"Well, he finally decided to clean the attic. Almost had the job done, too..."

"...Yeah, until he tried to lift me. It sure put his back out of whack. His doctor's got a real job to do—trying to ease both the pain and the strain."
When stress results in muscle strain and pain

When the normally sedentary person suddenly turns active—cleaning the attic, for instance—the outcome is sometimes a strain or sprain in the back, neck or shoulders.

Fortunately, however, most patients with muscle spasm and pain are highly responsive to therapy with Robaxisal. This rationally based formula provides the well-known relaxant benefits of methocarbamol for strained, tense skeletal muscle plus the dependable analgesic and anti-inflammatory effects of aspirin. Investigators have found methocarbamol a well-tolerated agent with "specificity of action." And methocarbamol potentiates the salicylate levels of aspirin so that, in combination, higher salicylate levels are produced than with equivalent doses of aspirin alone. When the Robaxisal combination was administered to a group of 22 patients with painful musculoskeletal disorders, 20 (91 per cent) showed an excellent or good response.

With Robaxisal you can conveniently fulfill the most important objectives in treatment of muscle spasm: relaxation of skeletal muscle, relief of pain, restoration of mobility and normal muscle tone. And when mild anxiety is a factor in the spasm-pain syndrome, consider Robaxisal®-PH.

*In this investigation, 400 mg. methocarbamol was combined with 300 mg. aspirin.


Robaxisal® brings relief for both

Robaxisal® and Robaxisal-PH are indicated when both analgesic and skeletal muscle relaxant effects are required, as in strains and sprains, painful disorders of the back, "whiplash" injury, myositis, pain and spasm associated with arthritis, torticollis, and headache associated with muscular tension.

Contraindications: Hypersensitivity to any one of the components.

Side Effects: Lightheadedness, slight drowsiness, dizziness, and nausea may occur rarely in patients with unusual sensitivity to drugs, but usually disappear on reduction of dosage.
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Mechanism of Energy Transformations in Biological Membranes*

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One of the most fundamental problems of biology is how energy is transduced in living systems. It is a problem that has fascinated and absorbed a great many distinguished chemists, biochemists and physicists. I believe we have reached a stage in the development of our knowledge of the mechanism of energy transduction which now permits us to see the direction which leads to the final solution. It is with this development that I shall be concerned in this evening's lecture.

All of us are aware that "energy" in some way is garnered by the "burning of food." The oxidations which underlie this so-called burning of food take place within the cells of living organisms and within organelles called mitochondria. In plant cells there are comparable organelles which are called chloroplasts. Both the mitochondrion and the chloroplast are concerned with the transduction of oxidative energy into a special form of chemical energy, and in this regard they are first cousins at the molecular level.

In the mitochondrion a molecule related to sugar (pyruvate) is oxidized to CO₂ and water by molecular oxygen in a series of discrete steps. At each step, the oxidation leads to the liberation of what we may loosely call "hot" electrons, i.e., electrons with high reducing potential. These hot electrons traverse a chain known as the electron transfer chain and are transferred from one component to another in this chain in such a way that the fall in energy is gradual as the electrons proceed through the chain. In the chloroplast, the hot electrons are generated by the action of light on chlorophyll, and here again these hot electrons traverse an electron transfer chain rather similar to the chain of the mitochondrion. The passage of the hot electrons through the electron transfer chain, be it of the mitochondrial or the chloroplast, is linked to the synthesis of ATP. That is to say, in the oxidative reactions involved in the transfer of electrons through the chain, free energy is released, and this energy is coupled to the formation of a bond between inorganic phosphate and ADP, leading to synthesis of ATP. The burning of food by molecular oxygen involves this electron transfer chain and the passage of hot electrons through the chain, ultimately, to molecular oxygen. The capture of energy by the burning of food is then the coupling of the energy released by oxidation to the formation of a bond between the two molecules which have to be united to make ATP. The problem of energy transduction in a nutshell reduces to the question of how the released oxidative energy can be utilized for the synthesis of ATP.

