CONTENTS

JOSEPH ERLANGER
1874 - 1965

Joseph Erlanger was the sixth of seven children born to immigrant parents who migrated from southern Germany. Joseph was born January 5, 1874 in San Francisco. He was the only one of the children who received a higher education. He entered the College of Chemistry of the University of California after two years of high school and received his B. S. Degree in 1895. While at Berkeley he became interested in research. This interest continued during summer vacations while attending the medical school at Johns Hopkins University. He worked in Lewellyn Barker's histology laboratory on the locus of the anterior horn cells that innervated a given voluntary muscle. During his second year at Hopkins he published his first research paper, "A Study of the Metabolism in Dogs with Shortened Small Intestines" (American Journal of Physiology 6, 1, 1901).

He received his M.D. degree in 1899 and was Resident Medical officer at Hopkins Hospital, 1899-1900. His interest was definitely research and teaching so he joined the staff of W. H. Howell in physiology at Hopkins serving as assistant to associate professor from 1901 to 1906. While with Howell he assembled a sphygmomanometer for measuring arterial blood pressure which was later manufactured by a New York firm. During 1902 he spent some time in Hofmeister's biochemical laboratory in the University of Strassburg learning the latest composition and metabolism of protein sulphur compounds. As indicated by his research his interests and knowledge of physiology and physiological chemistry were broad.

On Erlanger's return to Baltimore he teamed up with Donald R. Hooker (who later became managing editor of the AJP) to study orthostatic albuminuria primarily from the circulatory standpoint. Their results demonstrated that albumin output depends on pulse pressure changes rather than blood pressure changes. Also while at Hopkins, Erlanger devised a clamp with which controlled pressure could be reversibly applied to the auriculoventricular bundle of the dog's beating heart. This enabled him to produce all degrees of reversible auriculoventricular block from 1:1 to complete block.

In 1906 the new medical school at Wisconsin offered Erlanger the professorship of physiology and physiological chemistry which he accepted. During the organization of the new department Erlanger engaged a young instructor, Walter J. Meek, who was then professor of biology at Penn College, Iowa (Meek later became head of the physiology department and still later dean of the medical school at Wisconsin. Meek also became President of the American Physiological Society and wrote the first history of the Society in 1938). While at Wisconsin, Erlanger was one of the first to use an Einthoven string galvanometer to make electroencephalographic recordings.

In 1910 he accepted the position of professor of physiology at the newly organized school of medicine at Washington University at St. Louis. During the years of World War I Erlanger worked on many projects,

again proving his breadth of knowledge and interest - from instrumental flying for aviators to the mechanism of sound production in arteries and traumatic shock. Later his interests centered more and more around electrical manifestations of nervous energy. Much of this later work was done in collaboration with Herbert Gasser. Gasser had studied, with difficulty amplified action potentials in nerves, using the string galvanometer. About this time Western Electric Company was developing a cathode ray tube which they were not as yet prepared to market. Erlanger and Gasser made their own cathode ray tube out of a distillation flask with deflecting plates mounted on the inside and a pair of solenoids attached to the outside. The sweep circuit was provided by a revolving potentiometer. After some encouraging results with this home-made apparatus they finally were able to rent cathode ray tubes from Western Electric. The full report of these early experiments may be found in AJP, 62, 496, 1922. It was this early work that finally led to the Nobel Institute awarding the prize in Physiology and Medicine in 1944 jointly to Erlanger and Gasser for their discoveries regarding the highly differentiated functions of single nerve fibers.

Dr. Erlanger became professor emeritus in 1946 and remained fairly active until his death December 5, 1965.

Besides the Nobel Laureate Erlanger received many honors. He held honorary degrees from California, Hopkins, Wisconsin, Pennsylvania, Michigan, Washington University and Brussels University. He was a member of many domestic and foreign learned societies.

Dr. Erlanger was elected to the American Physiological Society in 1901, became a member of Council in 1910, serving in one capacity or another until 1929. He was Treasurer of the Society, 1913-1923 and President, 1926-1929. As President of the Society he attended the XIIth Physiological Congress at Stockholm in 1926 and extended to the Congress an invitation to meet in Boston for the next meeting in 1929. During his long treasurership Dr. Erlanger helped shape the financial policies of the Society, contributing especially toward the activity and financial readjustments in the transfer of the American Journal of Physiology to the Society in 1922. He was always characterized by his conservative leadership in the business and organization work of the Society,of which he carried a large share of responsibility.

TWELFTH BOWDITCH LECTURE

Coupling Between Transport Processes In Intestine

PETER F. CURRAN

The transport of solutes and water by the intestinal mucosa has been the subject of rather extensive study since the latter part of the 19th century. In spite of many experiments, the fundamental mechanisms involved in the transport phenomena exhibited by this tissue have remained relatively obscure. There are many reasons for our failure to advance more rapidly, but a number of the problems encountered in study of the intestine arise from the complex nature of the tissue when considered from the point of view of a membrane system. Thus, the intestinal mucosa is capable of bringing about net transfer of certain materials across an intact cell layer against differences in electrochemical potential, a process usually referred to as active transport. The transported substances almost certainly pass through the cells rather than between or around them so that in passage across the mucosa, a solute must cross at least two barriers, the membranes at the mucosal and serosal sides of the cell layer. The existence of active transport processes in such systems imposes the requirement that these two barriers have different functional properties. It is becoming increasingly apparent that an understanding of such epithelial membranes requires knowledge about the properties of the individual barriers and the way in which they contribute to the overall function of the system. Much of what I have to say this afternoon will be concerned, directly or indiractly, with this point. In addition, relatively recent evidence has indicated, that transport processes in intestine are not entirely independent. My discussion will deal primarily with these interrelations or coupling phenomena between transport processes and with possible mechanisms involved. In particular, we will be concerned with the relation between Na and water transport and between Na and non-electrolyte transfer.

As you know, one of the properties of many animal cells is the ability to extrude Na from the cell against rather substantial electrochemical potential differences. In addition, many epithelial systems are able to bring about net transcellular Na transport against or in the absence of differences in electrochemical potential of Na in the solutions at the two sides of the barrier. This Na transport plays an essential functional role in many cases, and my major thesis this afternoon is that active Na transport is one of the primary transfer processes in intestine. I hope to show how certain processes depend on Na and would like to suggest that metabolic energy used to bring about Na transfer can also be utilized to carry out other important functions of the intestine. This hypothesis represents a gradual development of ideas over the past several years based in part on work in our laboratory and in part on the contributions of many others.

Na Transport

In agreement with observations on other epithelial membranes, Na appears to be actively transported across the intestinal mucosa (25).

Since I will suggest that coupling with Na transport may provide an explanation for the apparent active transport of certain other substances, I should begin by attempting to define active transport adequately. The usual definition is that active transport is a process that gives rise to a net flux of a substance against an electrochemical potential difference (23). However, recent developments suggest that we should also specify that the process cannot be explained by coupling to ther transport phenomena and involves a direct coupling to energy yielding metabolic reactions. Thus, a more appropriate definition might be that active transport is a process that cannot be explained by differences in electrochemical potential measured external to the membrane system or by coupling to externally measured flows and is directly coupled to metabolic reactions (15). The reasons for suggesting this extended definition should become apparent during the course of our discussion.

In most of my considerations, I shall refer primarily to studies on in vitro preparations of intestine because, for our purposes, more definitive experiments can often be carried out under these conditions. In many cases, similar results have been obtained in vivo. Table 1 shows some of the evidence that Na can be transported across in vitro intestine from mucosa to serosa against or in the absence of an electrochemical potential difference. Isolated rat and rabbit ileum bathed on both sides with solutions having identical Na concentrations exhibit an electrical potential difference of 5-10 mv oriented with the serosal side positive relative to the mucosal side. This potential difference should give rise to a net Na flux from serosa to mucosa, but a net flux in the opposite direction, against the electrical force, is observed. These tissues can also be short-circuited (the spontaneous potential difference reduced to zero by passing electric current through the tissue from an external source). Under these conditions, there is no net driving force on the Na ion because the electrochemical potential of Na is identical in the two bathing solutions, but a net flux from mucosa to serosa is observed. There have been suggestions that this Na flow is the result of coupling to other flows, particularly solvent or volume flow, rather than of a metabolically linked active transport process. There is, however, no unequivocal evidence to support this hypothesis and several

TABLE 1

Na Transport in Intestine in vitro

Tissue	Na Concentration		$\Delta\psi$*	Net Na Flux
	Mucosal	Serosal		
	(mM)		(mv)	(μeq/hr cm^2)
Rat Ileum (4)	140	140	+7.2	4.0
Rat Ileum (2)	140	140	0	1.8
Rabbit Ileum (26)	140	140	0	3.1

* $\Delta\psi$ = electrical potential of the serosal solution relative to the mucosal solution; $\Delta\psi$ = 0 indicates a short-circuited preparation.

** A positive value indicates flux from mucosa to serosa.

observations seem quite difficult to reconcile with it. Rather than attempting to discuss these alternatives suggestions in detail, I shall assume that there is an active Na transport process in the mucosa, in the sense defined above, and will try to show how this concept leads to a self-consistent and reasonable picture of certain properties of the epithelial cells. If we assume the existence of a Na transport system, a Na-pump if you will, we can further postulate that this pump must be localized at the serosal and/or lateral membranes of the cells rather than at the mucosal side. An average intracellular Na concentration of 50 meq/1 cell water is observed in strips of the mucosa of rabbit ileum incubated for 30 to 60 min in Ringer's solution containing 140 mM Na (28). If there is a single Na pump accounting for Na transport from mucosa to serosa, it must be located at the serosal side and extrude Na from the cell in order to explain the relatively low intracellular Na concentration. A pump at the mucosal side transferring Na into the cell would lead to a cellular Na concentration greater than that in the external medium. According to this concept, Na enters the cell across the mucosal border by diffusion or facilitated transfer down a concentration difference and is then extruded from the cell at the serosal or lateral side. The net result is a steady flow of Na from the mucosal to the serosal side with maintenance of a low cellular Na concentration. As expected, inhibition of the Na transport system leads to a rapid rise in cellular Na concentration to a level equal to that in the bathing medium (29). Thus, the mucosal cells appear to handle Na in much the same way as do other cells; the net transcellular transport comes about as a result of differences in functional properties of the membranes at the two sides of the cell.

Na Transport and Volume Flow

I would now like to examine relations between this Na transport system and the transport of other substances and to consider possible mechanisms by which these phenomena might come about. We shall first consider volume flow and Na transport. A number of observations have indicated that the intestine is capable of an apparent active transport of water or an active fluid transport. For example, both in vivo (12) and in vitro (13, 20) preparations are capable, under appropriate conditions, of bringing about volume flow from mucosa to serosa against an osmotic pressure difference. As shown in Fig. 1, the osmotic pressure of the mucosal solution can be raised by addition of NaCl to a level 100 mosm/1 greater than that of the serosal solution before volume flow across isolated rat intestine ceases. This process is dependent on metabolism since it is inhibited by removal of substrate (20) so that it conforms to some aspects of our general definition of active processes. However, the metabolic dependence could be indirect and coupling to other transport processes could be involved. There is considerable evidence suggesting that volume flow is dependent in some way on Na and it is worthwhile to ask if a coupling to the postulated active Na transport process occurs. The initial suggestion that such a relation might exist was the observation, in in vivo experiments on rat ileum, that there was a correlation between the rate of Na absorption from isotonic NaCl solutions and the rate of volume absorption (6). However such an observation does not provide information as to which process, Na absorption or

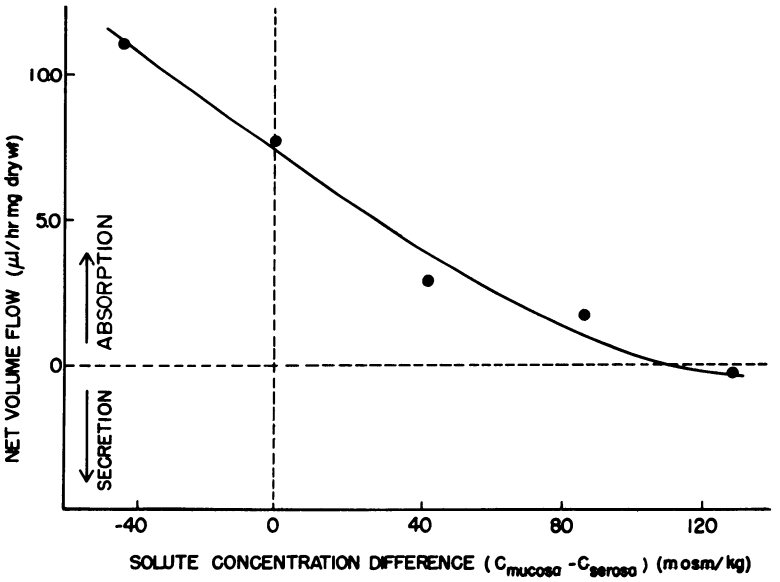

Fig.1. Effect of osmotic pressure difference on volume flow across rat ileum in vitro. Data from Parsons and Wingate (20).

volume flow, is the primary step. We, therefore, examined the effect of changing the Na concentration of the solution bathing the mucosal surface of the intestine. In these studies, the Na concentration was lowered by replacing NaCl with mannitiol so that the mucosal solution always had the same osmotic activity as the serosal solution. The results of some experiments on rat ileum in vitro are shown in Fig. 2. Net volume flow is markedly reduced as Na concentration is decreased and there appears to be a rather close correlation between the rate of Na transfer and volume flow. Because water activity remained constant in all cases, we felt that these observations suggested that volume flow was not due to an independent active fluid transfer. In view of these results, we developed the hypothesis that volume absorption from isosmotic solutions might be the result of osmotic pressure differences generated by net solute transport. We felt that the best test of this hypothesis would be to bathe both sides of the mucosa with isosmotic solutions and arrange conditions so that there would be no net transport of solute during an experimental period. Under these conditions, there should be no osmotic gradients within the system and if there were no volume flow, our hypothesis would be supported while if volume flow were observed, we would be forced to conclude that additional factors were involved. Such an experiment is difficult to perform in practice because the proper conditions for zero net solute transfer cannot always be achieved. It can, however, be performed in principle by considering the results of a series experiments in which the rate of solute transport varies. This approach is illustrated in Fig. 3 in which net volume flow

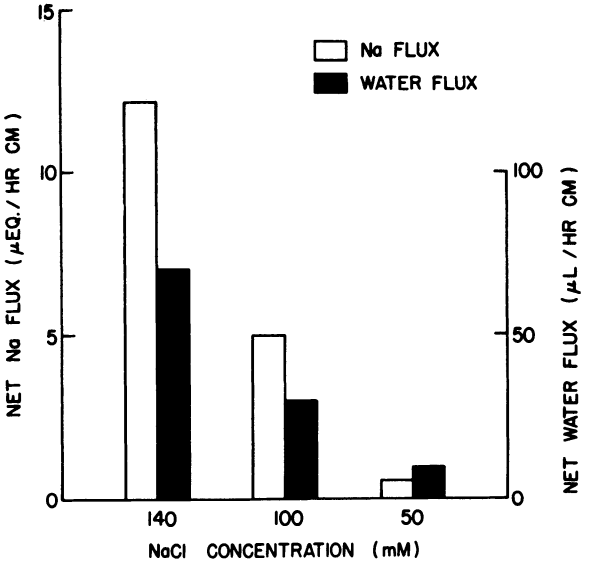

Fig.2. Effect of Na concentration on Na transfer and volume flow across rat ileum in vitro.

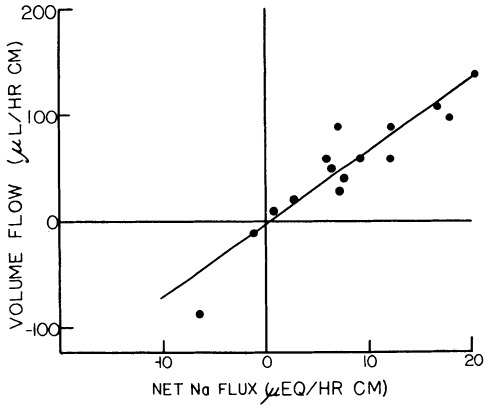

Fig.3. Relations between volume flow and Na transfer in rat ileum in vitro. (From J. Gen. Physiol. Rockefeller Univ. Press).

is plotted against the simultaneously measured net Na transfer. Variations in Na transport were achieved by varying NaCl concentration in the mucosal solution but the solution was kept isosmotic by replacing NaCl with mannitol. There is a linear relation between the two flows, and the intercept of the least squares line is almost exactly at the origin. Since there was no volume transfer between isosmotic solutions when solute (Na) flow was zero, we concluded that volume absorption

was coupled to Na transfer and was not the result of an independent active transport process. Additional evidence of a similar nature has been obtained in both in vivo (17) and in vitro (1, 13) intestinal preparations.

Such an interaction seemed to offer a reasonable explanation for a number of observations on intestinal absorption but the precise mechanism involved was by no means clear. Although Visscher et al. (32) demonstrated that plasma placed in the lumen of dog intestine became slightly hypotonic during absorption, changes in solute concentration of the mucosal or serosal solutions clearly could not explain all the observations on volume flow. Thus, increases in solute concentration of the serosal solution bathing in vitro intestine were found to have little effect on volume flow (11) and several workers (13, 20) have demonstrated that volume transfer can occur from mucosa to serosa even when the mucosal solution has a higher osmolality than the serosal solution (Fig. 1).

Consequently, we sought a mechanism whereby solute transport could provide the overall driving force necessary for volume flow by generating osmotic pressure differences within the tissue. Such a system can be devised by making use of some of the properties of complex membrane systems involving barriers arranged in series. This type of system was appealing because it might be easy to imagine appropriate structural analogs in a membrane system such as intestines. The mechanism we have proposed (4, see also Durbin (9) is based on the principle of the effective osmotic pressure generated across a membrane permeable to the solute. As indicated by Staverman (30), the effective osmotic pressure, $\Delta\pi_{eff}$, caused by such a solute will be less the calculated van't Hoff pressure and can be described by the relation

$$\Delta\pi_{eff} = \sigma RT\Delta C \qquad (1)$$

in which σ is the reflection coefficient of the membrane for the particular solute. For simple systems, the value of σ varies from unity for a solute that cannot penetrate the membrane to zero if the membrane is completely non-selective for the solute. There is now an appreciable amount of experimental data confirming this type of relation for both artificial and biological membranes.

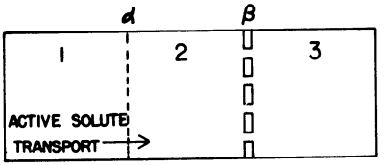

Fig.4. Model system for volume flow.

Fig. 4. shows a model system that incorporates the concept of the reflection coefficient and that could account for coupling between active solute transport and volume flow in intestine. The model consists of two membranes or barriers in series separated by a closed compartment. We consider only a single solute at equal concentrations in compartments 1 and 3 and assume that the two barriers have different

reflection coefficients for the solute; membrane α is a tight membrane with a relatively high value of σ while membrane β is a loose barrier with σ near zero. The solute is assumed to be actively transported across membrane α from compartment 1 to 2. This transport raises the solute concentration in compartment 2 above that in 1 and the resulting effective osmotic pressure causes a volume flow from 1 to 2. The solute concentration difference causes almost no volume flow from 3 to 2 because the effective osmotic pressure across membrane β is nearly zero ($\sigma \approx 0$). However, since compartment 2 is closed, volume flow from 1 to 2 leads to an increase in hydrostatic pressure in 2 and this pressure in turn causes a volume flow, mainly from 2 to 3 across the loose barrier which has a higher hydraulic conductivity. The net result is a volume flow from 1 to 3 even though there is no osmotic pressure difference between these two compartments. In addition, volume flow from 1 to 3 should take place even if the solute concentration in 1 is greater than that in 3 providing the active transport system can maintain a higher concentration of solute in 2 than in 1. These qualitative predictions can be verified from a consideration of the expressions for volume flow obtained from nonequilibrium thermodynamics, and the theory of this type of system has been discussed in detail by Patlak et al. (21).

In a more practical sense, we undertook construction of an artificial system to test some of these predictions experimentally (5). The model consisted of a lucite chamber separated into three compartments with the end chambers equipped with graduated tubes for measurement of volume changes. Membrane α was a piece of dialysis tubing and membrane β, the loose barrier, was a sintered glass disc. Sucrose was used as solute and the process of active transport was simulated by introducing a relatively high concentration into compartment 2. After a short time, the system achieved a quasi-steady state in which the volume changes in compartments 1 and 3 were equal and opposite and the flow was approximately constant in time. Fig. 5 shows the results of some of these studies. Volume flow from a relative concentrated sucrose solution (compartment 1) toward a relative dilute solution (compartment 3) could be demonstrated as long as the solute concentration in 2 was greater than in 1. These observations indicate that our predictions for the behavior of the system are qualitatively correct, and other studies (19) have indicated that flows can be predicted quantitatively from knowledge of the properties of the barriers.

