, the evaluation of these experiences carried out in these countries will prove of great usefulness for the rest of the Latin American Schools of Medicine.

Based on the foregoing comments, it is suggested that the Pan American Health Organization, which has been carrying out important and valuable studies through its Department of Human Resources, intensify its intervention in this area, in the promotion of studies, research, and experimental programs

in relation to this problem of medical education, seeking the ways and means deemed most adequate to assure that these important observations are made known to all the Latin American universities and the possible manner found to apply the same in benefit of the teaching of them all.

To this effect, I believe that it would be useful to create a subcommittee which, in collaboration of the Department of Human Resources, meets periodically to discuss the results of the research made in this field. This subcommittee must be moreover capable of advising and suggesting suitable modifications to the educational systems in force, having regard to the peculiarities proper to each school. This subcommittee, the creation of which I now propose, could provide valuable information yearly to the Advisory Committee on Medical Research and would also be in a position to propose, on the basis of its findings, a policy of medical education in Latin America.