The transduction of energy from one form to another (in this case from oxidative to bond energy) requires a machine. We are all familiar with the innumerable devices by which electric current can power appliances which cook, blow air, refrigerate, translate radio waves into sound, stir, give off light, etc. All these appliances are devices which transduce energy from one form to another. It would appear obvious from our experience with energy transformations in our kitchens and homes and factories that some kind of machine or contrivance would underlie the transformation of energy in the mitochondrion or the chloroplast. But, strange to relate, the biochemist has for at least two decades proceeded on the assumption that there is no need for a machine to account for the coupling of oxidation to synthesis of ATP in mitochondria. The evidence that appeared to justify this assumption was the fact that there is indeed a secondary system also in mitochondria that links the oxidation of α-ketoglutarate to synthesis of ATP, and this system operates by purely chemical principles. If the transduction achieved by the secondary system can be apparently accounted for without invoking a machine, then why invoke a machine for the primary system?

In point of fact, a machine is always required for energy transductions, but since the enzyme that catalyzes the synthesis of ATP coupled to oxidation of α-ketoglutarate is the machine, the crucial point was missed. The question was not whether a machine was required but whether the particular transducing device peculiar to the α-ketoglutarate dehydrogenase was the prototype for the primary transducing systems of mitochondria and chloroplasts. It took 20 years of unremitting failure to convince the

* Presented to the Sigma Xi Society, Medical College of Virginia, February 8, 1968.
biochemist that his original assumptions about the form of the mechanism were not correct.

It will be my thesis this evening that the mitochondrion and the chloroplast are biological machines specialized for transducing oxidative energy into the bond energy of ATP. The gross and detailed molecular structure of these organelles have provided the crucial clues to the nature of the transducing machine and to its mode of operation. It is, thus, to the structure of the mitochondrion that we must turn for the insights that eventually led to the first realistic definition of the transduction problem.

The mitochondrion is in its general form a rod-shaped organelle made up of two boundary membranes (usually referred to as outer membranes), which enclose the organelle, and a set of inner membranes (cristae), which are approximately at right angles to the boundary membranes (Fig. 1). The cristae are tubes which are closed at one end and, at the other end, open into and connect with the inner of the two boundary membranes.

A membrane is a closed system (no open ends) built up from repeating units which nest together to form a continuum like the surface of a hollow ball. The thickness of the membrane is always equal to the thickness of one particle. The repeating particles which make up the boundary membranes are different from the repeating particles that make up the cristal tubes. The boundary membranes have a vesicular or spherical form; the cristal membranes have a tubular form. In any membranes, all the repeating units have the same geometry, but there are usually multiple species, each chemically and functionally distinct. Thus we have, on the one hand, geometric uniformity; on the other, chemical diversity among the repeating units of a given membrane. The fit of repeating units one to another is of paramount importance, because membranes must act as barriers to the movement of ions and molecules; and this can only be achieved by close to perfect fit of the nesting repeating units.

The transducing elements in the mitochondrion are localized exclusively in the cristal membranes, and the transducing elements have been identified with the repeating units in these membranes. The electron microscope has revealed in detail the fine structure of the repeating unit of the cristal membrane (Fig. 2). This repeating unit has a tripartite structure—a cylindrical stalk which connects at one end to a cuboidal basepiece and, at the other end, to a spherical headpiece. All the repeating units of the cristal membrane have this tripartite structure.

In our laboratory we have been able to localize some of the enzymic functions of the mitochondrion in the different sectors of the
MECHANISM OF ENERGY TRANSFORMATIONS

The electron transfer chain is localized in the basepiece (the membrane-forming sector); the capacity for forming or hydrolyzing ATP is localized in the headpiece; the stalk is some kind of communication link which transmits change from headpiece to basepiece and from basepiece to headpiece.

The picture we must form is that of thousands of identical machines (repeating units) nesting together to form a membrane continuum. Each crista is a large collection of identical machines; the mitochondrion is in turn a large collection of cristae. The individual machine works best when part of a membrane continuum, and the individual crista works best when part of an organized, intact mitochondrion.

We are dealing with "collectivized" machines that are intrinsic parts of membrane systems and membrane networks.

Several years ago David Slatterback of the University of Wisconsin published a remarkable paper on the electron microscopy of the mitochondria of canary heart muscle in situ (Fig. 3). The remarkable feature of these electron micrographs is that they show three kinds of structures which the cristae membranes can assume. Within the mitochondrion there are domains in which a set of cristae show one of these three structural forms. The three forms are set forth in Figure 4. These are, respectively, the cristae with linear structure (parallel membranes); cristae with vesicular structure; and finally, cristae with zigzag structure. It became obvious to us that the cristae membranes of mitochondria were going through a cycle of ultrastructural changes, and that each of these three domains represented a different stage in this cycle. The process of transducing oxidative energy into the bond energy of ATP had to be related to these ultrastructural changes in the cristae membranes.