Since such a system could explain a number of observations on water transfer we might next ask whether structures analogous to the model exist in intestine. Fig. 6 is an attempt to illustrate possible analogs. We have previously argued that the active Na transport system is located at the serosal and/or lateral membranes of the cell so that this barrier would represent membrane α. The cell interior would be compartment 1 and the blood capillary in vivo or the serosal solution in vitro would be equivalent to compartment 3. The lateral space between the cells together with the subepithalial structures could play the combines role of compartment 2 and membrane β. For the system to operate, there need not be a discrete barrier corresponding to membrane β; the major requirement is for the presence of a structural

arrangement that will prevent rapid diffusion of actively transported solute and hence dissipation of the necessary concentration difference. In this analogy, we have not taken into account the mucosal barrier or brush border of the cell so that we have over-simplified the system somewhat. This additional membrane must be considered in any attempt to make quantitative predictions. The major effect of adding another barrier in the series appears to be a tendency to lower the effective tonicity of the transported fluid so that this barrier may be important in terms of maintaining an approximately isosmotic fluid transfer.

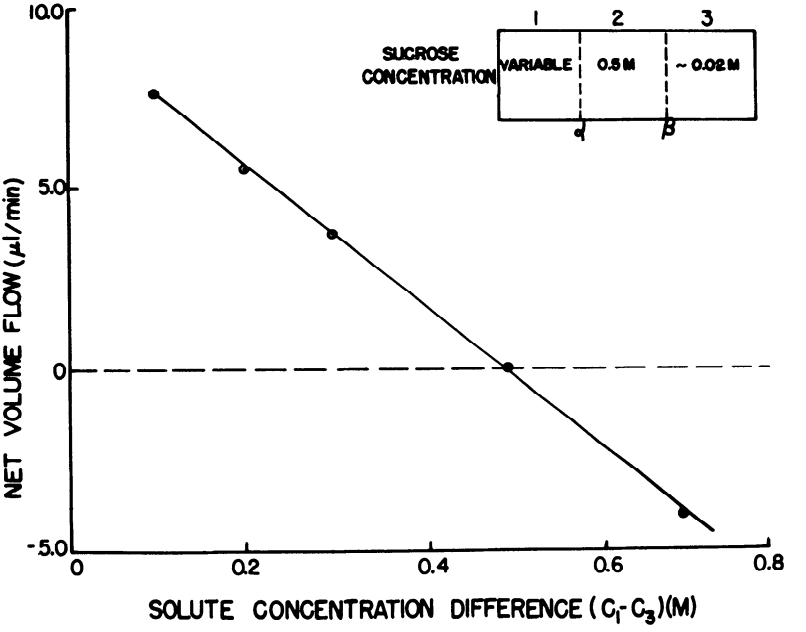

Fig.5. Volume flow in model system. A positive net flow indicates a volume increase in compartment 3 and a corresponding decrease in compartment 1.

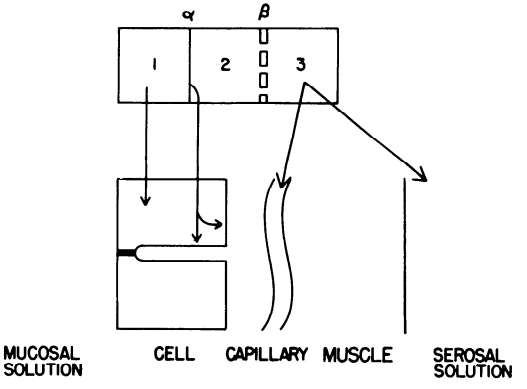

Fig.6. Possible analogs between model system and the intestine.

Recent observations by Clarkson and Toole (2) have shown that transfer of solute through the tissue is essential for coupled, isotonic volume flow. In their experiments, isolated rat ileum was short circuited and the transfer of ions and of volume were determined. Under these conditions Na, which is actively transported, was transferred through the tissue while Cl, which is not actively transported, was moved from the mucosal to the serosal solution via the Ag-AgCl electrodes used in the current passing circuit. Examination of their data suggests that only Na was effective in causing volume flow. As shown in Table 2, volume transfer is approximately isosmotic if Cl transfer (via the current passing system) is excluded. If Cl transfer is included in the calculation, the volume flow would be markedly hypertonic, a situation not observed in intestine. I should also note that there has been some recent evidence, particularly for gall bladder, but also for intestine that the lateral intercellular spaces play a role in fluid transfer (8, 16). These spaces appear small or closed in electron micrographs of non-transporting tissues but are rather markedly distended when there is a large volume transfer. Diamond and Tormey (8) have recently discussed the role of these spaces in terms rather similar in principle to the more simplified series barrier model described above. In their considerations, the role of Na is much the same but they treat the lateral space as an unmixed compartment in which a concentration gradient of the actively transported solute exists. The resulting relation between volume and solute transfer is determined in part by the length and other dimensions of the spaces.

TABLE 2

Solute and Volume Flows in Rat Ileum*

Total Solute Flow (μosm/hr)	Short-Circuit Current (μeq/hr)	Solute Flow through tissue (J_S)** (μosm/hr)	Volume Flow (J_V) (ml/hr)	$\frac{J_S}{J_V}$ (μsoml/ml)
146	67	79	0.25	316
154	55	99	0.32	310
299	162	137	0.40	343

*Data from Clarkson and Toole (2).
**J_S is the difference between total solute flow and current.

The electron micrographs lend support to these models for the mechanism of coupling between active solute transfer and volume flow, but further study is necessary before the hypothesis can be considered firmly established. The mere facts that the artificial system described in Fig. 4 works as predicted and that analogies can be drawn between the model and structural aspects of the mucosa, do not indicate that the intestine actually functions in this manner. The hypothesis we have proposed suggests that the coupling between flows has as its basis certain structural features peculiar to the membrane system rather than to more basic molecular mechanisms. Thus, the next logical step in exploring the concept is to obtain information on specific properties of these structures. However, such an approach will require development

of new experimental techniques.

Na and Amino Acid Transport

I would now like to turn to an entirely different aspect of coupling between flows in the intestine, the relation between Na transfer and the transfer of other solutes such as sugars and amino acids. In this case, we have been able to obtain more specific information regarding possible mechanisms because direct measurements of events at the barrier involved in the coupling phenomena have been possible. It is perhaps interesting to note that the initial suggestions of a relation between Na and the transfer of sugars in intestine stem from observations made by Reid in 1906, but the phenomena have been studied extensively only in the last few years since the work of Riklis and Quastel (22), called attention to them. In this discussion, I will deal mainly with Na and amino acids because most of our own work has been on these solutes.

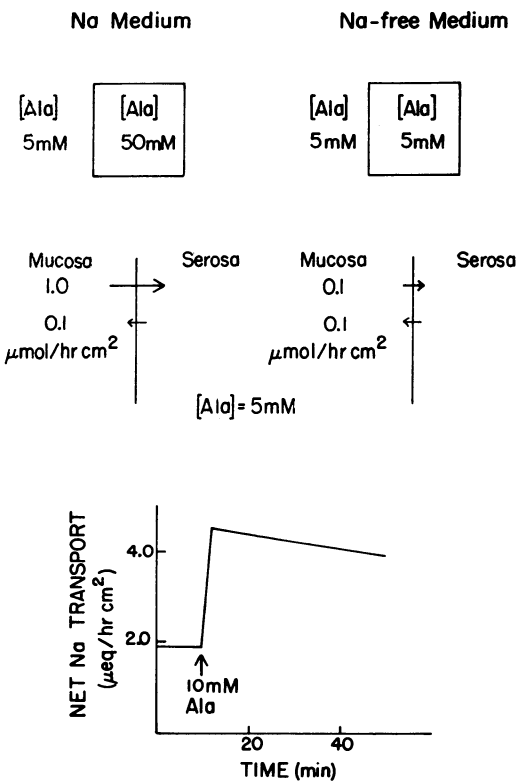

Fig.7. Relations between Na and amino acids in isolated rabbit ileum.

Fig. 7. illustrates three species of the overall relation observed in rabbit ileum between Na and the neutral amino acid, alanine. The mucosal cells of this and other species have the ability to accumulate amino acids to concentrations far in excess of those in the solution in

which strips of mucosa are incubated (24, 28) (Fig. 7, top). In rabbit ileum, we have obtained clear evidence from changes in cell volume that most of the alanine in the cells is in a free, osmotically active form (28). If strips of mucosa are incubated in Na-free solutions in which Na is replaced by a variety of other solutes, the ability of the cells to accumulate alanine is completely abolished. The second aspect of this relation is shown in the middle section of Fig. 7; rabbit ileum mounted as a flat sheet separating two Na-containing solutions having equal alanine concentrations is able to bring about a net transport of alanine from mucosa to serosa. This active transport is completely inhibited by removal of Na from the bathing solutions (10). I should note at this point that the observation of a cellular alanine concentration greater than that in the medium, coupled with an active transport from mucosa to serosa, suggests that the "active step" is located at the mucosal border of the cell. Thus, we would postulate that alanine is transported into the cell from the mucosal solution and leaves the cell down a concentration difference across the serosal barrier by a process that does not require energy. The third aspect of the relation between Na and alanine is shown at the bottom of Fig. 7. Addition of alanine to the solution bathing the mucosal surface of rabbit ileum causes a rapid and sustained rise in the rate of net Na transport across the tissue (27). I would now like to summarize experiments designed to examine these interactions in more detail.

Early in our investigations, it became apparent to us that measurement of alanine fluxes across the mucosal border of the cell was essential since this barrier is the site of the apparent active transport. Measurements involving the whole cell or both cell borders would not be sufficient to provide the desired information and interpretations would be open to question unless we had at least some direct information on the properties of the mucosal barrier alone. In order to measure Na and amino acid fluxes from mucosal solution into the cell, we have developed a method involving a brief (usually 20 to 60 seconds) exposure of the mucosal surface alone to solution containing C^{14} labeled amino acid and Na^{22} (29). The influxes can then be estimated from the amounts of tracers taken up by the tissue. A variety of control experiments have provided convincing evidence that the technique does measure the unidirectional fluxes across the brush border from the mucosal solution to the cells. In my subsequent discussion I shall use the term influx exclusively to denote this flux.

Our initial measurement of alanine influx produced results that were in agreement with known characteristics of amino acid transport by intestine and that provided indirect support for the concept that the influx is the primary step in the active process. As shown in Fig. 8, at constant Na concentration, alanine influx increased with increasing concentration but showed a tendency toward saturation. Transmural fluxes of amino acids across intestine are well known to exhibit this behavior. Removal of Na from the system caused a substantial depression of alanine influx at all concentrations tested although the saturation phenomenon remained. In view of the results shown in Fig. 7, a depression of influx might be expected in the absence of Na. The curves shown in Fig. 8, have the mathematical properties of rectangular hyperbolas. That is,

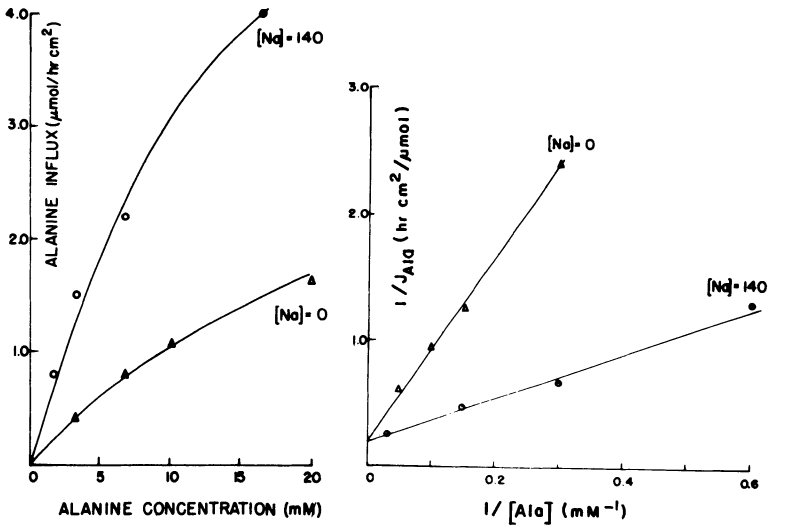

Fig.8. Alanine influx as a function of alanine concentration in rabbit ileum. (From J. Gen. Physiol. Rockefeller Univ. Press).

if the reciprocal of the influx is plotted against the reciprocal of alanine concentration, straight lines with non-zero intercepts are obtained as shown. Thus the alanine influx, J^i_A, can be described as a function of concentration by an expression of the form.

$$J^i_A = \frac{J^{im}[A]_m}{K_t + [A]_m} \qquad (2)$$

in which J^{im} is the maximal influx, $[A]_m$ is alanine concentration in the solution bathing the mucosal surface and K_t is the "apparent Michaelis constant", the value of alanine concentration for which J^i_A is equal to one half J^{im}. The data in Fig. 8 indicates that removal of Na from the bathing solution does not alter J^{im} (determined by the intercept of the lines) but causes an increase in K_t (increased slope with constant intercept). Table 3 summarizes the effects of Na concentration on the value of K_t for three neutral amino acids. In all cases, K_t is increased markedly by reduction in Na concentration. There was, however, no systematic effect on maximal influx and the same value of J^{im} was observed for all three amino acids. Further, alanine influx is competitively inhibited by valine and leucine, both in the presence and absence of Na and the degree of inhibition can be predicted quite accurately from the K_t values given in the table (7).

These observations led us to consider the question of whether intracellular or extracellular Na was essential for normal alanine influx. An answer to this question is important in distinguishing among possible mechanisms of the effect but data such as those shown in Fig. 8 do not provide the necessary information because both cellular and extracellular

Na were altered in those experiments. However, a direct answer can be obtained with the technique used. The experimental setup allows us to deplete the tissue of Na by preincubating it in Na-free media. Since the influx measurements can be carried out in a time as short as 20 seconds, it is possible to measure influx into Na depleted tissue from a solution containing 140 mM Na without appreciably altering cellular Na. Table 4 shows the results of a series of experiments testing the effects of intra- and extracellular Na on alanine influx. Comparison of series A and B indicates that a reduction in total cellular Na by preincubation in Na-free solution does not alter alanine influx providing the external Na concentration is 140 mM during the influx measurement.

TABLE 3

Effect of Na Concentration on Amino Acid Influx*

Amino Acid	[Na] (mM)	K_t (mM)
Alanine	140	9.1
	70	16.3
	22	31.2
	0	70.0
Valine	140	5.0
	0	31.5
Leucine	140	4.2
	0	29.0

*From Curran et al. (7).

TABLE 4

Effects of Cellular and Extracellular Na on Alanine Influx

Principle Cation*

Series	Preincubation	Test	Influx (μmol/hr cm^2)
A	Na	Na	2.1 ± 0.2
B	Choline	Na	2.2 ± 0.2
C	Choline	Choline	0.6 ± 0.1

* Preincubation was for 30 min. in the solution indicated, and influx was measured over a 20 to 60 sec. period from the test solution. From Schultz et al. (28).

If external Na is also reduced during the influx determination (Series C) there is a marked depression in alanine influx. Thus extracellular Na appears to be essential for normal alanine influx but the influx is not altered by a substantial decrease in cellular Na. In the experiments presented, Na was replaced by choline but identical results are obtained if Tris is used or if NaCl is replaced by mannitol. Thus, the observed

effects appear to be due to removal of Na and not to the solute used to replace Na. In addition, neither Li nor K can substitute for Na in maintaining alanine influx (29). We have also found that influx is independent of cellular alanine concentration. That is, influx is not altered by preincubating the tissue in 5mM alanine, a procedure that leads to rather high cellular concentrations Fig. 7.

This series of observations has led us to the development of a model to describe the interaction between Na and alanine at the mucosal border of the intestinal cell (7). This model is shown in Fig. 9. We assume the existence of a "carrier" or "site" (X) in the brush border membrane that can combine with alanine or another amino acid (A). The resulting complex (XA) can undergo translocation across the membrane or can combine with Na to form a ternary complex (XANa) which then undergoes translocation. In analyzing the kinetic behavior of this model, we have made use of a number of experimental observations to justify certain simplifications. For example, the observations that neither cellular Na or cellular alanine affect alanine influx and that maximal influx is unaffected by external Na concentration require that the translocation steps (denoted by P_1, P_2, P_3) be slow relative to the other reactions and that $P_1 \simeq P_2 \simeq P_3$. The requirement that alanine can enter the cell

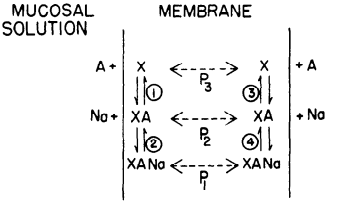

Fig. 9. Model for Na-alanine interaction at mucosal border of intestine. (From J. Gen. Physiol. Rockefeller Univ. Press).

in the absence of Na by a process that shows saturation kinetics and is competitively inhibited by other amino acids is the basis for assuming that the site must first combine with the amino acid. The fact that maximal influx is the same in the presence and absence of Na indicates that we cannot be dealing with two parallel paths, one Na dependent and one Na independent. Given these assumptions, the alanine influx predicted by the model is

$$J_A^i = \frac{X_t P [A]_m}{\frac{K_1 K_2}{K_2 + [Na]_m} + [A]_m} = \frac{J^{im} [A]_m}{K_t + [A]_m} \qquad (3)$$

in which X_t is the total concentration of sites (assumed to be constant), P is the coefficient for translocation, K_1 is the dissociation constant for the reaction $X + A \rightleftharpoons XA$ and K_2 is the dissociation constant for the reaction $XA + Na \rightleftharpoons XANa$. As indicated,

$$J^{im} = X_t P \qquad (4)$$

so that maximal influx is independent of Na concentration, and

$$K_t = \frac{K_1 K_2}{K_2 + [Na]_m} \qquad (5)$$

so that K_t increases with decreasing $[Na]_m$ as observed (Table 4). Further, taking the reciprocal of equation 5, we find that

$$\frac{1}{K_t} = \frac{1}{K_1} + \frac{[Na]_m}{K_1 K_2} \quad (6)$$

so that the model predicts that $1/K_t$ should be a linear function of $[Na]_m$. As shown in Fig. 10, this behavior is indeed observed for alanine and from the slope and intercept of the line, we find that K_1 = 70 mM and K_2 = 17 mM.

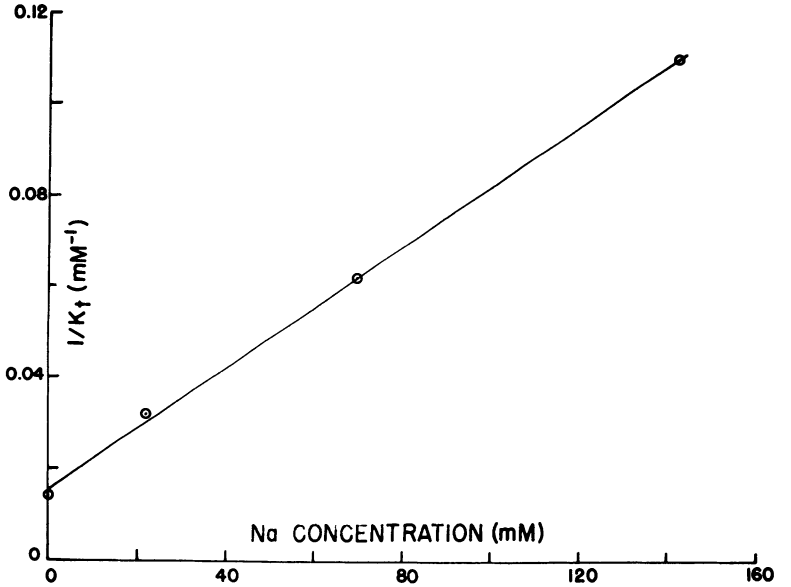

Fig.10. Relation between K_t and Na concentration. (From J. Gen. Physiol. Rockefeller Univ. Press).

Finally, the model predicts a relation between the influxes of Na and alanine. From the kinetic analysis, we find that

$$J^i_{Na} = \left[\frac{[Na]_m}{K_2 + [Na]_m}\right] J^i_A + J_{Na} \quad (7)$$

in which J^i_{Na} is the total Na influx and J_{Na} is that portion of Na influx taking place by a path other than that depicted in Fig. 9. Our experimental data indicate that there is a positive linear correlation between Na and alanine influxes at all Na concentrations tested from 5 mM to 140 mM (7). Since we know the value of K_2, we should be able to predict the relation between the fluxes. Fig. 11 shows the comparison between the observed values of $\Delta J^i_{Na}/\Delta J^i_A$ at various Na concentrations and those predicted from equation 7. We feel that the good agreement provides strong support for the validity of the model because this appears to represent an independent test.