We may summarize the various ways in which energy can be manipulated in the mitochondrion by means of a simple diagram (Fig. 5). Electron transfer or hydrolysis of ATP can give rise to an energized state. This is a reversible process. The energized state can lead to the synthesis of ATP or drive the electron transfer process in reverse. In addition to driving the synthesis of ATP from ADP and Pi, the energized state can be linked to a set of work performances—translocation of monovalent ions, translocation of divalent ions, and transfer of a hydride from DPNH to TPN* to an extent that is far beyond the equilibrium point for the non-energized transhydrogenation. Thus, there is a cycle of generating and discharging the energized state which underlies synthesis of ATP or translocation or transhydrogenation.

The critical question was whether the energized state could be equated

Fig. 3—Electron micrograph of a canary heart mitochondrion in situ. The cristae are arranged in sets (domains) which show the same configuration. Three configurational patterns are readily recognized.

Fig. 4—The three configurations of the cristae membrane in canary heart mitochondria: (A) nonenergized, (B) energized, (C) zigzag (energized-twisted).
with one or more of the three ultrastructural states of the cristae membrane seen in Slatterback's electron micrographs. Before we consider the evidence that equated the energized state of the mitochondrion with one or other of the ultrastructural states, let us digress to take up two points relevant to and crucial to the argument. There is evidence that there are in fact two energized states: (1) the state induced by electron transfer or ATP in the absence of inorganic phosphate, and (2) the state induced by electron transfer or ATP in the presence of inorganic phosphate. The zigzag state of the canary mitochondrion corresponds to the phosphate-induced energized state; the vesicular state of the canary mitochondrion corresponds to the energized state in absence of added inorganic phosphate.

Isolated mitochondria undergo a cycle of ultrastructural change that is similar to but not identical with that seen in situ. The difference in appearance can be accounted for in terms of the presence of sucrose in the media used for isolating mitochondria. In the presence of sucrose, the cristae membranes of mitochondria undergo geometric deformation, and it is these deformations that underlie the different ultrastructural appearance of the nonenergized and energized states of mitochondria in situ as compared to mitochondria in isolation. The three ultrastructural states of beef heart mitochondria are shown in Figure 6. The snake-like forms (energized-twisted configuration of the membrane) correspond to the zigzag forms seen in the mitochondria of canary heart muscle. The compressed tight membranes (nonenergized configuration of the membrane) correspond to the linear forms seen in the mitochondria of canary heart muscle. The expanded membranes with a lumen (energized configuration of the membrane) correspond to the vesicular forms seen in mitochondria of canary heart.

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**Fig. 5**—Diagram showing how the energized state of mitochondria is generated and utilized to do work.

**Fig. 6**—Electron micrographs of beef heart mitochondria in three configurational states: 1A and 1B, nonenergized; 2A and 2B, energized; 3A and 3B, energized-twisted. Osmium-fixed sections.
Now we may return to the question of how the energized states of the mitochondrion can be identified with the different ultrastructural states. If the two are identical, then the generation of the ultrastructural changes should be inhibited by inhibitors of electron transfer when powered by electron transfer, by inhibitors of ATP hydrolysis when powered by ATP, and by uncouplers when powered by either electron transfer or ATP. Furthermore, the ultrastructural form of the energized state should be discharged by reagents which can lead to any of the work performances. Lastly, the speed of the ultrastructural changes should be of the same order of magnitude as the speed of electron transfer in ATP hydrolysis. Experiment has shown that all these predictions of the energy diagram can be verified. In other words, there is an exact correlation between the energized state and the configurational state of the cristal membrane. Thus, we can identify the ultrastructural changes in the membrane with the formation and dissipation of the energized state.

The repeating units of the cristal membrane have a particular geometry in the nonenergized state. It is this geometry of the repeating units that determines the ultrastructural form of the membrane. Suppose that the geometry of each repeating unit were to change in a specified way, e.g., the basepieces would undergo a transition from the cuboid form to a spherical form. What would happen? The whole membrane would undergo a change in configuration to accommodate to the geometric change in each of the repeating units. In other words, a change in geometry of the repeating unit would be reflected in a change in geometry of the membrane itself. Therefore, when changes in geometry of the membrane are observed, such as the changes from tubular to vesicular to zigzag forms, we are dealing not only with gross changes in the membrane but also with the molecular changes in the repeating units which determine the gross changes in the membrane. In other words, the molecular changes in a single repeating unit are magnified enormously because of the interaction and packing of multiple repeating units within a membrane continuum.