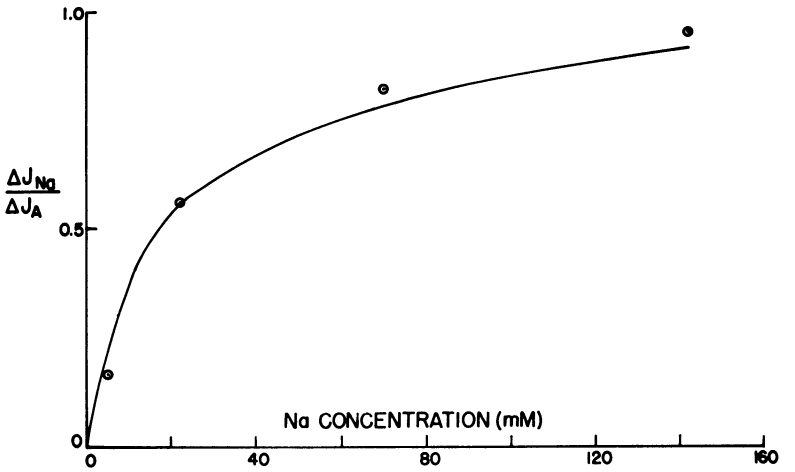

Fig.11. Relation between influxes of Na and alanine across the mucosal border of rabbit ileum. The points are experimental values and the line is calculated from equation 7 using K_2 = 17 mM as determined from data in Fig.10. (From J. Gen. Physiol. Rockefeller Univ. Press).

There are several aspects of this model that are of considerable interest and merit further investigation and I would like to describe briefly some of the additional steps we have taken. First, we have investigated the possibility that it might not be necessary to specify that the transport site combine first with alanine and then with Na. In particular, we asked is it possible to fit our data by assuming that there is no specified order of combination? Because the equations describing this situation are quite complex, we have had recourse to a digital computer to approach the problem. By carrying out a series of computations using different values for rate coefficients we have found that our data cannot be fitted even approximately unless the probability of the site first combining with the amino acid is at least 500 times greater than the probability of its first combining with Na. We have also confirmed the necessity for the translocation steps to be slow relative to the association-dissociation reactions. Thus the model as depicted in Fig. 9 seems to be the most adequate to describe our present observations.

According to the model, the role of Na is to stabilize the amino acid-site complex as indicated by the observation that $K_2 < K_1$. This stabilizing role of Na immediately suggests a mechanism by which cellular accumulation and net transport of amino acid against a concentration difference can occur. Since the intracellular Na concentration is normally lower than that in the mucosal solution, the amino acid-site complex would be less well stabilized at the cytoplasmic side of the membrane and dissociation would tend to occur. This effect would lead to

cellular accumulation of amino acid and subsequent diffusion to the serosal solution giving rise to the observed active transport. According to this concept, the driving force for amino acid transport could be provided entirely by the difference in Na concentration between the cell and the external solution. This concentration difference is, in turn, maintained by the active Na extrusion mechanism as previously discussed. Thus, amino acid transport may not be coupled directly to metabolism; energy is supplied to the Na transport system which in turn drives the amino acid transport by maintaining a relatively low cellular Na. Similar hypotheses have been proposed by others to explain transport of sugars (3) and amino acids (24) in intestine and other tissues (14, 18, 31) but the mechanisms suggested differ in some details.

Unfortunately, direct and unequivocal tests of this attractive hypothesis are rather difficult to carry out in intestine and our first steps have been somewhat indirect. On the basis of the evidence I have discussed, we cannot rule out involvement of metabolic energy directly in the amino acid influx process. For example, the reaction $XA + Na \rightleftharpoons XANa$ could depend on splitting of ATP to give rise to the stabilization of the complex and there are other possible modes of metabolic coupling in the system. If a step involving a Na-activated ATPase were included, an explanation would also be provided for the observation that ouabain inhibits active amino acid transport. We have tried to approach this particular question directly by examining the effect of several metabolic inhibitors and ouabain on the alanine influx process.

In these studies, the tissues were always preincubated in Na-free medium to provide comparable conditions for both control and inhibited preparations, and influx was measured from solution containing 140 mM Na. Experiments were also carried out to determine the effects of the inhibitors used on the net transport of alanine across the whole intestinal wall by measuring transmural fluxes. As indicated by the results shown in Table 5, cyanide and ouabain almost completely abolished net transport in the absence of a concentration difference. These agents did not, however, have a significant effect on alanine influx across the mucosal border of the cell. Iodoacetate and 2, 4-dinitrophenol had similar effects.

TABLE 5

Effect of Inhibitors on Alanine Fluxes*

	Net Flux (μmol/hr cm^2)	Influx
Control	1.2	2.4
Cyanide (2mM)	0.1	2.4
Control	1.5	1.9
Ouabain (10^{-4}M)	0.3	1.7

* Net transmural flux from mucosa to serosa was determined as the difference between unidirectional transmural fluxes. Influx denotes flux from mucosal solution to cell. Control and inhibitor experiments were carried out on tissue from the same animal.

From these experiments, we concluded that direct coupling to metabolic energy is not involved in the influx process. In terms of our model, this means that the steps indicated by reactions 1 and 2 and the translocation steps do not involve a direct connection to metabolism.

The effect of inhibitors can, however, be explained qualitatively within the context of the model by simply assuming that the system is symmetrical so that events at the cytoplasmic side of the membrane are similar to those at the mucosal side. The amino acid efflux from the cell would then be determined in part by the level of cellular Na. Some predictions based on this concept are shown in Fig. 12. Under control conditions, cell Na is relatively low so that efflux is low and amino acid accumulates in the cell. The actual concentration would be determined by a balance between influx into the cell at the mucosal side and diffusion out at the serosal side. Removal of Na from the bathing solution leads to loss of cellular Na and amino acid is no longer accumulated by the cells (28). Influx drops markedly and efflux from the cell should also fall because of the reduction in Na concentration. These two fluxes should become approximately equal so that there is no net flux.

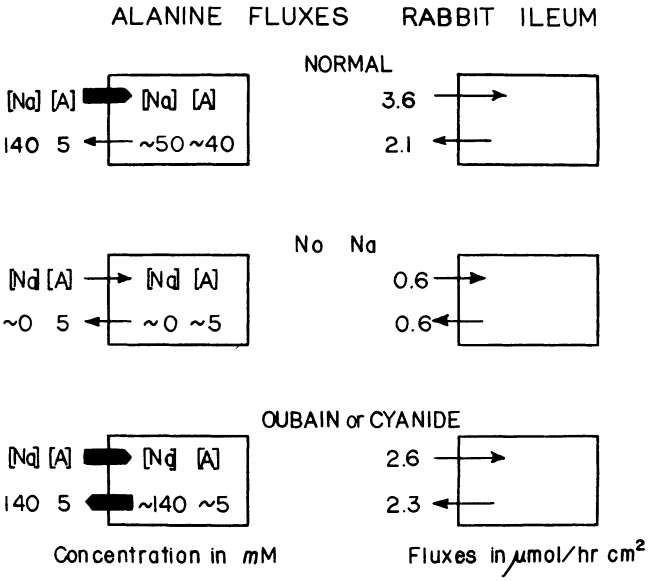

Fig.12. Alanine fluxes at the mucosal border a) predicted behavior, b) observed values. Efflux was taken as the difference between influx and steady state net flux determined on tissue from the same animal under the same conditions.

In the presence of inhibitors such as ouabain and cyanide quite a different situation applies. Cell Na increases to the level of the external solution and there is no accumulation of amino acid (28). Again influx and efflux should be equal with no net flux, but in this case, both fluxes should be high because cellular and extracellular Na concentrations are

high.

By making the simple assumption that net flux across the brush border must be equal to net flux across the whole tissue when the system is in a steady state, we can also estimate the efflux. The results of such experiments are also shown in Fig. 12, and they conform to the predictions. According to these ideas, Na removal and ouabain inhibit amino acid transport for essentially the same reason; the Na concentration difference between cell and mucosal solution is abolished. However, the two conditions are not equivalent. In one case, the fluxes across the brush border are low and equal, in the other they are high and equal. These results can be predicted on the basis of the model without postulating any direct involvement of metabolic energy in the amino acid transport. The experiments to date cannot rule out direct energy coupling at the cytoplasmic side but there is no compelling evidence as yet to require such a process. However, study of this point must await development of methods for direct and precise measurement on amino acid efflux from the cells.

Summary

I have tried to present for you some thoughts on two aspects of coupling between transport processes. Both of these ideas must still be considered as hypotheses requiring further study but, to my mind, they lead to a rather attractive and relatively self-consistent overall picture of the mucosal cell. Our primary hypothesis is the existence of an active transport mechanism that extrudes Na from the cell at the serosal side. This Na transport step appears to be coupled to the transfer of volume. The mode of coupling may well lie in certain structural features of the epithelium in that it appears to depend on certain particular arrangements of compartments and barriers. At the mucosal side of the cell, there appears to be coupling between Na and amino acid transfer. Here we have suggested a chemical or molecular basis for the coupling that might, for example, involve allosteric changes in a transport site, and have proposed that the driving force involved is the Na concentration difference maintained by the active Na extrusion mechanism.

I would like to make two final somewhat speculative points about these models. First, both of the coupling processes provide a relatively simple explanation for transport processes that appear to be active. That is, in intestine volume flow can occur against an osmotic pressure difference and amino acids can be transported against electrochemical potential differences. The schemes discussed show how these phenomena could occur without direct coupling of metabolic energy to the transport process in question. To be sure, energy is required but we propose that it is derived ultimately from the energy utilized in the extrusion of Na from the cell. This extrusion process produces Na concentration differences across both the serosal and mucosal membranes and these differences provide the energy to drive other processes. My second point is simply that such an arrangement of transport makes very good sense from the point of view of the energetics of the cell. Such coupling phenomena would appear to make possible much more efficient utilization

of a limited energy supply than would a system in which, for example, direct utilization of ATP is required for each transport process. It is because Na appears to play a central role in the coupling phenomena and because its transport may involve the direct link to metabolism that I initially suggested that it might be considered the primary process in intestinal absorption.

I am deeply indebted to my colleagues who participate in this work, particularly Drs. A. K. Solomon, Stanley G. Schultz, Robert E. Fuisz, and Ronald A. Chez. Their contributions far exceed mine.

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COMPARATIVE STATISTICS OF APS REGULAR MEMBERS

The following gives some indication of the composition of our Society and the research interests of its regular members.

TABLE 1

CITIZENSHIP AND SEX

	Male	Female	Total	%
U.S.A.	2375	163	2538	89.5
Canada	106	9	115	4.1
Other	177	5	182	6.4
	2658	177	2835	
		6.0%		

TABLE 2

DISTRIBUTION BY DEGREES

	1960	1965	1968
Total number of regular members	1767	2413	2835
Average age	47.8 yrs.	48.9 yrs.	48.9 yrs.
Those with Ph.D. degree	870-49.2%	1183-49.0%	1378-48.6%
Those with M.D. degree	600-34.0%	855-35.4%	1049-37.0%
Those with Ph.D. & M.D. degrees	256-14.5%	315-13.1%	341-12.0%
Those with other degrees	41-2.3%	60-2.5%	67-2.4%
Those doing research 25+% of time	1493-84.5%	2093-86.7%	2538-89.5%
Those with Ph.D. doing research 25+% of time	750-86.2%	1041-88.0%	1243-90.0%
Those with M.D. doing research 25+% of time	516-86.0%	752-88.0%	953-90.8%
Those with Ph.D. & M.D. doing research 25+% of time	194-75.8%	248-78.7%	283-83.0%
Those with other degrees doing research 25+% of time	33-80.5%	52-86.7%	59-88.0%

TABLE 3

THOSE DOING RESEARCH 25+% OF TIME

Primary Area of Research	1960	1965	1968
Anatomy	16 - 1.1%	13 - 0.6%	10 - 0.4%
Biochemistry	16 - 1.1	19 - 0.9	25 - 1.0
Blood	51 - 3.4	82 - 3.9	95 - 3.7
Cardiovascular	264 -17.7	358 -17.1	455 -17.9
Cellular & Tissue	78 - 5.2	103 - 4.9	123 - 4.8
Comparative Physiology	31 - 2.1	46 - 2.2	58 - 2.3
Electrolytes	66 - 4.4	77 - 3.7	101 - 4.0
Endocrines	170 -11.4	243 -11.6	291 -11.5
Energy & Temperature Reg.	16 - 1.1	36 - 1.7	42 - 1.7
Environmental	72 - 4.8	111 - 5.3	126 - 5.0

Table 3 (Continued)

Gastrointestinal	60 - 4.0	80 - 3.8	92 - 3.6
General Physiology	6 - 0.4	13 - 0.6	12 - 0.5
Gerontology	7 - 0.5	10 - 0.5	14 - 0.6
Lipids & Steroids	15 - 1.0	23 - 1.1	33 - 1.3
Minerals, Bone & Teeth	7 - 0.5	19 - 0.9	23 - 0.9
Muscle & Exercise	60 - 4.0	84 - 4.0	104 - 4.1
Neurophysiology	249 -16.7	327 -15.6	408 -16.1
Nutrition	18 - 1.2	19 - 0.9	19 - 0.7
Pharmacology	49 - 3.3	63 - 3.0	65 - 2.6
Radiation	51 - 3.4	46 - 2.2	47 - 1.9
Renal	54 - 3.6	90 - 4.3	107 - 4.2
Reproduction	16 - 1.1	31 - 1.5	43 - 1.7
Respiration	81 - 5.4	132 - 6.3	156 - 6.1
All other categories	40 - 2.7	68 - 3.3	89 - 3.3
Total	1493	2093	2538

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GASTROINTESTINAL SECTION LECTURE

Thomas R. Hendrix, M.D., Associate Professor of Medicine at The Johns Hopkins University School of Medicine, Baltimore, Maryland will give the Eighteenth Annual Lecture before the Gastrointestinal Section of the American Physiological Society on Tuesday, April 16, 1968, during the spring meeting of the Federation of American Societies for Experimental Biology in Atlantic City. His topic will be, "Clinical Implications of the Study of Esophageal Function in Man."

NEWS FROM SENIOR PHYSIOLOGISTS (Concluded)

This year we asked senior physiologists about their health, their current activities, their interests in a position, their chief sources of satisfaction and invited their advice on retirement. This went to all active members born before 1903 and to all retired members. In addition we invited retired members to comment on "Retirement Crisis" Science, 7 July, 102-103, 1967. Excerpts from many of the early replies were published in the November issue. The inquiries to the retired members were mailed last, and most of the 40 items that follow are therefore from retired members. In addition we sent the letter with an explanatory note to honorary members; a few replied. While the 170 replies give a broad picture of physiologists born before 1903, their diversity limits the generalizations that can be drawn particularly since about 177 did not reply. However, we can say that most of those who replied are in good health; nearly all who wish to remain active do continue in professional activities, but usually at a reduced level. Many report satisfaction in what they are doing and several gain special satisfaction in helping young assistants. There is a wide range in post-retirement activities but there was nearly unanimous agreement that one should plan for retirement and keep busy after retirement. The members of the committee wish that they could find time to acknowledge individually the many fine and interesting replies that were submitted, but we too are still busy.

Committee on Senior Physiologists
D. B. Dill, Chairman
Hallowell Davis
Hiram E. Essex
Eugene M. Landis

Hiram Essex reports that immediately after his retirement he was director of undergraduate research at St. Mary's College, Winona, for two years. In 1961-62 he and his wife made a world tour. After completing his tour of duty as President of the National Society for Medical Research he has spent his time most pleasantly: 1) Painting works in oil, acrylic and wax encaustic mediums - very modern in style; 2) Seeking data on the geneology of the Essex family. He recommends this occupation to senior physiologists as a different kind of research that can result in shocks and thrills. It is lots of fun but the danger is you may get out on a limb of the family tree! 3) Working on his dairy farm near Rochester, Minnesota. No, he doesn't milk the cows himself. There he is applying his studies of genetics to the breeding of better Holstein-Friesian cattle (the black and white cows, lest you have forgotten or never knew); 4) Traveling as already mentioned. He and his wife spent a couple of months a year ago touring the British Isles and Italy, where emphasis was put on Art Centers, Cathedrals and Cows.

Bruce Dill described his laboratory and activities in the February Physiologist.

E. M. Landis became emeritus (Harvard) in June, 1967 and began an appointment as Adjunct Professor of Biology, Lehigh University

September 1, 1967. "I have a laboratory in the Biology Department, have given one Biology lecture and one seminar so far this autumn and have one graduate student. Half-time is devoted to pushing on with some micro-studies on capillaries and related topics, with modest support by a research grant from NIH. Tuesday and Thursday are devoted to manicuring the inside and environs of a house, newly built from our plans and situated in a woods on top of Swoveberg Hill - a micro-estate with a mega-view about four miles southeast of Lehigh University and Bethlehem. Our home address is R.D. 1, Box 22A, Hellertown, Pa. 18055. General conclusion is that retirement is fine, presenting more advantages than disadvantages."

Allen and Marian Keller had Bruce and Chloris Dill as their dinner guests at their home in Elizabethtown on September 26.

Walter S. Root will retire in 1968 and will then make his home at Woods Hole.

Dietrich C. Smith keeps busy one or two days a week during the spring and fall as Secretary of the Maryland Society for Medical Research and as Editor for their quarterly Bulletin. He enjoys the leisure and the freedom which retirement brings. An ardent traveller, he goes anywhere he can afford whenever he pleases.

Victor E. Hall will retire in June 1968, but will go immediately into a full program at UCLA. Half of his time will go to continuing the directorship of the Brain Information Service, part to serving as physiological consultant to the Division of Pediatric Cardiology, and the rest to being scientific advisor to the Nurse Scientist Program of their School of Nursing. All these depend on federal grants and are no more stable than their funding. On the side he will go on with editing of the Annual Review of Physiology and of the UCLA Forum in the Medical Sciences.

Eugene U. Still is in excellent health; he comtinues his interest in the application of electronic instruments to physiological measurements. He has worked with several fine surgeons, one of whom was his student and is presently a Colonel in the Air Force. Among his hobbies is sailing coupled with celestial and electronic navigation. "I observe many retired people who just sit down and wait to die. I would suggest: keep busy; keep interested; stay physically in shape; and practice the endocrine and dietary maintenance therapies we have taught for so many years."

Dickinson W. Richards is associated with the Institute of the Study of Science in Human Affairs. "In this ambitious but still rather diffuse program, I am active only in one small corner - that of developing at Columbia the History of Science and the History of Medicine. This has been a pleasant exercise, though moving slowly, to arouse interest in the faculty. The students are more responsive. Just as a special endeavor, I have been trying to find someone who will go to work to write the life of L. J. Henderson, before everyone who remembers his work and his vivid personality has died. There is a man in Wisconsin, Aaron J. Ihde, biochemist and historian who claims that he has a young man

named John Parascondola, who might take on the job."

Samuel Bellet continues with research on exercise and the heart, radioelectrocardiography, and various aspects of cardiovascular pharmacology. In addition, he is actively engaged in the revision of his book, "Clinical Disorders of the Heart Beat."

Joseph C. Hinsey retired as Director of the New York Hospital - Cornell Medical Center on July 1, 1966. He is staying on for three years as consultant to the Center. He became emeritus professor of neuroanatomy in July of this year. In addition, he has been occupied with the following: Chairman of the China Medical Board of New York; Member of the panel of the Bureau of State Services of the PHS which reviews all applications for support of medical center construction; Chairman of National Research Council Commission to study the status of academic radiology; Member of the committee on Scientific Policy of the Memorial-Sloan Kettering Cancer Center and a member of the three main boards of that Center.

E. A. Boyden is in excellent health at age 81. He continues in research as Research Professor in the Department of Biological Structure, University of Washington Medical School. His advice is "to leave the place from which you retired and begin life anew; to do some teaching, if possible, so that you keep in touch with young minds; to get an Irish setter that makes you walk four times a day; and to find or continue some avocation or other interest that rounds out your sense of values."

Charles M. Gouber retired at Jefferson in 1953, at Loma Linda in 1957, and at the University of Redlands in 1963, where he was visiting Professor of Biology. His health is poor but he continues gardening. He is proud of having been selected by two of the classes at Loma Linda as one of the three outstanding teachers they had during the four years.

C. N. H. Long continues until 1969 as Sterling Professor of Physiology. He participates in research programs and, to a small extent, in the teaching program of the department.

Harry P. Smith spends full-time on research on some of the educational problems incident to an expanding economy. Many of his friends think that they will be supremely happy in boating, fishing, and playing golf after retirement but they are soon bored. "I recommend planning long in advance for some type of activity which has reasonable prospect of rounding out and supplementing academic careers."

Frank A. Hartman's good health permits him to continue research. Ornithology and photography provide recreation.

Carl H. Green has had a succession of illnesses that have left him physically incapacitated.

Carl G. Hartman is laid low with a myeloma.