The ultrastructural changes arising from the energy cycle can be demonstrated not only in mitochondria but also in other membrane systems. When chloroplasts are illuminated, the internal structure of the membranes is profoundly different than the internal structure of the membranes in the dark. The granae, which are the membranous analogies of the cristae in the chloroplast, contract in the light and expand in the dark. Similar ultrastructural changes can be recognized when retinal rods are illuminated or when the plasma membrane of the red blood corpuscle is energized by ATP or deenergized by discharge of ATP. All the indications are that we are dealing with a universal mechanism of energy conservation in membrane systems—a mechanism whereby the transduction involves configurational changes in the membrane itself. That is to say, the membrane is the transducer. When energized by electron transfer or ATP or light, depending on the membrane, it undergoes an appropriate molecular convulsion. In this convulsed state the energy is trapped and conserved, and in turn there are ways by which this conformational energy can be utilized to do physiological work.

Electron transfer or hydrolysis of ATP triggers the configurational changes in the membrane. Does this mean that oxidative energy is directly transduced into conformational energy? We have good reason to believe that this is a two step transduction. Electron transfer leads to the generation of electrostatic energy by the delivery of two electrons to molecular sites which are very close together. It is then the conformational change compelled by the buildup of electrostatic energy that leads to the transduction of electrostatic energy into conformational energy.

The question has been raised whether enough conformational energy can be packed away to drive the synthesis of ATP. The answer is that there is no limit to the amount of conformational energy that can be stored. The more pertinent question is whether the extent of the configurational change is compatible with the energy that has to be invested in synthesis of ATP from ADP and Pi. Present indications are that there is no basis for worry on that score. The magnitude of the configurational changes is very great—extending over 100 Å within a single repeating unit. But, most important, the exact correspondence between the configurational changes and the energized state effectively rules out the possibility that these changes are not the primary changes underlying the transducing events.

References


Histamine and a Possible Unity of Autonomous Microcirculatory Dilator Responses*

Histamine and Autonomous Dilatation

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Introduction

In two previous papers I have presented a microcirculation-based unified theory of glucocorticoid action (Schayer, 1964, 1967). To link the microcirculation to the major effects of these hormones requires the reasonable postulate that autonomous dilator responses result from a well-defined intrinsic mechanism, not from haphazard formation of "dilator metabolites" in other tissues.

In this paper I will try to show how the proposed intrinsic dilator mechanism may, with due allowance for a variety of modifying factors, underlie the dilator phases of reactive hyperemia, post-exercise hyperemia, hyperemia due to local warmth, autoregulation, vasomotion, inflammation, and shock.

These ideas are based on histamine studies (Schayer, 1962, 1963, 1966). However, since there is much misunderstanding about histamine, and since the theory can be largely developed without need to identify the dilator, this paper will be presented in two parts. First, interpretation of the above phenomena in terms of an intrinsic dilator mechanism will be attempted. Second, evidence supporting histamine as the dilator will be given.

Requirements for an Intrinsic Dilator Mechanism

The theory requires that the dilator be continuously produced within microvascular smooth muscle cells by an inducible enzyme system, and that it act primarily on intracellular "intrinsic" receptors.

It is obvious that the microcirculation requires means for adaptation; this may be accomplished through alteration of enzyme activities. An intrinsic site of formation and action is supported by repeated failure to find dilator activity in fluids from dilated tissues, and by the inability of any blood-borne substance to mimic natural dilator phenomena (Alexander, 1963; Barcroft, 1963; Folkow, 1949, 1964; Hilton, 1962; Zweifach, 1953).

Normal Distribution of Intrinsic Dilator Molecules

If a dilator were continuously synthesized within microvascular smooth muscle cells, it would be distributed into three distinct categories. (1) Intracellular: Some molecules would remain free in the cytoplasm of the smooth muscle cells. Since intrinsic receptors are stimulated, the intracellular concentration of dilator would determine the magnitude of the dilator action. (2) Loosely Bound: As dilator molecules diffuse from the cell, some are loosely bound in the cell wall. (3) Extracellular: Dilator molecules reaching the lumen of the vessel will be washed away when blood is flowing, or accumulate if flow is blocked. Dilator molecules in the blood stream, because of dilution or inactivation, are of no further significance.

The autonomous microcirculatory phenomena listed in the Introduction may all relate to this distribution of dilator, or to modifications of it.

Reactive Hyperemia

When blood flow is mechanically blocked, dilator molecules accumulate extracellularly. There follows a gradual increase in dilator concentration—first, in the cell wall, then intracellularly, and, finally, at intrinsic receptor sites. When the obstruction to flow is removed, muscle immediately relaxes to a degree roughly proportional to the time of occlusion. As extracellular dilator is washed away, the intracellular concentration gradually drops to normal.

Interpretation of a number of key experiments relating to reactive hyperemia is shown in Table 1.

Vasomotion

This periodic opening and closing of precapillary sphincters, said

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* Supported by USPHS Grant AM 10155.
to provide the most precise adjustment of nutritive blood flow, may arise as follows: In the sphincter of a closed capillary, dilator accumulates until relaxation occurs and blood flows. As extracellular dilator molecules wash away, the intracellular concentration gradually decreases. When constrictor forces (intrinsic “tone force” plus circulating constrictors) again predominate, the sphincter closes and the cycle is complete.

The process of vasomotion can adjust to environmental requirements through an adaptive resetting of the rate of intrinsic dilator synthesis.

**Post-Exercise Hyperemia**

The rapid production of heat in working skeletal muscle causes a local increase in tissue temperature. Intrinsic dilator production is immediately increased as a result of the temperature effect on enzymes. Precapillary sphincters immediately open, thus initiating a “conducted vasodilatation” of arterioles and arteries (Hilton, 1962). Presumably, moderate warming of a tissue by any means could have a similar effect; on the other hand, moderate cooling, by reducing intrinsic dilator production, could lead to the observed vasoconstriction.

**Autoregulation**

In an isolated perfused tissue, a moderate increase in perfusion pressure may increase flow through precapillaries, expedite washout of extracellular dilator, reduce the intracellular concentration, cause sphincters to close more rapidly than they normally would, and thus increase resistance to flow.

Conversely, a drop in perfusion pressure, by reducing the rate of dilator washout, would permit

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>Observation</strong></td>
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<tr>
<td><strong>Comment</strong></td>
</tr>
<tr>
<td>1. In isolated gastrocnemius of cat, 30 seconds of artery occlusion and 30 seconds of maximal exercise gave approximately the same increase in flow. However, after ischemia, flow subsided more quickly (Hilton, 1953).</td>
</tr>
<tr>
<td>1. In both cases, removal of excess dilator would depend on diffusion from cell. However, after exercise, the rate of dilator synthesis remains elevated until muscle temperature returns to normal.</td>
</tr>
<tr>
<td>2. Reactive hyperemia in skeletal muscle is soon lost during perfusion with saline (Folkow and Lofving, 1956).</td>
</tr>
<tr>
<td>2. Production of an intrinsic dilator would be reduced as substrate and co-factors were removed.</td>
</tr>
<tr>
<td>3. The longer the period of circulatory arrest, the greater the subsequent hyperemia. The increase is mainly in duration of high flows, the peak value being relatively little increased (Patterson and Whelan, 1955).</td>
</tr>
<tr>
<td>3. Accumulation of intrinsic dilator should relate to time of occlusion. After the concentration required to cause maximal dilatation is reached, further accumulation should, following release, prolong the period of high flow.</td>
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<tr>
<td>4. Reactive hyperemia is most readily demonstrated when a limb is warm.</td>
</tr>
<tr>
<td>4. Dilator synthesis is temperature dependent, and accumulation should occur more rapidly in a warm tissue.</td>
</tr>
<tr>
<td>5. Reactive hyperemia is reduced if forearm is packed with blood during period of arrest (Duff, Patterson, and Whelan, 1955).</td>
</tr>
<tr>
<td>5. Packing would provide additional blood into which the dilator could diffuse; intracellular accumulation would be reduced.</td>
</tr>
<tr>
<td>6. In reactive hyperemia in the human leg, the rate of return of flow to initial levels was exponential (Dornhorst and Whelan, 1953).</td>
</tr>
<tr>
<td>6. The rate of loss of accumulated intrinsic dilator molecules should be roughly proportional to the number remaining and, therefore, exponential.</td>
</tr>
<tr>
<td>7. From studying effect of reduced arterial pressure on reactive hyperemia and post-exercise hyperemia, Dornhorst and Whelan (1953) concluded that in both cases the vasodilation could be due to an intracellular metabolite, the removal of which from the vessel wall is limited more critically by its diffusion gradient than by the rate of blood flow through the tissue lumen.</td>
</tr>
<tr>
<td>7. The interpretation of Dornhorst and Whelan indicates that an intrinsic dilator best explains the findings of these experiments.</td>
</tr>
<tr>
<td>8. Accumulated intrinsic dilator molecules can presumably diffuse from smooth muscle cells and be washed away by normal blood flows within five minutes.</td>
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</table>