Kenneth S. Cole has resigned from administrative and non-scientific

jobs. His new title is Senior Research Biophysicist. He is on loan for the winter quarter to the University of California, Berkeley, as Professor of Biophysics in residence. His new book, "Membranes, Ions, and Impulses" will appear during the winter.

George H. Whipple is in his ninetieth year; his heart, blood vessels, and other organs are in good condition. After retirement, he was given an office in the Pathology area and a secretary to carry on his office work. The experimental work was given up as space was not available. He continued to do some teaching, to associate with members of the department of pathology, and to attend some meetings of societies there and elsewhere. "My advice is to keep busy and indulge in a reasonable amount of physical activity. I still do some fishing and game shooting for pheasants."

E. S. Nasset is in excellent health. He is in the department of nutritional sciences at Berkeley. He has grant support for research. He conducts a seminar in one quarter of the academic year and has initiated a course in scientific writing for graduate students. "Don't wait until age 65 before making some plans. Perhaps a little change in direction is desirable. My scientific writing course fills the bill for me, but in addition to that I'm about to start building a new house on a lot we have owned for some time and which provides us a spectacular view of San Francisco Bay."

Frieda Robscheit-Robbins (Sprague) enjoys life in Tucson nine months of the year, travelling in the summer months to escape the heat. She and her husband enjoy the cultural advantage of the University of Arizona.

Lester R. Dragstedt continues at the University of Florida. He is active in research, having several young men working with him. He has been made an honorary member of the German Surgical Society, Fellow of the Royal College of Surgeons of England, and while in Istanbul last year received the following cable from the consul general of Sweden: "It gives me great pleasure to inform you that His Majesty the King of Sweden has bestowed on you the Royal Order of the North Star in recognition of your outstanding contributions to surgical science."

Harold C. Bradley is in good health. For the last twenty years, since becoming emeritus and moving back to Berkeley, he has done nothing in the field of science, "beyond trying to keep the glimmer of its tail-lights still in view. All of my time and effort has been directed toward the problems of preserving some of our samples of America the Beautiful, of which we all sing lustily. As a Sierra Club member, dating back to before the earth quake, but essentially inactive, until I retired, I have put in all my time and energy on its programs. This involved field work of course back in the wild country of mountains, lakes, rivers, State and National Parks and regional reservations. This took the place of the laboratory of course. It produced papers, slides, lectures, moving pictures, etc., and innumerable letters to legislators both State and National."

W. W. Swingle now lives in a retirement city at Laguna Hills,

California. He enjoys the use of the library at the University of California, Irvine. "My only word of advice to those approaching retirement is to keep active always and in preparation, to scan the academic or industrial scientific horizon for another position in your field of competence and should one come your way hang on until the wear and tear of age forces final retirement."

Helen Graham is in good health. While her scientific activities are less in number her position and the climate of the Department of Pharmacology of Washington University gives her all the opportunities she could desire.

Leland C. Wyman is active in anthropology (Navaho Indian ceremonialism). He has published three books and four or five papers since he retired. "Retirement is wonderful - you work harder than ever but - you work when, as and if you damn well feel like it."

Hugh Dukes is in good health. He has been quite busy scientifically since he retired - mostly teaching and lecturing as Professor of Veterinary Physiology at Iowa State University. Also he has given "Demonstrations in Living Biology" live to 82,000 young people in secondary and elementary schools in several states. "The opportunity to work with large numbers of young people in secondary and elementary schools has been most satisfying. I have found these young people to be eager learners with receptive minds. Lecturing to students in other universities and new opportunities for travel have given me a lot of satisfaction."

Carl Schmidt reports "particular satisfaction out of attempting to make use of an intrinsically academic type of activity (research in physiology, biochemistry, biophysics and experimental psychology) to promote the cause of optimizing man's role in present and future aerospace vehicles. Essentially this means minimizing the untoward effects on normal man of abnormal environmental states, which is legitimate and rewarding for a member of the medical profession and a retired pharmacologist. During my incumbency here I have seen the following practical results from in-house fundamental research undertaken with no thought of practical applications:

1) Discovery of the desirable properties of Nomex fiber and development of flame-resistant clothing for aviators (Air Force, Navy, Marines), ground troops (infantry, marines) and automobile race drivers.

2) Development of automatically triggered goggles to protect the eyes of aviators from flash blindness and retinal burns.

3) Discovery of a set of novel chemical protectants against injury by ionizing radiation, based on the ability of one free radical to neutralize another.

4) Development of a biochemical indicator of stress, based on changes in the phospholipid pattern in blood and brain.

5) Development of an objective indicator of attention to a visual task

based on a single line display of the alpha waves of the electroencephalogram.

6) Development of a 50-foot human centrifuge, intended originally to investigate the effects on man of flight in World War II airplanes, into a dynamic flight simulator capable of reproducing the effects on man of exposure in modern swept-wing commercial and military aircraft, to the force fields generated by flight in clear air turbulence, spins, and emergency ejections. Results of studies of the psychomotor and physiological behavior of men under these circumstances have recently led to new instruments and procedures for commercial flights."

He advises those about to retire to:

"1) Try to line up some sort of job in which you can use your peculiar capabilities while obviating the need to kid yourself about the importance of your comings and goings.

2) Get out from under the feet of your successor. He is entitled to freedom to do what he wants, unencumbered by your presence as a possible critic and as a shoulder on which your former associates can weep."

Jerzy Kaulbersz retired from the Cracow Medical Faculty six years ago to become head of the Department of Physiology at the Higher School of Physical Education. "It is always my eager wish to participate not only in the meeting of the Polish Physiological Society but also in the International Congresses of Physiological Sciences. I attended nine of them (Stockholm, Rome, Leningrad, Zurich, Copenhagen, Brussels, Buenos Aires, Leyden, Tokyo) and it is my great desire to be present at the next meeting in Washington. Digestive problems and high altitude physiology including hypoxia and irradiation, also physical efforts are the main subjects of abstracts presented at the meetings.

"As you certainly know your Polish pupil Missiuro deceased suddenly on April 11 leaving the Institute for Physical Education and Physical Culture without leadership."

Eleanor Mason who has lived in England for several years visited the Women's Christian College in Madras in August and September. Having taught there for 35 years she found many friends among former colleagues and students.

Theodore Boyd reports his general health is excellent, except for defects of eyesight and hearing. He finds his present mode of life satisfying because it enables him to fill his time with physical activity, carried on at his own pace. He is glad to be away from the crowds, the noises and the smog of the New York area, where he spent his last 20 active years. He has a small house and 20 acres of ground in rural Tennessee. He gives no advice on retirement: he thinks the simple, rustic life would bore most old men to death, especially those who were city-bred. He comments on the "Retirement Crisis" (Science, July 7, 1967) - "We have too damned many workshops like the one there described,

no particular one aimed at conceptualization of the retirement crisis in developmental terms. Maybe some of the speakers at the meeting had something to say worth listening to, but the summary in Science fails to reveal it.

" I would expect the retirement crisis to grow as long as medical science continues to prolong the process of dying. For me personally, retirement was not a crisis at all. I find no trouble in accepting the realization that I am mortal, and that the time had cause for me to make my exit from active life just as an actor does when his part in a play is finished."

George E. Wakerlin comments on retirement. He was pleased to note from the "Retirement Crisis" in the July 7, 1967 issue of Science that NICHD's Adult Development and Aging Branch is moving toward the setting up of an active research program in retirement. "In my judgment, one of the most important aspects of retirement for many people in the United States is the problem of financial security. Many of the retirement plans which have been in operation for the last 20 or 30 years, and are now coming to fruition, are inadequate from this standpoint. Thus, the maximum retirement income available from one of the large midwest universities is $4,500 per year (except for the President, whose limit is $6,000). I might add that the maximum retirement from this same university was $4,000 in the year 1937.

"A number of universities now have retirement plans which provide for an income of approximately two-thirds of the average salary for the last 5 years. This, to my mind, is an adequate provision. Although my knowledge of financial retirement provisions for other senior citizens is a good deal less complete, the financial status of the majority of people over 65 in this country, is at best, precarious.

"Within the next decade or two I believe serious consideration should be given to raising the retirement age at least to 70 years, if not to 75, since the proportion of senior citizens will continue to grow as medicine advances, and an undue burden will be placed upon young and middle aged adults. I hope, too, that medical and biological research will enable us to determine more accurately than at present true biologic age which, of course, would be tremendously helpful in determining those who are suited to continue at productive employment."

Julius Sendroy, Jr. is continuing his activities as a Science Advisor, attached to the Office of the Commanding Officer. Also he is Assistant for Biochemistry at the Research Division of the Bureau of Medicine and Surgery, Navy Medical Department.

Ernst Fischer, after his retirement in 1966, accepted a Fulbright Teaching Fellowship for the academic year 1966-67 at Hacettepe Medical Center, University of Ankara, Turkey. Just a few days before he returned home, Hacettepe Medical Center became independent of Ankara University and was renamed Hacettepe University with its own direct state support, and with Dr. Dogramacia as its president. Ernst lectured at Hacettepe with the help of an interpreter in the integrated

course and gave a course in neuro- and sensory-physiology, in English to a selected group of advanced students of experimental psychology. His major function was in-service-training of the three senior and seven junior members of the physiology department. He gave lectures to them and led discussion sessions. He helped them also with planning their own research, instructing them in methods and teaching them the use of modern electronic equipment. "My experience as Fulbright Teaching Fellow was in all respects satisfactory. I recommend that retired professors in good health apply for such fellowships. Good health is necessary even for Turkey. My office was on the 7th floor, and the elevator worked only 15% of the time I was there. A heavy snowfall early in the morning stopped transportation, and to reach Hacettepe in time I had to walk six miles."

Irvin H. Blank reports that his research in the Department of Dermatology dealing with percutaneous absorption and sweating brings him into the field of physiology of the skin.

Gordon Marsh will not retire until 1970.

Leon Saul keeps in good health with golf and ice skating. He is busy with private practice, reading and writing.

Gerald T. Evans is in good health. He is busy building a home.

Richard Ashman reports that since the thirties, he has thought more about or (in) political analysis than about cardiology. He arrived at views close to that of the late Herman J. Muller. "My experiences since retirement have led me to believe that only the uninformed will go into teaching. The best minds now, I learn often go into business."

Rolland J. Main enjoys the delightful climate of Guadalajara, Mexico. His good health permits him to help "this very small and very badly needed O. P. Clinic affiliated with Autonoma U. Med. School, and writing M. D. N. for Eaton Laboratories and mailed to U. S. Physicians. There are more cultural activities in Guadalajara (over a million people) than in Chicago. "I felt, and still do, that on retiring it is essential to keep occupied and I have found that travel and a radical change in environment is most helpful. Having to learn spoken Spanish is a challenge in itself."

Walter Alvarez at age 83 is in very good health. He edits several medical journals, writes newspaper columns and has a weekly TV show besides practicing and some lecturing. He keeps three secretaries busy typing replies from column readers: 100,000 a year.

Esther M. Greisheimer is in excellent health. She retired at 65, again at 70 and now is teaching again and is revising her two books. "If you are used to hard work, and love it, continue to be active. Do not ever permit your mind to atrophy. Keep it as active as the body."

Maurice B. Visscher will resign the headship of the Department of Physiology in 1968, and will retire from the University as a professor in June, 1970. He is continuing his scientific activity. "If you have been

a department head or other administrative officer, don't try to choose your successor (I say this not because of my own experience as a prospective retiree, but because of tragedies I have seen in some of my colleagues in department head categories)."

John Haldi after three busy post-retirement years has requested that he be put on the inactive list because of health. "One of my many blessings is to have my grandchildren near by. I see them almost every day."

Ross A. McFarland will continue in his post as Guggenheim Professor of Aerospace Health and Safety at least until 1969. He is in excellent health.

Donald E. Gregg will continue as Chief, Dept. of Cardiorespiratory Diseases, Walter Reed, for another four or five years.

Isaac Starr has less space and fewer assistants. However, he has several research projects in collaboration with younger clinicians and a few people still come from a distance to work for him for a short period of time. He expects to publish about two papers a year; in addition he got out a book last year in collaboration with Noordergraaf.

Walter Fleischmann is in good health and is continuing as consultant in pathology to the VA Hospital in Johnson City, Tennessee. While not active in research, he is organizing for publication experimental data gathered during the last few years.

Louis B. Flexner reports that he is continuing his scientific and teaching activities. He advises those who are approaching retirement to do everything they want to do so long as they can afford it.

Simon Shlaer retired this summer from Los Alamos and moved to Miami Beach because of his wife's cardiac insuffiency. His own plans are fluid.

Chalmers L. Gemmill will continue as Professor of Pharmacology until age 70. He has a PHS grant and gives a course in the History of Medicine. He gets particular satisfaction out of having the time now for more intensive reading and work in the History of Medicine without having his time divided by many administrative duties.

A. H. Hegnauer has been with the US Army Research Institute of Environmental Medicine since September 1964, as Research Program Officer (coordinator between in-house research and that of investigators working on contracts with the US Army Medical Research and Developmental Command). "I am seriously considering retirement for next summer. Additionally, the older I get the more irksome is a desk job as opposed to greater physical activity. With respect to advice for those approaching retirement I have nothing to offer that has not been offered many times before; i.e., develop before-hand strong interests to fill the void. I cannot think of anything which will lead more rapidly to complete physiological and psychological disintegration than total

idleness and lack of goal."

Philip B. Armstrong will not retire at the Upstate Medical Center before 1968. He retired last year as Director of the MBL but continues to work there in the summer. In addition to his research, he is Chairman of the Building Committee (MBL) with a $5,000,000 program in progress, a new modern instruction building and a dining-hall-dormitory.

Grayson McCouch is continuing his scientific activities. His sources of satisfaction include riding horseback, reading, travel, and above all, continuing professional contacts.

B. A. Houssay is in good health and active in research. Invited to comment on the "Retirement Crisis" (Science, 7 July 1967) he replied, " I am only 80 years old."

G. Liljestrand reports that his good health permits him to work every day, sometimes including Sunday, in his old laboratory, mainly with different aspects of medical history. He finds experimental work rather tiresome at 81 years, but he collaborates with younger colleagues; they take the burden of the practical work. "It is a great privilege to be able to continue my work on interesting problems after retirement (1951). Of course one must lessen the intensity of the work; in my opinion the best method is to concentrate on a few topics in order to get somewhere, and to become a layman in others. The freedom from administration, faculty meetings and reports on everything is a blessing. I rarely listen to the numerous lectures given here by prominent people from abroad, but I quite regularly visit the meetings of our Academy of Sciences, which brings me in excellent contact with nice people from many fields of science.

"I think that some little planning for the retirement will often be useful - it depends on local conditions and personal interests. Personally, I feel happy in my old laboratory and get on well with my successor, never intruding on his field. But, as you know, in many cases people prefer to start anew in another laboratory than their old one. Whether this is advisable depends of course on the personal relations, in many cases it is undoubtedly a good solution.

" I have just read with great interest the article on "Retirement Crisis" Science, July 7, 1967, pp. 102-103, to which you refer. It shows clearly the great variations, which I have certainly also seen. Some of my old colleagues are still working successfully at 70-80 years with valuable contributions to the medical sciences as well as to international cooperation. Others are only too glad to do nothing. But is not this only an accentuation of differences to be observed long before the retirement? There are all types from those who are intensely active as ordinary professors (and not only before getting that position) and some may even be worn out, to those who resemble more or less the clinician, about whom it was said: 'Now, the only book he opens is his pocket-book.' What I think ought to be done is facilitation of the work for those old people who are still interested and able to do some useful work, especially by providing them with technical and secretarial help. The situation is probably most difficuly for the retired clinician. This is a difficult problem,

for it only applied to a minority of the aged, and a certain control is necessary."

Carl A. Dragsted replies as follows:

THREE SCORE AND TEN - 1965

Three score and ten
Is a might have been
Place of regrets and remorse;
A place of repentance
and penance too
For it's nearly the end of the course.

But three score and ten
Is a real happy glen
If you but give it a chance;
You can travel about,
Sing, whistle or shout
Or kick up your heels in a dance.

There are friends everywhere
Who really do care,
Who ask not the why or the when;
At a signal they'll come
And with bugle and drum
They'll salute your seven times ten.

* * * * * * * *

ALTITUDE ACCLIMATIZATION, A HISTORICAL INTRODUCTION EMPHASIZING THE REGULATION OF BREATHING*

RALPH H. KELLOGG

Discussion of altitude acclimatization properly begins with the first clear report of its existence. This report accompanies one of the first (and perhaps the first clear) description of mountain sickness, published by Father José de Acosta (Fig. 1), a Jesuit missionary who went out from Spain to Peru in 1570, crossed the crest of the Andes and spent time in the Altiplano, the high plateau just east of the crest. His great report on his observations, Historia Natvral y Moral de las Indias .....(1) was published in Seville in 1590 (Fig. 2) and was subsequently translated into

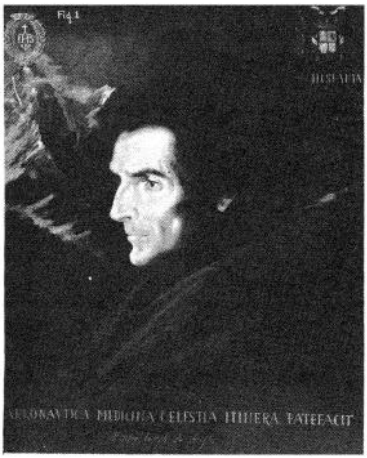


Fig.1. Father José de Acosta, ca. 1540-1600, painted by A. Pezzi, 1964, and presented to the School of Aerospace Medicine, Brooks Air Force Base, Texas, by Dr. Luis de la Serna on behalf of the Higher Council for Scientific Research, Madrid, Spain. (Reproduced through the courtesy of Mrs. Sarah L. Peterson, Librarian, and Dr. Stephen M. Cain).

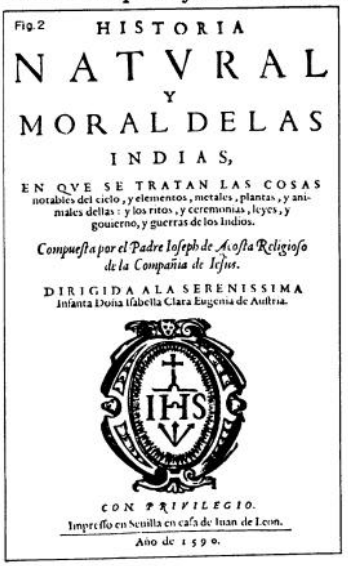


Fig.2
HISTORIA
NATVRAL
Y
MORAL DELAS
INDIAS,
EN QVE SE TRATAN LAS COSAS
notables del cielo, y elementos, metales, plantas, y animales dellas: y los ritos, y ceremonias, leyes, y gouierno, y guerras de los Indios.
Compuesta por el Padre Ioseph de Acosta Religioso de la Compañia de Iesus.
DIRIGIDA A LA SERENISSIMA
Infanta Doña Isabella Clara Eugenia de Austria.
IHS
CON PRIVILEGIO.
Impresso en Seuilla en casa de Iuan de Leon.
Año de 1590.

Fig.2. Title page of the volume containing the first clear description of mountain sickness and altitude acclimatization (1). The first two books of this work had previously been published in Latin under the title De natvra Novi orbis, libri dvo (1588). From the library of Congress copy by courtesy of Mr. Frederick R. Goff, Rare Books Division Chief. Retouched to eliminate the name of an early owner, which had been scratched out, and to reconstruct the first S in COSAS.)

*Taken from the introductory remarks given at the session on Altitude I at the 1967 Federation Meetings. Some of the work was supported by NIH Grant GM-09262.

several other languages including English, published in London in 1604 (2). In Book 3, Chapter 9, after describing how everyone became ill in crossing the high pass at Pariacaca for the first time, he wrote: "..... and not onely the passage of Pariacaca hath this propertie, but also all this ridge of the mountaine, which runnes above five hundred leagues long, and in what place soever you passe, you shall finde strange intemperatures, yet more in some partes then in others, and rather to those which mount from the sea, than from the plaines....." (2, p. 147). The point is that those coming up from sea level were exposed to the high altitude of the pass without prior acclimatization to it, whereas those that had been on the "plaines" or Altiplano east of the Andean crest had had a chance to undergo some acclimatization to high altitude and thus were not so affected by the altitude at the summit of the passes.

Although the fact of acclimatization was well known to the Inca empire, and Monge (30) has published an interesting essay on their laws that take acclimatization into account, there was remarkably little scientific study of acclimatized man until the middle of the 19th century. Perhaps the first important figure is Denis Jourdanet, a French physician who worked at various places in Mexico between 1842 and 1861. He became interested in the effects of high altitude on the native populations and wrote a book about it upon his return to France in 1861 (24). In this and a short work published two years later (25) he compared the symptoms of high altitude to those of anemia at sea level and suggested that both might be due to lack of oxygen in the blood, for which he coined the term "anoxemia". His own writings culminated in his Influence de la pression de l'air sur la vie de l'Homme (26), published in two handsome volumes in 1875 and reprinted in cheaper format the following year. Perhaps more important, he also stimulated Paul Bert (Fig. 3) to become interested in an experimental approach to the physiological problems of high altitude (35).