8. In the forearm, after a five-minute period of arrest, circulation was released, but flow kept from rising above the resting level for an additional five minutes by compressing the brachial artery. There was no reactive hyperemia when the artery was released (Blair, Glover, and Roddie, 1961).
sphincters to remain open for a longer than normal period and thus reduce resistance to flow.

**Slowly Developing Dilator Responses**

If the mechanism for intrinsic dilator production is adaptive and is normally required for coping with minor, everyday, environmental changes, then a marked increase in production, caused by drastic local or systemic stimuli, could lead to the slowly developing microvascular dilatation observed in inflammation and shock, respectively.

Many authors have emphasized the similarities between inflammation and shock in this respect (Lewis, 1927; Moon, 1938). According to Zweifach (1961), the development of shock seems to involve progressive activation of a mechanism primarily concerned with local blood flow.

As evidence that microvascular opening in inflammation and shock may be exaggerated manifestations of the normal intrinsic dilator mechanism, I cite the ability of this concept to provide a reasonable unification of glucocorticoid effects (Schayer, 1964a, 1967). If these hormones function by moderating the action of the microcirculatory dilator, their vital stress role and their anti-inflammatory effect could relate to antagonism of the increased dilator influence in stress and inflammation; the metabolic effects of glucocorticoids could be derived from suppression of the normal dilator influence in vasomotion. The microcirculatory effect of glucocorticoids is their earliest known action; it is a tendency to potentiate effects of vasoconstrictors. The glucocorticoid-intrinsic dilator relationship will be mentioned in a later section.

In inflammation, endothelial changes also occur; this fact causes no difficulties in interpretation, provided that histamine is the intrinsic dilator (Schayer, 1964b).

**Other Factors in Microcirculatory Dilatation**

Numerous substances or conditions have been proposed to account for opening of small vessels in vasomotion, hyperemia, autoregulation, inflammation, and shock. It is not denied that some may be of significance, particularly in brain, heart and kidney. However, preoccupation with a variety of mechanisms seems to have led to the unsatisfactory conclusion that there is no process inherent within microvascular smooth muscle cells which is an obligatory participant in their response to every stimulus. I believe this process involves continuous production of traces of histamine, catalyzed by an inducible, environment-responsive form of histidine decarboxylase. Since many pitfalls may be encountered in the experimental testing of this concept, the next section will be devoted to some of them.

**Comments on Experimental Testing of the Histamine-Microcirculation Theory**

Histamine metabolism is a very complex field whose facts are often inaccessible to available experimental procedures. It is obvious that, if experimentation on histamine led to unequivocal results, it should not have required 50 years to find a reasonable physiological role.

The complexities of the field may be illustrated by considering the significance of quantitative analyses for histamine.

The histamine content of a tissue is a composite value which includes some or all of the following: (a) histamine ingested in the diet; (b) histamine formed in the intestine by bacteria and then absorbed; (c) histamine formed by another tissue, e.g., stomach, which produces relatively large amounts of histamine concerned with gastric secretion; (d) histamine formed locally in mast cells and bound in them, in inactive form, in enormous concentrations; (e) histamine released from mast cells; (f) histamine associated with "non-mast cell" binding sites; (g) histamine of microvascular origin which is "on its way out"; and (h) the relatively minute quantities of histamine of microvascular origin still in a physiologically strategic position. Obviously, there is no simple means of measuring (h) in the presence of the other pools, particularly when concentrations fluctuate in accordance with many factors, often poorly defined. Plasma histamine assays also give composite values which are often meaningless or misleading.

Measurements of histidine decarboxylase activity are preferable, but here, too, there are problems. Histidine decarboxylase is found not only in microvascular cells but also in mast cells, stomach, and in certain specialized cells; each may vary in activity in response to its own specific stimuli and tend to obscure changes in microvascular histidine decarboxylase activity. Other difficulties in evaluating the physiological role of histamine have been presented elsewhere (Schayer, 1963, 1966).