Fig. 3. Paul Bert, 1833-1886. (From Bérillon (6)).

Paul Bert was Claude Bernard's pupil and successor at the Sorbonne, and Jourdanet was wealthy enough to provide Bert with financial support for his research there. Probably Bert's interest in high altitude was also stimulated by the report of the English meteorologist, James Glaisher,

who had gone up in a balloon as high as he could in order to get samples of air to see if the oxygen percentage remained constant all the way up. Glaisher became unconscious at about the altitude of Mt. Everest and illustrated this with a very graphic picture in his book, Voyages aériens, published first in Paris in 1870 (17). Glaisher's companion, incidentally, was the balloonist Gaston Tissandier, who was sole survivor of a more famous flight described by Paul Bert some years later (7, pp. 1058-1075; 8, pp. 963-974).

Bert equipped his laboratory with decompression chambers (Fig. 4) to simulate high altitude. He showed that the acute effects of high altitude decompression can be attributed to low partial pressure of oxygen (7, 8). Fig. 5 shows the title page of his famous book, never reprinted but made accessible to English readers by a translation published during World War II (8). Bert did not undertake to study acclimatization himself, but

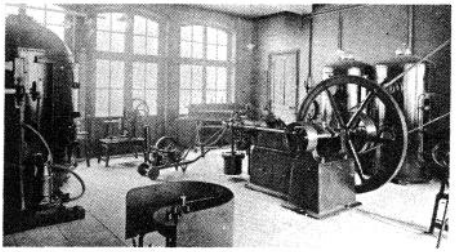
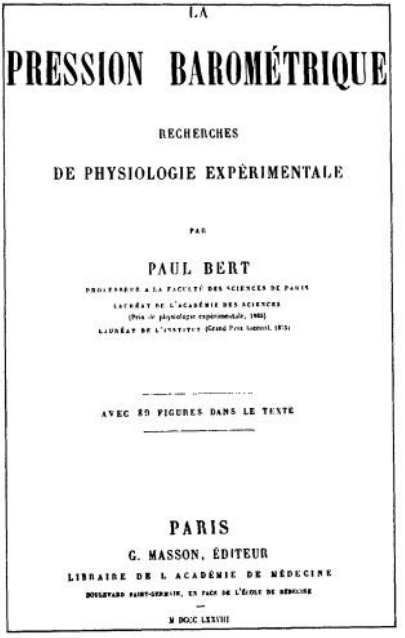


Fig.4. Salle des Pressions, Laboratoire de Physiologie de la Sorbonne, showing the chamber of M. Jourdanet at the left, the pair of large chambers used by Paul Bert on the right, and his horizontal animal chamber in the background (From Regnard (40) with permission of Masson et Cie., Paris.)



LA

PRESSION BAROMÉTRIQUE

RECHERCHES

DE PHYSIOLOGIE EXPÉRIMENTALE

PAR

PAUL BERT

AVEC 89 FIGURES DANS LE TEXTE

PARIS

G. MASSON, ÉDITEUR

LIBRAIRE DE L'ACADÉMIE DE MÉDECINE

Fig.5. Title page from the first (and only French) edition of Paul Bert's classic work on barometric pressure (7). (Reproduced with permission of Masson et Cie., Paris).

at the close of his book (7, pp. 1107-1116; and 8, pp. 1000-1005) he did suggest possible mechanisms that others might look for, since he thought they would assist in adaptation to high altitude:

1) A change in the amount of hemoglobin in the blood.

2) A change in the nature of hemoglobin so that it could carry more oxygen.

3) A decrease in the rate of oxygen consumption by the body, either in the form of some increase in the efficiency of metabolism or a decrease in heat loss.

4) Some inner modification of the tissues so that they are able to perform better despite their lack of oxygen.

5) An increase in the breathing so that the hemoglobin can be exposed in the lungs to somewhat better oxygenated alveolar gas.

Paul Bert made practical suggestions so that persons going to high altitude could provide critical tests of his suggested mechanisms. For example, he pointed out how samples of blood could be preserved for testing, and how it might be hard to carry a gas meter to high altitude but easy to analyze carbon dioxide in the expired air there, which must be lower if the breathing is increased. He realized that others of his suggested mechanisms, such as intimate changes in cellular metabolism, were completely beyond the range of study at his time.

It is interesting to see what has become of these suggestions of Paul Bert in the 89 years since his book was published:

1) Monsieur Viault, following his instructions in 1890, demonstrated increased hemoglobin concentration in the blood of men living in the Andes (43) and showed the same thing in native animals of the Andes the following year (44). Regulation of the amount of hemoglobin being produced, which we now know to be a function of the increased production of erythrocytes by the bone marrow, has become a subject of active investigation in recent years, but mostly by endocrinologists interested in erythropoietin rather than by environmental physiologists.

2) The nature of the hemoglobin at high altitude held the attention of physiologists for a long time. The oxyhemoglobin dissociation curve transiently shifts to the left during the period of respiratory alkalemia in the first few weeks of hypoxia, but careful studies have failed to show any fundamental difference in the structure of the hemoglobin at high altitude.

3) The rate of metabolism at high altitude was already a subject of controversy between Coindet and Jourdanet when Paul Bert wrote his book(7, pp. 276-281; 8, 265-269). Today it is well recognized that there may be minor differences but no major change in oxygen consumption at altitude. Hurtado and his associates, for example, have published data indicating that Andean natives accomplish a given amount of work

exercising on the treadmill with slightly lower oxygen consumption (in other words, a higher efficiency) than sea level natives (23), but it is not clear how far this can be generalized to other populations and circumstances. The subject is far from closed.

4) The intimate details of cellular biochemistry and metabolism, which Paul Bert could not begin to deal with, began to receive attention about 1937, when Hurtado and his associates reported that there was a higher myoglobin content in the muscle of dogs living at high altitudes (21). This aspect of tissue acclimatization has been repeatedly confirmed, and it led to study of the cytochrome system and other metabolic components. Such detailed biochemical analysis is still in its infancy but is potentially very exciting.

It is odd that Paul Bert did not include changes in the circulation in his list, since changes in pulse rate at altitude had been repeatedly described. It must have been obvious to him that an increase of blood flow to the tissues and an increase in the number of capillaries would each tend to improve cellular oxygenation. Both of these changes have been reported. There is still some disagreement concerning the degree and duration of the increase in cardiac output, and much more work is needed on circulatory changes and their mechanisms.

* * * * *

Rather than expand my discussion of the above items, however, I would like to refer the reader to a general review (42) and devote the rest of this paper to the changes in the regulation of breathing that occur during acclimatization, since this is the subject with which I am most familiar from personal work. Change in the regulation of breathing is probably the first important step in acclimatization. Tissue changes such as we have been talking about are obviously slow. Iron turnover is accelerated quite quickly by hypoxia, but it takes weeks for enough new red cells to accumulate in the blood to contribute significantly to improved oxygen transport. Circulatory changes probably begin pretty fast, but there is some reason to think they may take longer to stabilize than do the respiratory adjustments. Indeed, the respiratory changes are so rapid that one must face the question of where to draw the line between acclimatization and simple, direct responses to hypoxia.

This is, of course, a matter of definition. I think it is useful to distinguish the immediate responses, such as the stimulation of breathing that occurs reflexly from stimulation of the carotid and aortic bodies within seconds after a breath of nitrogen, from the slower changes that take hours, days, weeks, months, or even years to develop. Perhaps an even more useful distinction can be made on the grounds of reversibility. The increase in breathing that occurs as an immediate response to breathing a low oxygen mixture is quickly reversed when the oxygen pressure is raised again; but when acclimatization has occurred, restoring normal oxygen pressure does not immediately return the breathing to normal. Let me use some of our data to illustrate what I mean. The lower line in Fig. 6 shows the steady-state respiratory minute volume as the inspired, and hence the alveolar, oxygen pressure is lowered from

the sea level normal. These four points were obtained in less than an hour, 10 minutes on each point, in subjects acclimatized to sea level.

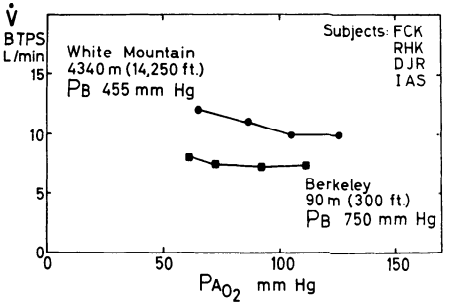


Fig.6. Average respiratory minute volume ($\dot{V}$) and alveolar oxygen pressure in 4 sea level residents breathing air and graded oxygen-nitrogen mixtures at sea level (lower line) and after the fifth day of a three-week sojourn at altitude (upper line). From Kellogg (28)).

The left lower point thus represents the effect of acute hypoxia. If the oxygen pressure is again raised to normal, the breathing promptly returns to the normal value. After these points were obtained, the subjects went to high altitude and stayed there for 23 days. Their breathing increased progressively during the first 5 days, moving from the lower left hand point to the upper left hand point as acclimatization developed. When higher oxygen pressures were then tested, the breathing was reduced as the direct reflex effect of chemoreceptor stimulation was removed, but the breathing remained above the sea level values because of the persistent effects of acclimatization. Thus we can define the four corners of this graph, starting at the lower right-hand corner and reading clockwise, as chronic normoxia, acute hypoxia, chronic hypoxia, and acute normoxia. The immediate effects of hypoxia itself can be distinguished by comparing the two ends of either of these lines. The effects of acclimatization, irrespective of the degree of hypoxia at the moment, can be distinguished by the differences between the upper and lower lines. The rest of my discussion will be primarily concerned with the differences between the conditions represented by these lines, the slowly-developing but persistent changes that I call acclimatization, rather than the effects of acute hypoxia.

Whereas acute hypoxia is most easily studied by lowering the oxygen percentage or the barometric pressure in the so-called "high altitude" chamber, acclimatization is most easily studied by actually going to high altitude and living there for a while. Thus it is appropriate to start this part of the discussion with the gentleman who established the first important laboratory for physiological work at high altitude. Figure 7 shows a picture of Angelo Mosso, Professor of Physiology at Turin, Italy, who began serious work in the Alps in a mountaineer's hut on Monte Rosa about 1894 (31) and then persuaded Queen Margherita of Italy to put up funds for a permanent building (Fig. 8), also used by Nathan Zuntz of Berlin and his associates (46). Although mountain climbers had been subjectively aware of increased breathing while they were climbing, Mosso became convinced that in his subjects living in the mountain hut the breathing at rest was reduced below that at sea level. He was misled into this view by using a pneumographic device that recorded on a smoked

drum the frequency and amplitude of the respiratory excursions of the chest or abdomen (31, chapter 3). His published kymograph record shows similar frequency but decreased amplitude of the respiratory movements of a subject on Monte Rosa compared to Turin, near sea level. I like to show his tracing to students to warn them against recording methods that are not precisely calibrated in absolute units. Mosso was confirmed in his error by his measurements of expired air with a gas meter, because he converted his readings to STPD rather than to BTPS (another object lesson for students).

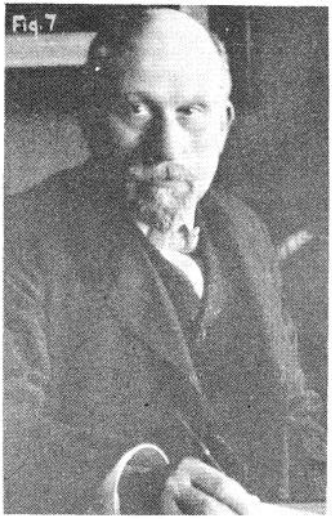


Fig.7. Angelo Mosso, 1846-1910, Professor of Physiology at Turin, Italy and father of the high altitude physiology laboratory on Monte Rosa in the Italian Alps. (From Franklin (16) with permission of Blackwell's Oxford).

Fig.8. Capanna Regina Margherita on the Gnifettispitze (4,560 m) on Monte Rosa, used as a laboratory by Angelo Mosso and others. (From Loewy (29) with permission of Julius Springer Verlag, Berlin).

Basically, Mosso disagreed with Paul Bert's ideas because he was unable to confirm them. Mosso pumped air out of a chamber until his assistant or a monkey inside was about to collapse, then noted the pressure and gas composition. He then let fresh air or oxygen flow in for a while and started pumping again, and this time found he could go to a considerably lower oxygen pressure before the verge of collapse was reached. In the second case, considerable CO_2 had accumulated in the chamber, and we now know that CO_2 stimulates breathing sufficiently to protect against hypoxia somewhat by bringing the alveolar Po_2 closer to that of the inspired gas. Mosso noticed the CO_2 but drew the conclusion from it that it was lack of CO_2 that was important - the extra percentage of CO_2 in the second case protecting the subject from the

lower pressure. This was not such an unreasonable interpretation, since the blood CO_2 content was already known to be low at altitude. Mosso noted that voluntary hyperventilation to lower the CO_2 at sea level reproduced the cerebral symptoms of high altitude (which we now know to be due to cerebral vasoconstriction that actually makes the brain hypoxic). From these observations, Mosso developed an elaborate theory of mountain sickness in which the primary trouble was attributed to lack of CO_2, which he supposed to be extracted from the body more efficiently by the partial vacuum of high altitude. He thought this lack of CO_2 (he coined the term "acapnia" to describe it) depressed the breathing (32). Unfortunately, he failed to recognize the necessarily inverse relationship between breathing and alveolar P_{CO_2}.

John S. Haldane (Fig. 9), however, was well aware of this relationship, as indeed Paul Bert had been. Thus Haldane saw the implication when one of his former Oxford subjects, a Mr. Ward, took Haldane's gas analyzer along on a trip to Monte Rosa and reported in 1908 that his alveolar P_{CO_2} fell by more than 10 mm Hg during 6 days on the summit and remained low for a while after he had descended to Zermatt at its foot (45). Moreover, the fall in alveolar P_{CO_2} was confirmed by Joseph Barcroft and C. G. Douglas in the course of the international expedition to the peak of Teneriffe led by Nathan Zuntz in 1910 (4). They found, directly contrary to Mosso's theory, that Douglas, whose alveolar P_{CO_2} fell furthest, was least affected by the altitude while Barcroft, who hardly hyperventilated and maintained the most normal P_{CO_2}, was practically incapacitated at the Alta Vista Hut (3350 m or 11,000 ft.)

The following year, in 1911, Haldane led an expedition to Pike's Peak (4,300 m or 14,100 ft.), taking with him C. G. Douglas of Oxford, Yandell Henderson of Yale, and Edward C. Schneider of Colorado (Fig. 10) (12). They arranged to study the alveolar CO_2 in three different ways:

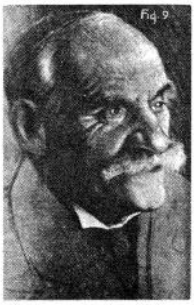


Fig. 9. John S. Haldane, 1860-1936, leader of the 1911 Anglo-American Pike's Peak Expedition of 1911. (From Franklin (16) with permission of Blackwell's, Oxford).

Fig. 10. Members of the Anglo-American Pike's Peak Expedition of 1911 on the summit of Pike's Peak, 4,300 m. Left to right: Henderson taking samples of alveolar gas, Schneider kneeling and recording his respiration, Haldane standing, Douglas wearing a "Douglas bag" to collect expired air for the determination of the amount of oxygen consumed during climbing. (From Henderson (19) with permission of Williams & Wilkins Co., Baltimore).

First, they measured their resting alveolar Pco_2 repeatedly before going to Pike's Peak, during their month there, and after their descent. Fig. 11 shows the progressive fall in alveolar Pco_2 during the first few days on Pike's Peak and its slower return toward normal after descent to sea level.

Second, one of Haldane's associates, Miss Mabel P. FitzGerald, spent that same summer of 1911 visiting villages and mining camps at various altitudes in Colorado (14) (and subsequently visited lower altitudes in North Carolina (15)) and getting alveolar samples from statistically significant numbers of local residents at each site so that she might plot resting alveolar Pco_2 as a function of altitude. Her data, which I have replotted in Fig. 12, show an essentially linear fall of alveolar Pco_2 in long-term residents from sea level to 14,000 feet (3,800 m) at the rate of about 4.2 mm Hg per 100 mm Hg fall in barometric pressure. It is interesting that Andean Natives, plotted in Fig. 13 as the upper, solid points from the studies of Hurtado and Aste-Salazar (20) and Chiodi (9), show much less fall in Pco_2 with altitude than do the residents of the United States, represented by the lower, open circles, plotted again from Miss FitzGerald's data. This fascinating difference is inder active study by several investigators at present.

Third, since the alveolar Pco_2 does not change very much with exercise (either at sea level or at altitude), respiratory minute volume during various grades of exercise must be increased by a nearly constant percentage at any given altitude to maintain the low alveolar Pco_2 characteristic of that altitude. This was demonstrated by Haldane's expedition (12), as shown in Fig. 14 plotted from that data by Bock and Dill (3). The upper line rises at a steeper slope because of this percentage increase, until the upper end, where presumably lactic acid makes it rise much more steeply.

About half of this increase in exercise hyperpnea represents the direct, immediate effects of hypoxic drive, and the other half represents the slow change of acclimatization that persists after hypoxia is terminated. A few years ago, Pierre Dejours, Nello Pace and I applied Krogh and Lindhard's technique of partitioning this exercise hyperpnea into a fast component, which occurs so promptly at the start and cessation of exercise that it must surely be mediated by the nervous system, and a slower component that is at least partly related to the chemical changes carried by the blood (10). We wondered if the increase seen at altitude might be restricted to the humoral component only: but it turned out that the fast or neural component (which might be a reflex or a learned response, for instance) could also be increased by acclimatization, even when the direct effects of oxygen were taken into account by comparing acute hypoxia with chronic hypoxia and acute normoxia with chronic normoxia. This subject needs much more work to elucidate the mechanism.

In that same summer of 1911 when Haldane and his associates went to Pike's Peak, Hasselbalch and Lindhard (18), by an amazing bit of serendipity, made a key observation that opened the door to our understanding of the mechanism producing the increased breathing in resting

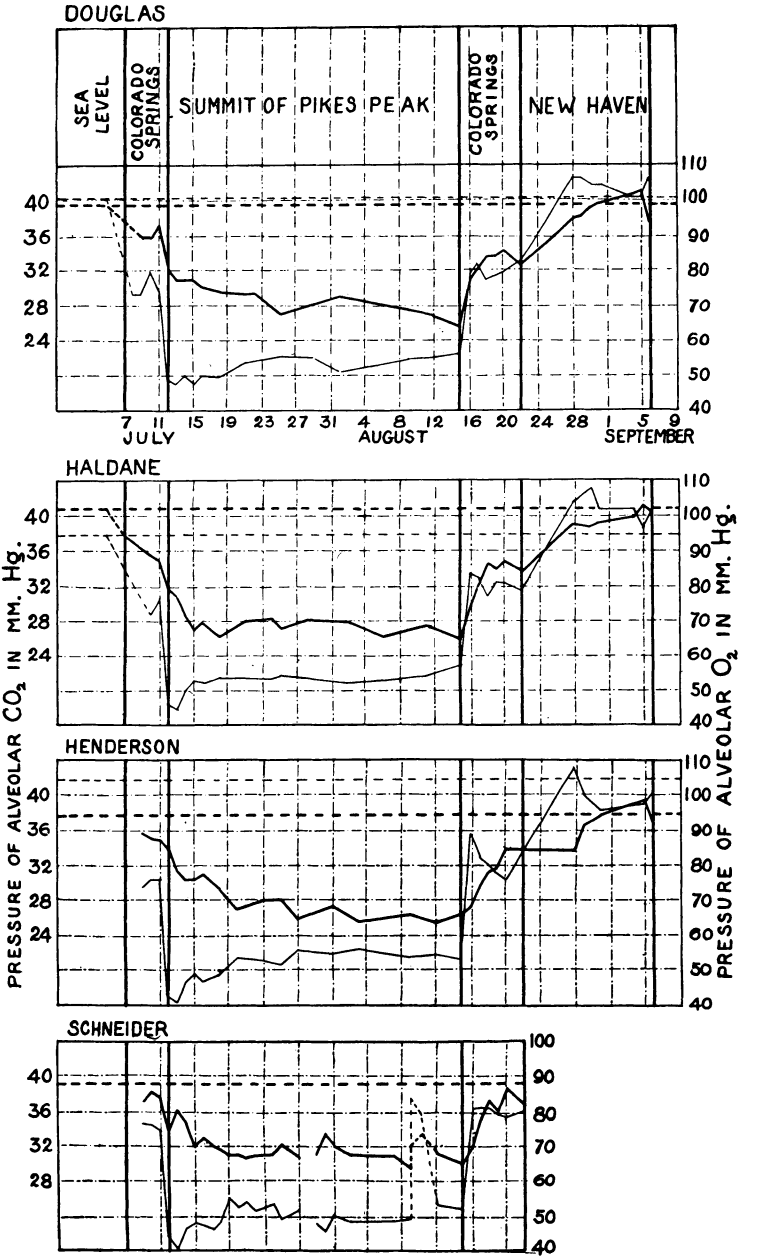


Fig.11. Alveolar gas data from the Pike's Peak Expedition of 1911. The heavy line represents alveolar P_{CO_2}; the thin line represents alveolar P_{O_2}. (From Douglas et al. (12)).

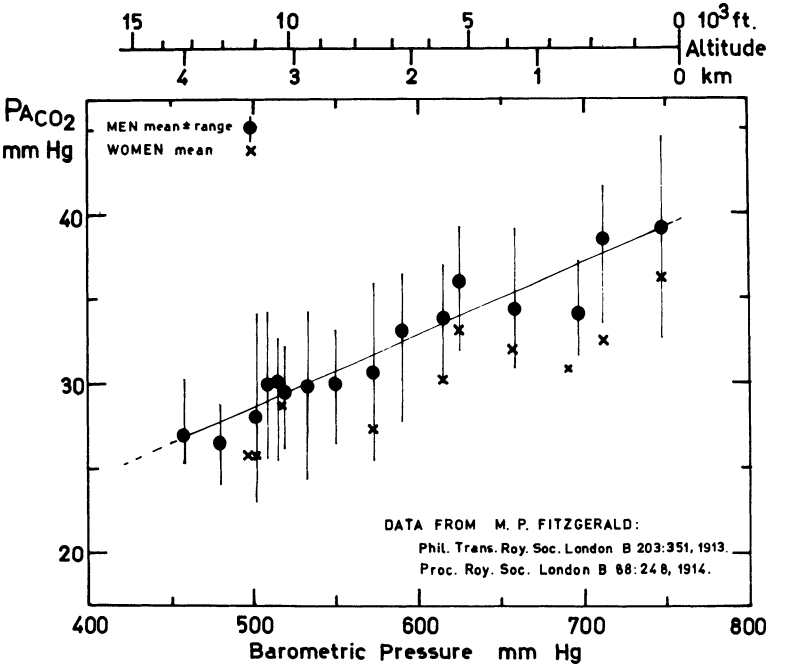


Fig.12. Resting alveolar P_{CO_2} of residents of various altitudes in Colorado and North Carolina. (Replotted from FitzGerald (14,15).

individuals who have acclimatized to some extent. They had been studying the sensitivity of respiration to carbon dioxide inhalation, and they had an idea that perhaps this might be affected by ultraviolet radiation. To test their hypothesis, they measured their ventilatory response to graded CO_2 inhalation at Copenhagen and then went up to the Brandenburger Haus above Innsbruck in the Austrian Alps at 3290 m (10, 800 ft.) above sea level. Here they stayed for 8 days indoors wearing masks and gloves to protect themselves from sunlight. Then for 9 additional days they wore as little clothing as possible while skiing in the bright sunlight. One of their graphs has been reproduced in Fig. 15 to show how they plotted the results. Since they were interested in CO_2 sensitivity, they plotted each day's curve as the increase in alveolar ventilation from that day's resting value, against the increase in alveolar P_{CO_2} from its resting value, as graded CO_2 mixtures were inhaled. Although sunlight made no important difference, they found that the curve became considerably steeper at high altitude, a change which they attributed to sensitization of the respiratory center to CO_2.

I have replotted their key data on absolute scales (Fig. 16), and this makes it apparent that although the altitude curves of both subjects are

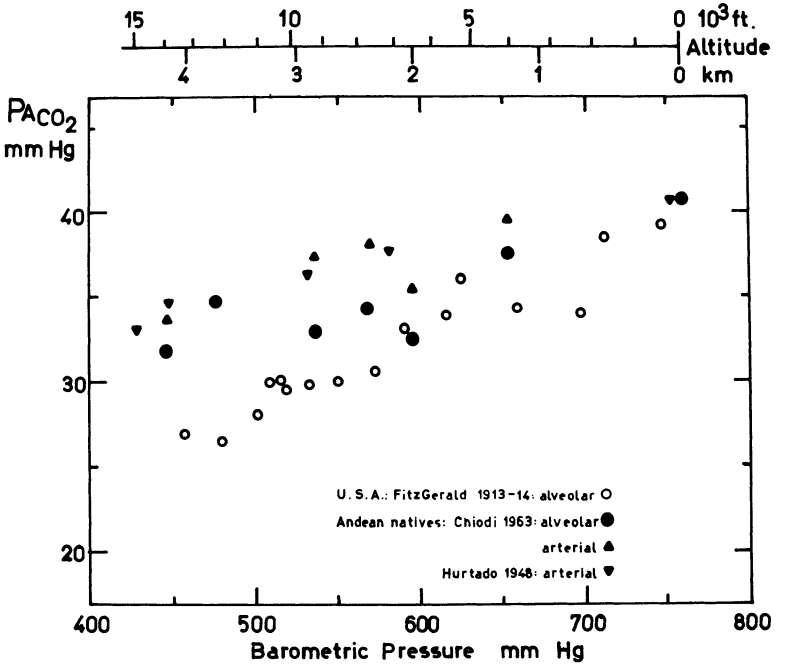


Fig.13. Resting alveolar P_{CO_2} of male residents of various altitudes in Colorado and North Carolina, compared with P_{CO_2} of Andean natives. (Plotted from data of FitzGerald (14,15), Hurtado and Aste-Salazar (20) and Chiodi (9)).

a little steeper, the striking change is that they are greatly displaced to the left. In other words, breathing was strongly stimulated by P_{CO_2} levels that would have been below threshold before acclimatization, and this was true even when they added oxygen, a fact confirmed by Rahn and his associates on Mt. Evans (37). Thus this was a true acclimatization effect, not just hypoxic interaction with CO_2 such as Nielsen and Smith described in 1952 (34).

Further evidence that this represents real acclimatization comes from the fact that the shift in position of the CO_2 response curve develops progressively during a sojourn at high altitude and is slow to disappear after return to sea level. Fig. 17 shows results that we obtained at the White Mountain Research Station in 1957 (27). All of these CO_2 response curves were measured with an inspired P_{O_2} equivalent to that of sea level air. Yet the curves moved progressively to the left during 3 weeks' residence breathing air at 4,340 m (14,250 ft.) above sea level, and they were not quite all the way back to control position even after 3 weeks at sea level again. This increase in breathing from sensitization to CO_2 raises the alveolar oxygen by as much as 10 mm Hg, most of the benefit developing within the first couple of days, and thus

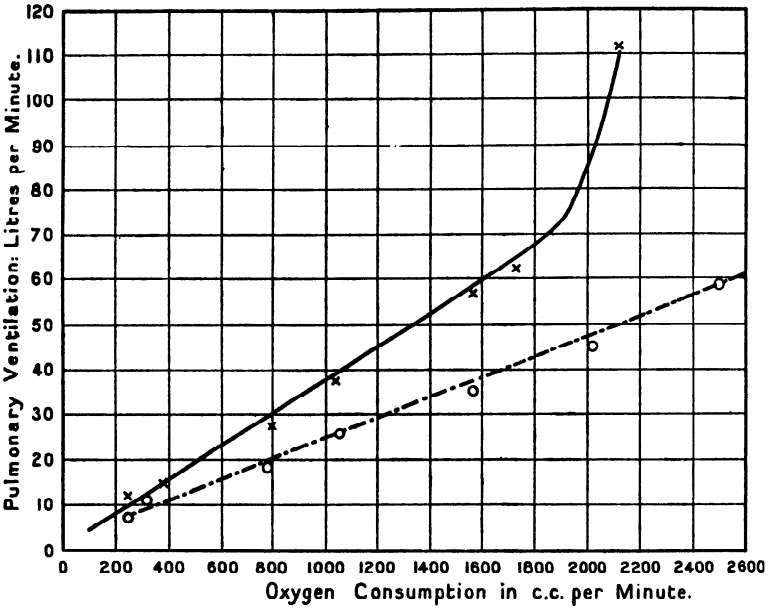


Fig.14. Respiratory minute volume at various exercise rates, measured at sea level and at altitude by the Anglo-American Pike's Peak Expedition of 1911, plotted by Bock and Dill. (Reproduced from Bainbridge (3) with permission of Longmans, Green and Co., Ltd., London).

plays an important role in minimizing tissue hypoxia and improving performance at altitude.

Fig. 18 is plotted from data that Donal J. Reed and I published a number of years ago (38, 39). The two right-hand curves show the well-known shift of the CO_2 response curve to the right by sleep at sea level. At the left, it is apparent that sleep similarly depresses the response to CO_2 at high altitude and depresses breathing, so that subjects become considerably more hypoxic while they are asleep. This probably accounts for the tendency of mountaineers to wake up with a morning headache that goes away during the day and returns the next morning, and for Everest climbers to insist on using oxygen tanks during the night.

Sensitization to CO_2 in altitude acclimatization was long assumed to be due to renal restoration of normal pH in arterial plasma following the initial alkalemia of hyperventilation. This view was supported by the observations of Dill et al. (11) during the International High Altitude Expedition to Chile in 1935 and the subsequent measurements of Hurtado et al. (22) on Andean natives showing that plasma bicarbonate had fallen

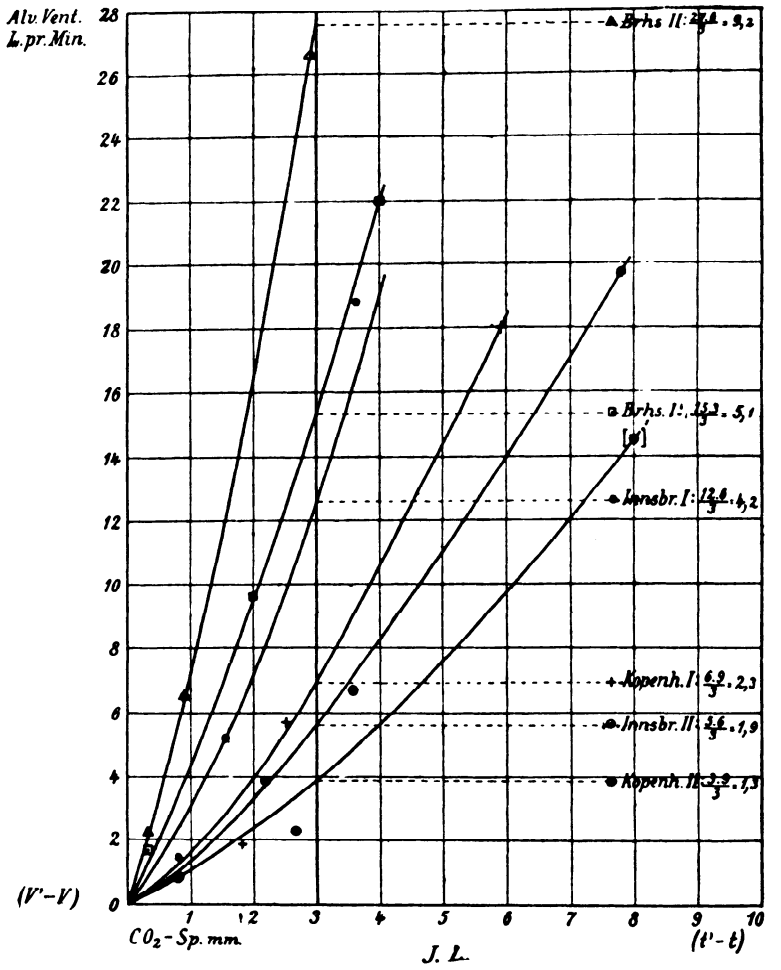


Fig.15. Effect of altitude on Lindhard's ventilatory response to CO_2 inhalation. The coordinates relate the increase in alveolar ventilation to the increase in alveolar P_{CO_2}, each from its resting level. (From Hasselbalch and Lindhard (18)).

in proportion to the P_{CO_2}, making arterial pH practically normal after considerable acclimatization had occurred. According to this view, when a subject begins to hyperventilate from hypoxic stimulation of his chemoreceptors, his blood becomes alkaline and this partially offsets the stimulatory effects of his hypoxia. After his kidneys have excreted enough bicarbonate to restore his arterial pH to normal, however, any resaturation of his hemoglobin by restoration of normal oxygen pressure, or any increase in P_{CO_2} above its new low level, would tend to make his

arterial blood more acid than normal and thus produce the observed stimulation of his breathing at low P_{CO_2} and normal P_{O_2}. This misconception shows the disadvantage of ignoring the time-course of the process of acclimatization and focussing merely on the end-result after a prolonged residence at altitude, for the data of Nielsen in 1936 (33) showed that the blood stayed alkaline for several days after the P_{CO_2} had fallen, and this fact was confirmed by the German expedition to the Jungfraujoch in 1939 (5).

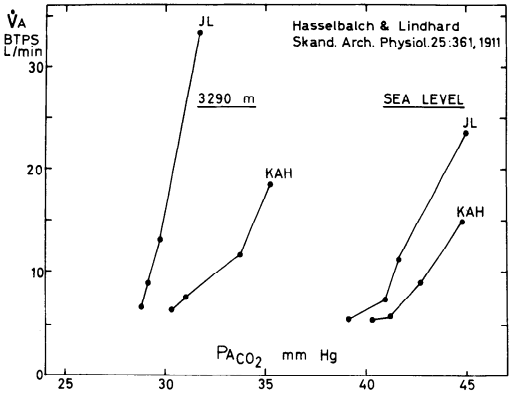


Fig. 16. Data of Hasselbalch (KAH) and Lindhard (JL) (18) replotted to show the CO_2 response curve on modern coordinates, which emphasize the shift of the curve to the left at altitude as well as its increased slope.

In 1957, we decided to put the above theory to critical test by studying ventilatory response to CO_2 inhalation, the CO_2 response curve, while simultaneously measuring the arterial pH and supplying enough oxygen to prevent hypoxia, at intervals during a three-week sojourn on the summit of White Mountain at 4340 m (14, 250 ft.) (27). In the left hand panels of Fig. 19, the respiratory minute volume is plotted against the alveolar P_{CO_2} during inhalation of graded CO_2 mixture with sea level oxygen pressure, while in the right hand panels it is plotted against arterial pH (28). It is apparent that the breathing of each of these three subjects while acclimatizing to high altitude was stimulated at a low P_{CO_2} while his blood was more alkaline than at sea level and not hypoxic.

Thus we pointed out the problem, but it was John W. Severinghaus and Robert A. Mitchell and their associates who provided the probable explanation (41). After discovery of the medullary chemoreceptors, four of them in 1962 went to the Barcroft Laboratory of the White Mountain Research Station (3800 m or 12, 470 ft.) and measured CO_2 response curves while following the acid-base relationships in their cerebrospinal fluid as well as their arterial blood. Their blood studies (Fig. 20) confirmed and refined our finding that the change in plasma bicarbonate was relatively slow. They discovered, however, that the change in cerebrospinal fluid bicarbonate was quite rapid. Its rapid removal would restore the CSF pH to normal within 2 days. When they plotted their CO_2 response curves in terms of calculated CSF pH instead of arterial pH, the alkalinity of the blood was appropriately offset by a slightly more acid pH in the neighborhood of the medullary chemoreceptors (Fig. 21)

which they believe to be sufficient to account for the ventilatory responses observed.

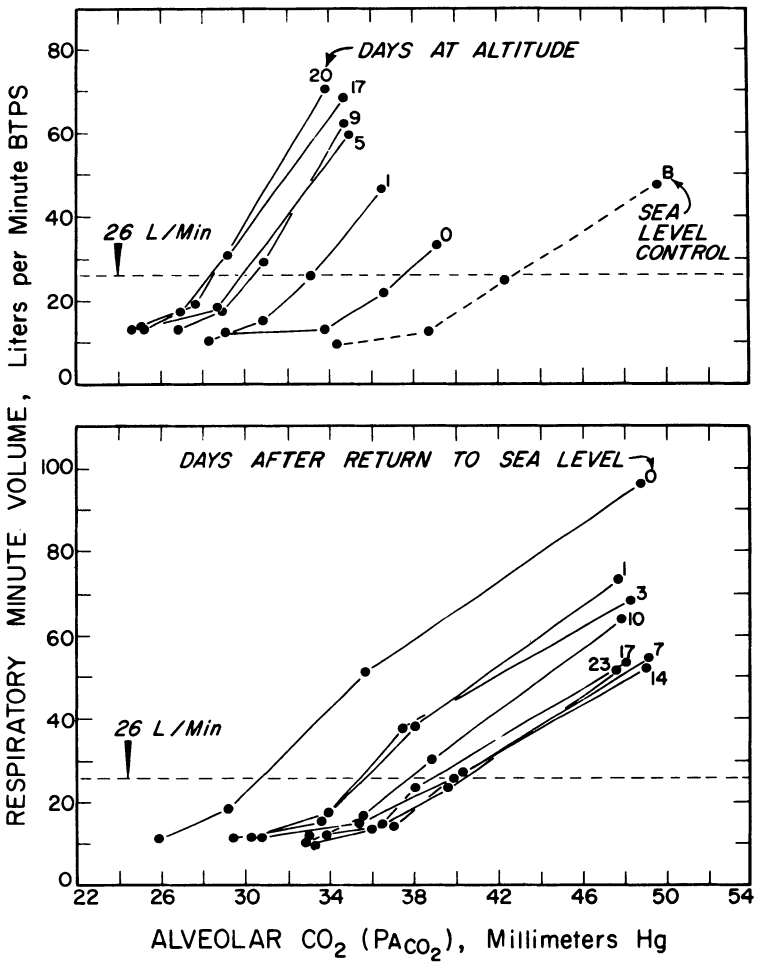


Fig.17. Averaged CO_2 response curve of three subjects measured repeatedly with sea level inspired oxygen pressure at sea level, during a three-week sojourn at the Summit Laboratory of the White Mountain Research Station (4,340 m, 14,250 ft.) and during recovery at sea level, from the data of Kellogg, Reed, and Todd (27). (From Pace (36) in The Air We Breathe, 1961. Courtesy of Charles C Thomas, Publisher, Springfield, Illinois.)

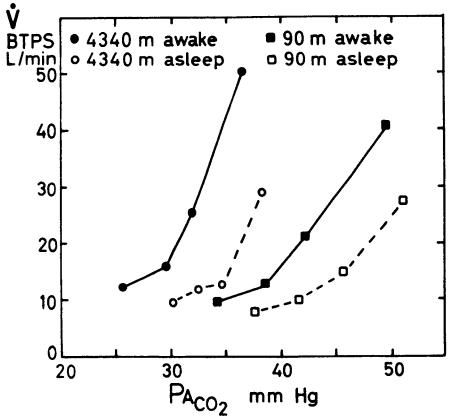


Fig.18. Averaged CO_2 response curves of subjects measured awake and asleep at sea level and at the Summit Laboratory of the White Mountain Research Station. (Plotted from data of Reed and Kellogg (38,39)).

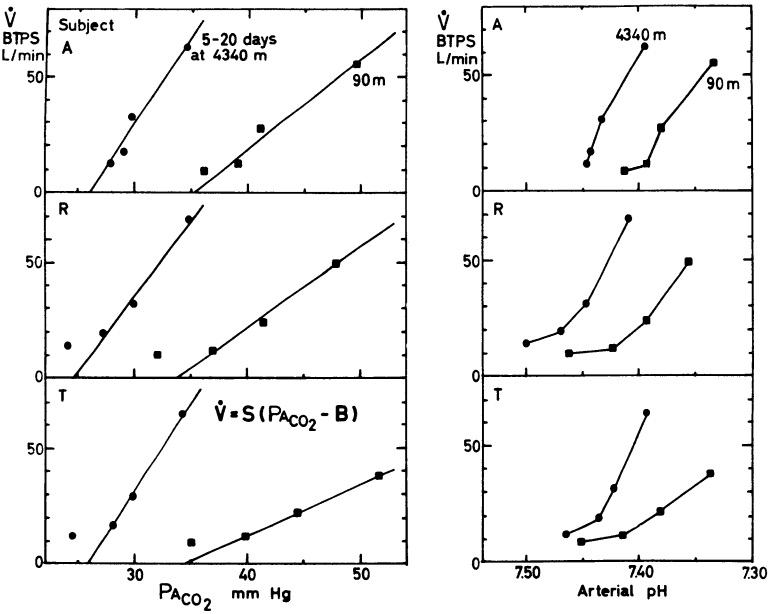


Fig.19. Data from the experiments of Fig.17, replotted to show each subject's response as a function of alveolar P_{CO_2} and of the simultaneous arterial pH. The lowest point at each altitude (0% CO_2) has been ignored in calculation of the reduced major axis for construction of the straight line. (From Kellogg (28)).