For the most part, my findings on histamine have been confirmed in other laboratories (Graham, Kahlson and Rosengren, 1964; Graham and Schild, 1967; Johansson and Wetterqvist, 1963; Kahlson and Rosengren, 1964, 1968; Kahlson, Rosengren and Thunberg, 1966; Pearlm and Waton, 1966). The single exception is experiments reported by Burton Altura (Altura and Zweifach, 1965a, b; 1967); he feels that some results are compatible with the theory, while others are not. A detailed discussion of these experiments would require too much space, but I am confident that Altura's "negative" findings can be readily explained. Some of his experiments are too long and too complicated for clear interpretation. In others, histamine levels of tissue determined in other lab-
Histamine AND AUTONOMOUS DILATATION

oratories under different conditions were used for evaluation. Still others are based on a misinterpretation of the significance of the theory.

Experimental evidence and arguments, which I believe provide important support for the histamine concept, are listed in the next section.

Evidence Supporting Histamine as an Intrinsic Microcirculatory Dilator

Ability of Histamine to Mimic Natural Microcirculatory Dilation

Histamine dilates microvascular smooth muscle; at higher concentrations it affects endothelial cells. It also can initiate reflex dilatation of arterioles. If histamine were formed within these cells, there is no evident reason why it could not underlie the phenomena under discussion.

Adaptive Nature of Histamine Formation

It is now known that adaptation often involves induction of enzymes in cell types which require them. Histidine decarboxylase is inductible to activity many times the normal level but, under certain circumstances, can be reduced to subnormal levels; its activity is clearly responsive to changes in internal and external environment.

Vascular Locus of Histamine Formation

Histidine decarboxylase is present in arteries and veins and can be activated in them (Kahlson et al., 1966; Schayer, 1962). These vessels contain no significant number of cells other than smooth muscle and endothelium. Further, the inducible form of histidine decarboxylase has been found in all tested tissues of the commonly studied species. This widespread distribution, a rigorous requirement for a microvascular regulatory mechanism, has not been shown for any other inducible enzyme.

Autonomy of Histamine Production

Small vessels can dilate due to a local mechanism; histidine decarboxylase activation can also be local. Neither process requires any known nervous or endocrine mechanism or the presence of any dispensible tissue.

Time Course of Increased Histamine Production

Following a stimulus, local or systemic, histidine decarboxylase undergoes gradual activation, becoming first detectable in roughly 30 to 60 minutes and reaching near-maximum activity in three to four hours. The duration of the activated state depends on the persistence of the stimulus; activity may return to near normal in 12 to 24 hours (as after injection of catecholamines) or may remain elevated for at least ten days, the longest period tested (in turpentine-injected rat paws). The rate of activation is indistinguishable from the rate of development of the delayed phase of inflammation (Schayer, 1963, 1964b; Spector and Willoughby, 1963) and, allowing for constrictor effects of released catecholamines, activation parallels the gradual reopening of the small vessels in shock (Chambers, Zweifach, and Lowenstein, 1944; Schayer, 1961; Zweifach et al., 1957).

Effect of Inhibition of Histidine Decarboxylase Activation

The only drugs known to block activation of histidine decarboxylase are inhibitors of protein synthesis, e.g., puromycin, actidione (cycloheximide), and tenuazonic acid (Shigeura and Gordon, 1963). Actinomycin D, which inhibits synthesis of RNA, and, thus, indirectly blocks activation of most known inducible enzymes, fails to block histidine decarboxylase activation (Schayer, 1968). When these compounds were tested on turpentine inflammation in rat paw (a violent reaction virtually unaffected by cortisol or indomethacin), those drugs which blocked histidine decarboxylase activation also showed an extraordinarily great anti-inflammatory action. Actinomycin D failed to suppress either histidine decarboxylase activation or inflammation; in fact, under certain experimental conditions, it enhanced both processes. Since this drug indirectly blocks activation of many enzymes, the findings are strong evidence for a crucial role of histamine in slowly-developing inflammation.

Histamine and a Unified Theory of Glucocorticoid Action

If it is postulated that the principal target of glucocorticoids is the microvascular smooth muscle cell and that these hormones function to reduce the dilator action of histamine, one can derive a simple interpretation for the stress function of glucocorticoids, their anti-inflammatory effect, and their widespread influence on metabolic processes and body economy. This theory seems to be compatible with most of the major in vivo observations on glucocorticoid physiology and pharmacology (Schayer, 1964a, 1967). The histamine-microcirculatory theory may also help clarify the metabolic and developmental effects of thyroid hormone (Schayer, 1969).