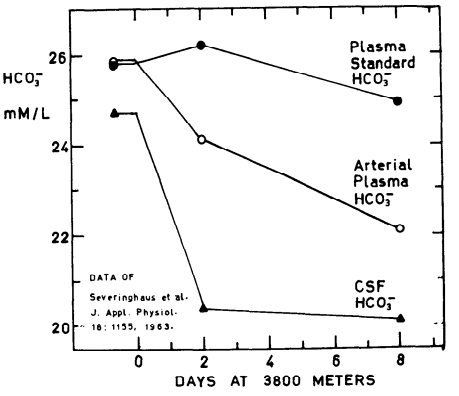


Fig.20. Bicarbonate concentration of plasma and cerebrospinal fluid during acclimatization. Standard bicarbonate is the plasma bicarbonate concentration after the blood has been equilibrated in vitro at 37° C with a Pco_2 of 40 mm Hg and Po_2 above 100 mm Hg. (Redrawn from Severinghaus et al. (41)).

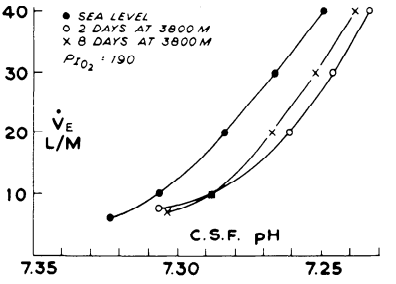


Fig.21. Non-hypoxic CO_2 response curves at sea level and altitude, with ventilation plotted as a function of CSF pH. (From Severinghaus et al. (41)).

One of the big questions now, in my opinion, is what happens to hypoxic drive of the chemoreceptors and the regulation of breathing during really long periods of hypoxia - years or generations - which may help to tie together the results in permanent residents described by Miss FitzGerald (14, 15) with the results in multi-generation natives observed in South America (9, 20). Several investigators are actively working on this at present. Another very important question is the nature of the mechanism that has the effect of decreasing bicarbonate in the cerebrospinal fluid so rapidly during altitude acclimatization. Dr. Eger and others have reported from our laboratory that this seemed to depend upon a curious interaction between the hypoxia and the hypocapnia (13), and we are still working on the problem, but without definitive results.

I hope this brief survey of points that have aroused my interest will serve to emphasize that, despite its long and colorful history, the study of high altitude acclimatization is still wide open to investigation along many important paths.

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AN EXCHANGE OF LETTERS*

Dr. John A. Robertshaw
Professor and Chairman
Department of Physiology
University of Winnemac

Dear Dr. Robertshaw:

Although we are on somewhat less than full-time friendship footing, I would like to call upon you for serious advice. Recently I was invited to an interview at a medical school for the purpose of appraising me as a candidate for chairmanship of their department of physiology.

Since I am only one of several candidates for the position, my problem may be purely academic. Nevertheless, there is a possibility that I will be offered the position, and I an in need of your thoughts on the general subject. Your success as an investigator, teacher and administrator is common knowledge.

When the feelers were extended I was greatly inclined to bow out, but my present chief felt it would be a valuable experience for me to go through an FBI check by a school in search of a chairman. He compounded the difficulties by writing a highly flattering description of me which whetted their appetite. The interview lasted for two days, and I believe I impressed the buyers favorably.

I am ambitious for the position of chairman as an eventual career goal. But I am also aware of my inadequacies for such a position at the present time. I have barely begun to develop a position in research, and my accomplishments are puny. I have had only two years of experience teaching medical students, and I have had no significant administrative responsibility. In short, I am uncertain about myself and feel it might be premature to make the leap at this time. On the other hand, I want to devote my energy to a worthwhile cause. The temptation is great because the job offers a challenge. The school is expanding, and the people I met in other departments seem to share a common goal. I could build a strong teaching unit in a growing center, and I would have an opportunity to try my ideas in medical education.

You must have stood at a crossroads like this when you accepted your first chairmanship in Deseret. How did you know you were ready? In retrospect what besides guts permitted you to run the risk of killing your research career in order to run the lives of

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*By request of the authors all names (persons and institutions) are fictitious but the letters are factual.

others?

I hope I am not imposing on you for your counsel.

Sincerely,

L. A. Gutman, M.D.

Dr. L. A. Gutman
Division of Physiology
McGurk Institute for Medical Research

Dear Laertes:

I had not intended to spend this afternoon writing to you, but I cannot resist stroking my long white whiskers and sounding off about Life in loud self-confident tones.

Lesson 1. A department chairman must budget something between one-fourth and one-half his time for the totally unexpected. He must be able to respond cheerfully and without annoyance to calls for any of a variety of services, and he must be able to switch back and forth from the unexpected to the routine without any clashing of mental or emotional gears.

Yesterday the Professor of Medicine in the school which is considering you called up to ask what I thought of you. I said that I could give no estimate of your ability as a teacher and administrator, that I was impressed by your research such as the recent AJP paper and that I would place very strong reliance on whatever your present chief said.

Lesson 2. There is an interlocking group which exchanges information. One's career may be determined by a few words of which one is probably never aware, and although the brilliant seminar may help it is the accumulation of small things which really counts. I doubtless didn't do you much good for the reason that I don't know enough, but I could have done you a great deal of harm.

Lesson 3. When you join the group which makes decisions and passes on information, it is essential to guard your reputation for candor so that what you say counts when you want it to.

There is a tremendous need for men to exert leadership and to assume responsibility in physiology as in everything else. If you have the capacity to do so, you are cheating society as well as yourself if you don't find the opportunity to exercise your talents to the fullest. You will probably find that you are always overstretched, but you will also find that people who do the world's work always are anyway. Consequently, one should not reproach one's self with ambition. The trick is to match ambition with capacity.

Lesson 4. Keep looking for jobs which are beyond your present skill.

I have a firm belief that it is very wise to go to the bush leagues first. One reason is that a small school is so thin that anyone in a position of responsibility learns a great deal very quickly. The first time I sat on an Executive Committee at the age of 32 I had to vote on a problem in anesthesiology. I can't tell the top from the bottom of a chest film, but I know a great deal about radiology departments. After eleven years in Deseret no one had to draw me a diagram to explain problems of a medical school or a university. One could live a hundred years in a big place like Winnemac without learning a tenth as much.

Lesson 5. If you pick the right place and behave properly, you can develop a large range of professional skills which are important to have and to exercise.

There is a real problem in picking the place to go. You must go to a school which is on the way up and which has a sufficient number of strong and progressive persons in its leadership. Deseret certainly was that way despite its poverty. You may not know that Terry Wickett got his start there. He says the smartest thing he ever did was not to look at the place before he accepted our job offer; otherwise he would never have taken the job which allowed him to grow into the National Academy and part of a Nobel Prize. It was really pretty obvious that a school with Benoni Carr and Gustaf Sondelius had something besides a few tar-paper shacks. I have no idea about the school you are looking at. Watch out for being oversold; try to discover the reality behind the professional job the search committee does on a prospective candidate.

Lesson 6. Somehow find out who the leaders are and where they want to go. Where did they train? What sets their standards? Who steals them away? Where do the students come from? Where do they intern? How many lights are on at night? How full is the parking lot on weekends and over holidays?

No matter what the quality of the faculty, it will certainly be full of conflicts. However, if the leading men are really big men they will sink their differences for the good of the common enterprise. Many a time in Deseret I saw men who disliked each other heartily support one another for the sake of the school.

Lesson 7. No one should expect a department, a school or a university to be one big happy family, and there is no rule which demands that you like a man before you can cooperate effectively with him. Keeping your distance socially helps, too.

I would not worry much about the problems involved in accepting responsibility for the whole of physiology. I assume you would take that responsibility. It is a mistake to limit the department to a narrow field. Since your department will be small you yourself

will have to try to cover almost everything. In Deseret I tried to keep up with every major field in physiology, and I taught everything, including neurophysiology. I don't think it matters much that a good bit of what I taught turned out to be wrong; a good bit on which I was the world's leading expert turned out to be wrong too. What counted was the zip I put into it, and I am grateful for the diversified experience and the intellectual capital I was forced to accumulate. I still remember the frequent occasions at medical grand rounds when the professor said: "Now, Dr. Robertshaw, would you care to comment on this case?" I would have to get up and say something sensible about a patient and a disease I had never heard of an hour earlier. That never happens here at Winnemac; I don't even know where the Department of Internal Medicine is.

Lesson 8. Quick wits, a good memory, ability to think on one's feet, frankness and modesty plus a great deal of hard work will see you through. Don't forget the rest of the staff is in the same position. This is one of the advantages of the "thinness" I spoke of above; the place simply isn't running over with experts to whom you can pass the buck. Yesterday the professor who called me asked me about your breadth. In return I asked him (a cardiologist) how much he knows about peptic ulcer. Whatever he knows about the heart, he still has to see to it that someone (probably himself) does something about the next ulcer that turns up on his wards. You earn your journeyman's ticket that way. You don't know you are ready until you have done the job, by which time there is the next job to do.

I also don't think you should worry about ruining your life bossing other people around. In the first place, you won't get much of a chance; faculty members don't boss easily. Either your associates (technically subordinates) voluntarily take on jobs, in which case you must be very careful to give them the authority which goes with responsibility, or you must plug the gap by doing the job yourself. In the second place, you have the responsibility of making up your mind about what you want to do with your life. That decision will be the same no matter where you are.

Lesson 9. Don't let yourself be kidded by the local mores. If you find you can't work after five, don't take your briefcase home because everyone else does. If you want to wash your own dishes in the lab, do so. If you don't want to build a grant-supported empire, don't try to do so because the professor of pharmacology is doing it. In this regard I should remind you that there were days when one didn't worry about his "research career." As I remember the departments at Penn and Yale and Rochester and Harvard (not a bad list) before the war all members from top to bottom did their jobs without worrying very much whether they had research careers or not. Of course, all of them did, just as they had teaching and service careers as well.

You will find that as a department chairman you have so much hidden power that you don't need the overt power expressed in bossing people. This comes in two ways: First, you are the channel

through which information flows to the top. I make a practice of feeding the dean a steady stream of tidbits about departmental activities; these help in forming decisions about budgets, promotions and so on. (I should say here that the better the job you yourself do, the better your recommendations to the dean fare.) Second, you are the only one who thinks five minutes ahead for the department. You will have to worry about a great many problems, and the fact that you have thought ahead and have solutions at least tentatively formed will go a long way in making your decisions the ones which are accepted.

Lesson 10. You make yourself count by doing your job well without much thought of where it will get you. I keep telling people that the highest form of selfishness is obvious unselfishness; you can get almost anything you want if you are not clearly out to get what you want. That goes for your science, too. I could not have done anything more calculated to advance my career than to write that paper which demonstrated the conclusions contained in my own Ph. D. thesis were wrong, yet I assure you it wasn't calculated.

I doubt I have been of much help, and the last lesson I could give is that no matter what you do there will be times when you bitterly regret your decision.

Yours,

John A. Robertshaw

THE FATE OF NOREPINEPHRINE AND THE EFFECT OF DRUGS*

JULIUS AXELROD

The catecholamines, epinephrine, norepinephrine, dopamine and N-methylepinephrine have been found to occur in mammalian tissues. Epinephrine is highly localized in the adrenal medulla and it exerts its effects mainly as a circulating hormone. Although norepinephrine is also present in the adrenal medulla, it functions mainly as the neurotransmitter in the sympathetic nervous system and generally acts locally on effector cells. The function of the dopamine is still obscure but is found in certain regions of the telencephalon (neostriatum). Both norepinephrine and dopamine are believed to act as neurotransmitters in the central nervous system.

During the past decade there has been a considerable increase in our knowledge concerning the formation, uptake, storage, release and metabolism of catecholamines. These rapid advances have been made possible by the development of specific and sensitive methods for measuring these amines in tissues, the availability of radioactive catecholamines of high specific activity, the use of histofluorometric methods that visualize biogenic amine-containing neurones and the use of drugs that effect the adrenergic nervous system.

Biosynthesis. The amino acid precursor for catecholamine synthesis is tyrosine. This amino acid is transported into the sympathetic neurone or the chromaffin cell by a concentrating mechanism and it is then hydroxylated to form dihydroxphenylalanine (dopa) (12). The enzyme, tyrosine hydroxylase, that carries out this reaction, requires a tetrahydropteridine cofactor and it is highly specific in that it will hydroxylate only l-tyrosine (36). The relatively low activity of this enzyme makes it the rate-limiting step in the synthesis of norepinephrine and thus it acts to regulate the synthesis of norepinephrine. Because of its low activity the tyrosine hydroxylase can be effectively inhibited in vivo by the amino acid analogue α -methyl-p-tyrosine (43). Thus the administration of this compound can almost prevent the synthesis of norepinephrine in many tissues. As a result, the tissue levels of norepinephrine are rapidly depleted.

The next step in the biosynthesis of catecholamines is the decarboxylation of dopa to form dopamine. This reaction is catalyzed by the enzyme aromatic l-amino acid decarboxylase (25). The enzyme is present mainly in the cytoplasm and requires pyridoxal phosphate as a cofactor. In contrast to tyrosine hydroxylase the decarboxylase enzyme is relatively nonspecific and can decarboxylase other aromatic amino acids such as 5-hydroxytryptophan and histidine to form the corresponding biogenic amines (34). The activity of aromatic amino acid decarboxylase or as

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*Taken from the introductory remarks given at the session on Catecholamines at the 1967 Federation Meetings.

it is commonly known, dopadecarboxylase, is difficult to inhibit completely because its activity is relatively high. It plays a negligible role in regulating the synthesis of norepinephrine.

The catecholamine, dopamine, formed from dopa, enters a vesicle in the sympathetic nerves that stores norepinephrine or the chromaffin granule in adrenergic medulla. When dpoamine enters these granules it is hydroxylated on the β position to form norepinephrine. This step is catalyzed by the enzyme, dopamine β -hydroxylase, in a reaction requiring ascorbic acid and oxygen (33). Many other phenylethylamines both normally occurring (tyramine) and foreign (amphetamine) can be β- hydroxylated by this enzyme (9).

Dopamine β -hydroxylase is localized in the norepinephrine storage granule and dopamine formed in the cytoplasm must enter this granule before it is β -hydroxylated (37). Since norepinephrine can effect the entry of dopamine into the storage vesicle, this can serve as a regulatory mechanism for norepinephrine synthesis (44).

The final step in the synthesis of catecholamines is the N-methylation of norepinephrine to epinephrine. This step is carried out by the enzyme phenylethanolamine-N-methyltransferase (1). S-adenosylmethionine serves as the methyl donor in this reaction (29). In mammals this enzyme is selectively localized in the adrenal medulla, while in amphibians, it is also present in sympathetic nerves, brain and heart. Besides norepinephrine, this enzyme can N-methylate other β -hydroxylated phenylethylamine derivatives including normetanephrine, octopamine, and even drugs such as norephedrine and amphetamine. The synthesis of phenylethanolamine-N-methyltransferase in mammals is under control of the corticoids arising from the adrenal cortex (48). Removal of the pituitary causes a profound reduction in the epinephrine-forming enzyme ACTH and large amounts of corticoids can restore the enzyme activity (Table 1).

TABLE 1

Control of epinephrine synthesis by the pituitary gland and corticoids

Treatment	Adrenal weight mgm	PNMT units/pair	Epinephrine µg/pair
None	69 ± 3	6.2 ± 0.7	32 ± 2
Hypophysectomy	27 ± 2	1.5 ± 0.1	24 ± 2
Hypophysectomy and ACTH	47 ± 2	4.8 ± 0.3	25 ± 3
Hypophysectomy and dexamethasone	26 ± 2	7.1 ± 0.4	29 ± 3

Rats were hypophysectomized and killed 21 days later. Some hypophysectomized rats received 4 units ACTH or 1 mg dexamethasone daily. PNMT is phenylethanolamine-N-methyltransferase (From Wurtman and Axelrod, J. Biol. Chem. 241: 2301, 1966).

The pathways for the formation of catecholamines are shown in Figure 1.

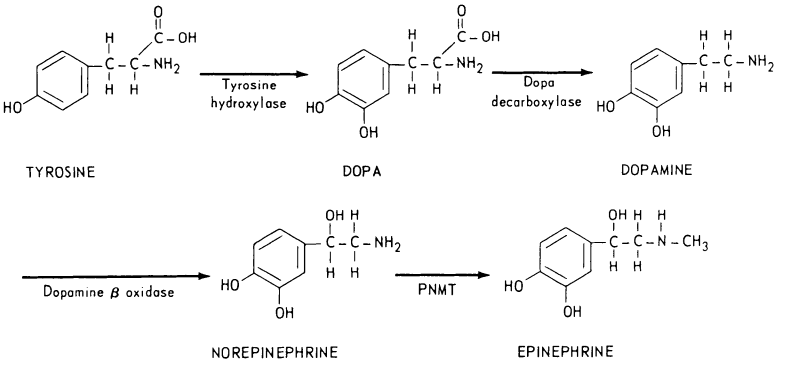

Fig.1. Enzymatic steps in the formation of catecholamines.

Metabolism. The catecholamines are metabolized via two main pathways, one involving deamination by monoamine oxidase and the other O-methylation by catechol-O-methyltransferase (2).

Monoamine oxidase is widely distributed throughout the body but it is highly concentrated in liver, kidney and brain (39). It is localized in the mitochondria and perhaps in other subcellular particulates. Monoamine oxidase is also present in sympathetic neurones (42) where it serves to regulate the levels of stored norepinephrine (30). The enzyme is relatively nonspecific, it can deaminate many alkyl and aromatic amines, including norepinephrine, epinephrine and dopamine to the corresponding aldehyde (8). Many amines of biologic and therapeutic interest are substrates of monoamine oxidase. In vitro and in vivo monoamine oxidase acts on amines which have an amino group attached to the terminal carbon atom; secondary amines are deaminated as rapidly as the corresponding primary amines. Phenylethylamines in which the amino group is not attached to a terminal carbon atom are not deaminated by the enzyme (ephedrine, amphetamine) (7). Monoamine oxidase more readily deaminates phenylethylamine derivatives which lack β -hydroxy substituted group. Thus, dopamine is a better substrate for this enzyme than norepinephrine and epinephrine.

There are many powerful inhibitors for monoamine oxidase, mainly hydrazines, which can produce long lasting irreversible inhibition (50). Monoamine oxidase inhibitors are used to treat psychic depression, hypertension and angina pectoris. These compounds have also served as useful tools in elucidating adrenergic mechanisms.

Catechol-O-methyltransferase is the other major enzyme concerned with the metabolism of catecholamines (5). This enzyme transfers the methyl group of S-adenosylmethionine to the meta hydroxy group of catechols. The presence of Mg^{++} is also required to carry out this reaction. This enzyme can O-methylate any catechol in which the two

hydroxy groups are adjacent on the aromatic ring. The O-methylating enzyme is widely distributed in all tissues but it is most abundant in liver and kidney. Catechol-O-methyltransferase is present mainly outside the neurone and is believed to be closely associated with the adrenergic receptor (15). Several competitive inhibitors have been found for this enzyme including pyrogallol (4), and tropolone (6). The administration of catechol-O-methyltransferase inhibitors will slightly prolong the physiological actions of catecholamines (49) while monoamine oxidase inhibitors will have negligible effects in prolonging the action of catecholamines (13). When both enzyme inhibitors are given together the physiologic effects of norepinephrine and epinephrine are still rapidly terminated indicating that there are other mechanisms for the inactivation of these compounds.

Norepinephrine undergoes a different fate depending upon whether it is liberated into the blood stream or from the sympathetic nerve terminal onto tissues. Studies on the metabolism of circulating catecholamines have been made by the intravenous injection of tracer amounts of the radioactive amines. The amount of the unchanged catecholamine and its metabolites were measured in the urine (32). When radioactive epinephrine is injected intravenously to man, only small amounts (6%) of the catecholamine are excreted unchanged, indicating that it is almost completely transformed in the body. The major metabolites are O-methylated products, free and conjugated metanephrine (40%), 3-methoxy-4-hydroxymandelic acid (40%) and 3-methoxy-4-hydroxyphenylglycol (7%). Negligible amounts of the deaminated catechol 3, 4-dihydroxymandelic acid are excreted. These observations indicate that the principal metabolic pathway for circulating epinephrine is O-methylation; this process taking place mainly in the liver (24). The O-methylated amine is then deaminated by monoamine oxidase, to form the aldehyde intermediate. In man, the major fraction of the aldehyde is oxidized to 3-methoxy-4-hydroxy-mandelic acid (VMA) and a smaller portion is reduced to 3-methoxy-4-hydroxyphenylglycol. In the rat more glycol than acid is excreted. Norepinephrine undergoes an analogous metabolic fate. Figure 2 describes the pathway for the metabolism of circulating catecholamines.

The norepinephrine in tissues undergoes a quantitatively different metabolic fate. The norepinephrine in tissues is present in sympathetic nerves, and is metabolized mainly by monoamine oxidase within the nerves (30). The physiologically inactive deaminated product leaves the neurone and is then O-methylated. The main metabolic products of endogenous norepinephrine found in the urine are VMA and 3-methoxy-4-hydroxyphenylglycol. These metabolites are derived mainly from the norepinephrine metabolized within the sympathetic nerves. Smaller amounts of free and conjugated (nor) metanephrine are normally present in urine. These compounds are formed mainly from the norepinephrine released from sympathetic nerves or epinephrine secreted from the adrenal medulla.

The fate of the norepinephrine in the sympathetic nervous system. Studies using the histofluorometric techniques and the electron microscope have elucidated the structure of the sympathetic neurone, as well

as the distribution of norepinephrine within these nerves. The sympathetic neurone consists of a cell body, preterminal axon and the nerve ending. The terminals of the sympathetic nerves are highly branched and have beaded swellings or varicosities along the nerve (35). At the nerve terminal the concentration of norepinephrine reaches concentrations of 10 mg/g while in the cell body of axons the concentration is only about 100 μg/g. The varicosities in the nerve terminal contain dense core membrane bound vesicles of about 500A (47) which serve to store the neurotransmitter. The nerve terminals are interwoven in the tissues forming a rich plexus. By means of the swellings on the nerve terminals each neurone can make synaptic contact with many thousand effector cells.

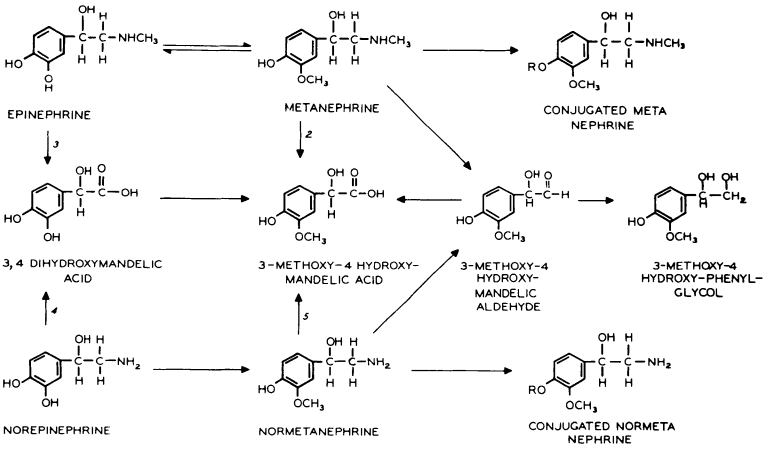

Fig.2. The metabolism of epinephrine and norepinephrine.

Radioactive norepinephrine provided a useful tool to study the uptake, storage and release of norepinephrine into the nerve terminal. When radioactive norepinephrine is injected into the blood stream of animals it is taken up by tissues rich in sympathetic fibers (46). The chronic denervation of the sympathetic nerves results in a negligible accumulation of radioactive norepinephrine in these tissues indicating that the catecholamines is selectively taken up by the postganglionic nerve terminal (21). In vitro studies have demonstrated that this uptake process requires an active transport of the amine and an optimal concentration of Na^{++} and K^{+} ions (28). When the norepinephrine crosses the axonal membrane of the sympathetic nerve into the axoplasm it is rapidly taken up into the dense core vesicle where it is retained and stored in a physiologically inactive form until it is released. This process of uptake and retention by the sympathetic nerves serves as the rapid and effective means for inactivating norepinephrine. The storage of norepinephrine in the intraneuronal vesicle appears to require an optimal electrolyte concentration. Subcellular studies have shown that the norepinephrine storage vesicles are associated with the microsomal fraction (37).

Since the norepinephrine is selectively taken up and stored in the sympathetic neurone, the neurotransmitter can be labeled and its fate studied. This was accomplished by the intravenous injection of H^3-norepinephrine of high specific activity (20). The spleen which contained considerable radioactive neurotransmitters was isolated and perfused with blood from a donor cat. After stimulation of the splenic nerve, H^3-norepinephrine and its metabolites were measured in the venous outflow. There is a marked elevation in the norepinephrine concentration in the venous outflow after each stimulation. An increase in the amounts of the O-methylated metabolite are also present after each stimulation but no deaminated products are detected. These experiments demonstrate that the norepinephrine liberated from the nerve ending of the spleen is inactivated by several mechanisms: part of it is discharged into the blood stream and carried away; part is O-methylated by catechol-O-methyltransferase and the major fraction returns to the nerve where it is rebound and stored again. A fraction of the stored norepinephrine is continuously leaving the storage vesicle. Most of the catecholamine liberated in this manner is inactivated by deamination within the neurone by monoamine oxidase (30). A diagrammatic representation of the fate of norepinephrine in the sympathetic neurone is shown in Figure 3.

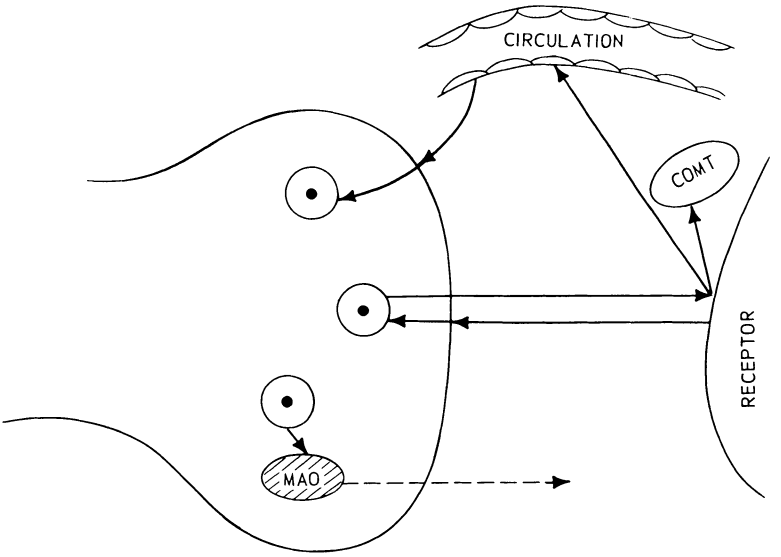

Fig.3. The fate of norepinephrine in the sympathetic neurone.

Effect of adrenergic drugs on the disposition of norepinephrine. Drugs that affect the adrenergic nervous system may exert their actions by interfering with the uptake across the neuronal membrane, the storage in the vesicles in the neurone, or the release of norepinephrine. Drugs such as cocaine, imipramine and sympathomimetic amines, prevent the entry of norepinephrine into the sympathetic neurone (23). Thus these drugs increase the response of the catecholamine

by interfering with its inactivation by binding. This allows more of the pressor agent to react with the receptor (Fig. 4). The supersensitivity resulting from chronic denervation of the sympathetic nerves may be explained in part by a similar mechanism. The degeneration of the sympathetic nerves destroys an important means for the inactivation of norepinephrine binding. In the absence of the nerves more of the catecholamine is available to stimulate the effector cells.

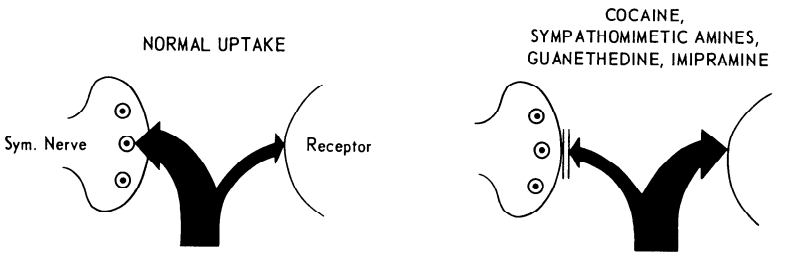

Fig.4. Supersensitivity caused by drugs that block uptake of norepinephrine across the neuronal membrane.

Sympathomimetic amines such as tyramine and amphetamine (38), release the bound norepinephrine from the storage vesicles. This causes a rise in blood pressure. Consequently these drugs produce their pressor effects indirectly by liberating norepinephrine (10). Certain drugs such as reserpine abolish the ability of the vesicle in the nerve to bind norepinephrine (26). This results in a marked depletion of the stores of norepinephrine of tissues. Though both sympathomimetic amines and reserpine reduce the content of the catecholamines in tissues, they appear to do this by different mechanisms. The sympathomimetic amine, tyramine, rapidly releases norepinephrine so that it leaves the nerve terminal in a physiologically active form and then it is metabolized mainly by O-methylation (30). Reserpine, on the other hand, appears to liberate the stored norepinephrine slowly so that it is more easily deaminated by monoamine oxidase within the neurone. Hence the norepinephrine discharged by reserpine leaves the neurone as the physiologically inactive product. After the repeated administration of sympathomimetic amines their effects are diminished. This phenomena, tachyphylaxis, is due to the gradual exhaustion of the catecholamines in the nerves caused by these amines (3). After the administration of small amounts of norepinephrine the response returns (14).

The storage vesicle not only binds norepinephrine but other related compounds as well. For example, epinephrine (41), octopamine (β-hydroxylated tyramine) (31) and several β-hydroxylated phenylethylamine derivatives can displace norepinephrine in the storage granules. Nerve stimulation can liberate these compounds so that they serve as false neurotransmitters. Certain drugs may also prevent the release of norepinephrine from the nerve. Examples of these compounds are guanethidine and bretylium (22). Ganglionic blocking agents and preganglionic denervation retard the spontaneous release of norepinephrine.

Catecholamines in the central nervous system. It had been shown that norepinephrine is unequally distributed in the mammalian central nervous system (45). Recent studies using histofluorometric techniques have found that the brain has a complex system of neurones that contain the biogenic amines norepinephrine, dopamine and serotonin (11). All of the enzymes necessary for the synthesis of the catecholamines (tyrosine, hydroxylase, aromatic amino acid decarboxylase and dopamine β -oxidase) have been found in the brain. In addition, catechol-O-methyltransferase and monoamine oxidase, the enzymes involved in the metabolism of catecholamines, are also present in the brain. Since catecholamines cannot cross the blood-brain barrier, the biosynthesis and fate of norepinephrine and dopamine were studied after the injection of precursors or the catecholamines into the lateral ventricle of the brain. The injection of C^{14}-tyrosine, dopa or dopamine into the lateral ventricle of the rat brain led to the rapid formation of norepinephrine (19). After the introduction of H^3-norepinephrine in the brain, normetanephrine and the 3-methoxy-4-hydroxyphenylglycol are formed. Considerable portions of the norepinephrine taken up by the brain tissues are retained and slowly released. Subcellular studies show that the H^3-noreponephrine is localized mainly in the "pinched-off" nerve endings similar to that of the endogenous norepinephrine. An examination on the uptake of H^3-norepinephrine in various regions of the brain show an unequal localization similar to that of the endogenous catecholamines (18). Autoradiographic studies of the rat brain confirmed the distribution found with H^3-norepinephrine (40). Intense labeling is observed in the periventricular and ventromedial nucleus of the hypothalamus, the medial forebrain bundle, and in specific tracts of the spinal cord apical dendritic layer of the hippocampus. The corpus striatum, an area which selectively stores dopamine, is also labeled with norepinephrine. Using H^3-norepinephrine as well as other techniques, marked differences in the rate of turnover of norepinephrine in various areas of the brain can be demonstrated (27). The cerebellum has the fastest turnover (half-life about 2 hours), the medulla oblongata and the hypothalamus have the slowest turnover (half-life about 4 hours), and the cortex and hippocampus have half-lives of about 3 hours.

The labeling of the stores of norepinephrine in the brain provided opportunity to examine the effect of centrally acting drugs on the uptake, release and metabolism of norepinephrine in the central nervous system. The accumulation of norepinephrine in the adrenergic structures of the brain involves transport across the neural membrane (uptake) and subsequent uptake and retention in the intraneural storage granules (binding). It was found that compounds such as imipramine (an antidepressant compound) interferes with the uptake of norepinephrine across the central adrenergic neural membrane. Other antidepressant drugs such as desmethyl-imipramine and amitriptyline also reduce the accumulation of norepinephrine in the brain, but structurally related derivatives of imipramine, clinically inactive as antidepressants, had no effect (16). The antidepressant drugs may act by preventing the reuptake of the released neurotransmitter and consequently more norepinephrine is available to react with the adrenergic receptors. Imipramine and chlorpromazine have also been found to slow the spontaneous release of norepinephrine in neurones of the brain (17). Amphetamine has many actions on nor-

epinephrine in the brain. Like imipramine, it blocks the uptake of norepinephrine across the neuronal membrane. It also releases the bound norepinephrine in a physiologically active form. Amphetamine has also been found to be an effective inhibitor of monoamine oxidase in the brain. Neither amphetamine nor imipramine has any effect on the uptake of dopamine in central adrenergic neurones. Figure 5 shows the effect of antidepressant drugs on the disposition of norepinephrine in the brain.

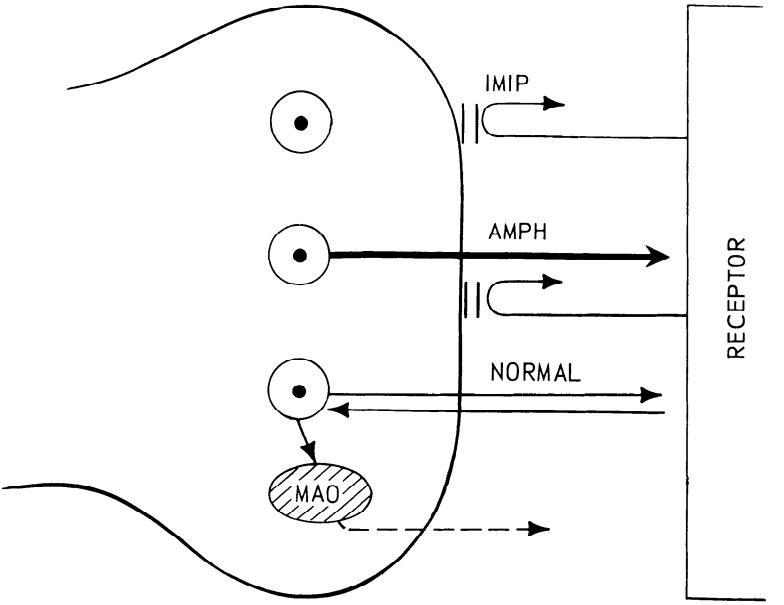

Fig.5. The effect of antidepressant drugs, amphetamine and imipramine on the uptake and release of norepinephrine in central adrenergic neurones.

Reserpine reduces the accumulation of H^3-norepinephrine in the brain (17). The drug appears to act by releasing the norepinephrine from the intraneural storage vesicles. The liberated norepinephrine is then deaminated by monoamine oxidase within the neurone so that it leaves the nerve as a physiologically inactive metabolite. Reserpine causes a marked depletion of endogenous norepinephrine in the brain and tissues. The behavioral effects due to reserpine are restored within a few days while the endogenous norepinephrine rises slowly over several weeks. The ability to retain small amounts of H^3-norepinephrine injected into the lateral ventricle of the rat brain recovers rapidly between 24 to 48 hours after reserpine treatment. At this time the rat recovers from most obvious behavior effects induced by this drug. Thus the behavioral effects of reserpine appear to be related to the recovery of the uptake process rather than the levels of the catecholamine.

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THE STORY OF A PAPER

or

"Equivalent Values"

PIETRO O. BRAMANTE

This project was supported by a grant -

Actually, the grant had been awarded to study lipogenesis in the squirrel. The fact that this paper deals with hemoglobin in the dolphin is only incidental.

Present address -

They kicked me out, in the meantime, but I'll show them.

A bibliographical survey of the subject revealed how little is still known -

One of us leafed for three solid days through seven issues of Current Contents and couldn't find a thing.

Conflicting reports from various countries -

- as long as they are in English.

Different tasks were assigned to the members of our team -

I killed the rats and Sue took the weight of the organs.

8 healthy volunteers served as controls -

Seven of them were fractures from Orthopedics, who sincerely believed that all those injections made part of their treatment. The eighth was a flunking sophomore who had better cooperate.

The animals were fed ad libitum and had access to water at all times -

Well, almost.

The animal's growth was closely followed -

For Pete's sake, get back our scale from Anatomy and weigh those animals. We haven't seen them for months!

...by a personal modification of Howard and Johnson's method -

In the original method, the readings are taken every five minutes, but we found that it makes little difference if you stretch the intervals to 15 minutes.

All the glassware was rinsed in triple distilled water -

Well, almost.

60% of the observations in the experimental group -

3 rats out of 5.

The reproducibility of our data -

A standard deviation 3 times as large as the mean is not bad, isn't it?

A second series of experiments essentially confirmed our previous results -

This time, the standard deviation was only twice the mean.

The highly significant difference -

P was actually 0.20, but so what? Nobody is perfect.

(personal communication)

At the last Federation Meeting, I met Bill on the Boardwalk. Imagine! We discovered that we are working on the same problem. He doesn't understand it either.

More data are needed to derive conclusions -

The computer man said that 5 rats is ridiculous.

Work is presently in progress -

The grant expires in two months. We had better think of something else, and quick.

(manuscript in preparation)

We have already written a terrific title.

(unpublished observations)

Remember, Ann, that stack of blood flow records? Last time I saw them, when we moved in 1957, they were in that red basket in the basement.

(in press)

Sometime next year.

(to be published)

That paper has already been rejected by 3 other journals, but we keep trying.

The suggestions and constructive criticism of Professor Loveless

are deeply appreciated.

The old man tried to get his name in the paper, but we licked him, this time.

We are grateful for the statistical assistance -

Dr. Pi Cosine of the Biometrics Dept. requested that his name be removed from the manuscript.

Our thanks to Miss Lin-ti Chang Ming Wong (Sue), Mrs. Marika Dolores Obrowsky Jimenez-Gutierrez and Mr. Brutus Clay for their skillfull technical assistance.

If Sue could only speak some English! Luckily, Dolores got pregnant and had to quit. In his 3 months with us, Brutus broke 13 beakers, 7 funnels, 32 pipettes and the hemoglobinometer. He was a nice boy, though.

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He must be kidding.

It is the opinion of the referees -

One wanted the whole thing changed. The other thought it was great.

The Editors suggest some minor changes in the manuscript -

Try to rewrite the first 3 pages of the introduction, the discussion and the conclusions. Then, we will see.

There is a minimal delay in the publication of a paper that is acceptable as to scientific content -

17 months.

Sorry, our supply of reprints is exhausted.

Gee, it makes you feel so good! Actually, of 25 copies ordered, 10 had to go to the Public Health, 4 to the Department, 7 to friends. Better keep the rest as a souvenir.

IF YOU CAN'T SOLVE A PROBLEM, APPOINT A GROUP TO STUDY IT*

One of the ways to solve acute problems in the United States is to study them. At this writing there are probably more committees making more studies of more problems than at any time in our history.

Professor Heinrich Applebaum has just completed a study on people who make studies, and the results are fascinating.

Professor Applebaum said, "I discovered that the average person making a study today has had five years of college, is married, has 1.6 children, earns $15,650 a year, lives in the suburbs, plays tennis or golf on weekends and believes in God."

"That's truly amazing."

"He will spend an average 8.9 months working on a study, 2.6 months discussing it in committee, 3.9 months writing a report which will be typed up by 5.6 secretaries and then it will be printed up and distributed to 1250 people, of which 5.9 persons will read it in in its entirety."

"That isn't too many people."

"It's a lot considering that only one out of every 23.6 reports are ever acted upon."

"What happens to the rest of them?"

"They're filed away and used as reference for other people who will be asked to make a future study on the same subject."

"That sounds rather discouraging."

"On the contrary, the main purpose of a study is not to solve a problem, but to postpone the solution of it in hopes that it will go away. If it doesn't go away, at least people will have forgotten about it by the time the report comes out."

"A study group's work is never done."

"I should say not. Making studies is now the third largest industry in the United States. Not only are large monies spent in making studies, but great sums are spent attacking studies that people don't agree with."

"Professor Applebaum, your report will make a great contribution to the study of studies. Can you tell me why you decided to do it in the first place?"

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* From: Art Buchwald, The Washington Post, October 3, 1967.

"I work for a foundation, and everything we wanted to study was being studied by somebody else. This was the only subject left that no one had made a study on."

"Has anybody read it?"

"My wife think it's the best thing I've ever done."

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BIBLIOGRAPHY OF TRANSLATIONS IN THE NEUROSCIENCES

A "Bibliography of Translations in the Neurosciences" covering the period 1950 through 1966, has been published by the National Institute of Mental Health. Copies are available on request from: Office of Communications, Information Services Branch, National Institute of Mental Health, 5454 Wisconsin Avenue, Chevy Chase, Maryland 20203.