Lack of an Alternative to Histamine

If one accepts the existence of an intrinsic microcirculatory dilator, it is necessary to consider the alternatives to histamine. To my knowledge, the only other substance seriously proposed as a "universal" dilator is bradykinin (Rocha e Silva, 1963).

The case for bradykinin is extremely fragile, and I have listed many objections to it (Schayer, 1963). Recently Webster, Skinner, and Powell (1967) have reported experiments which virtually elmi-
nate bradykinin as the dilator of skeletal muscle. The repeated failures to implicate bradykinin can not be attributed to an "intrinsic" site of formation, for the substrate of bradykininogen exists in plasma, not in cells. In contrast, free L-histidine is abundant in all cells and all body fluids.

**Effect of Antihistamines on the Microcirculation**

Topical application of antihistamines to microcirculatory preparations causes constriction of the small vessels; in this test antihistamines behave like catecholamines (Altura and Zweifach, 1965a, b; Conard, 1951; Haley and Andem, 1950; Haley and Harris, 1949). The constrictor effect is produced by antihistamines of many basic structures but is not shown by antiserotonin, anti-acetylcholine, or local anesthetic drugs as groups. The effective concentrations of antihistamines are high, but this is expected for antagonism of intrinsic histamine.

The most recent work in this field has been done by Dr. Altura; he has concluded that antihistamines are direct vasoconstrictors (oral communication, 1968) and cites their contractile effect on uterine (Rocha e Silva, 1955) and bronchiolar (Hawkins, 1955) smooth muscle in vitro as evidence of direct action (Altura and Zweifach, 1965b).

Since I reject this conclusion and regard the constrictor effect of antihistamines as near proof for the reality of microvascular histamine, it is essential to consider these two conflicting views in detail.

First, antihistamines are drugs of various structures which attach to histamine receptors and block virtually all histamine actions in vitro and in vivo; as a group they have no other identity. All antihistamines have side effects, but these vary in kind and degree.

Second, antihistamines have no catecholamine-like actions in vitro (Goodman and Gilman, 1965). Third, since antihistamines are selected for their ability to occupy histamine receptors, it is not surprising that many can release histamine by displacing it from binding sites (Mota and da Silva, 1960). The stimulatory action of antihistamines on uterine and bronchiolar smooth muscle is believed due to release of bound "intrinsic" histamine (Rocha e Silva, 1955; Hawkins, 1955). This stimulatory effect resembles that of histamine, not catecholamines. The anomalous relaxing effect of histamine on rat uterus (Altura and Zweifach, 1965a) mentioned by Altura is due to released catecholamines (Tozzi and Roth, 1967).

In conclusion, Altura's view implies that antihistamines, a large group of variously-structured compounds selected solely for ability to block histamine actions, also invariably possess a histamine-unrelated property of direct vasoconstriction. If true, this would be a most remarkable coincidence. The conservative interpretation suggests that microvascular smooth muscle cells are under the continual dilator influence of histamine produced within them.

**Summary**

Evidence based on recent research on histamine metabolism supports the following views:

(a) Microvascular smooth muscle cells are under the continuous dilator influence of minute quantities of histamine formed within them.

(b) This histamine is produced by action of an inducible form of histidine decarboxylase and acts on intracellular "intrinsic" receptors.

(c) Autonomous dilator activities of the microcirculation, e.g., vasomotion, reactive and post-exercise hyperemia and auto-regulation, may all involve this intrinsic dilator.

(d) Adaptation of the microcirculation to environmental changes may be accomplished, in part, by readjustment of the rate of histamine formation.

(e) Drastic stimuli which cause a marked increase in histamine output, locally or systemically, may lead to the microvascular changes in inflammation and shock, respectively.

(f) The proposed intrinsic dilator mechanism permits a reasonable unification of the major effects of the glucocorticoids in terms of a primary interaction of hormone molecules with microvascular smooth muscle cells.

**References**


The Potability of Sea Water

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On the 2nd of July, 1816, the French frigate, La Méduse, two weeks out of the Isle d'Aix, ran on a reef not far from her destination, the port of St. Louis on the west coast of Africa. Unable to heave the vessel off, the chief officers and some of the crew took to six boats. About 150 passengers, officers, soldiers, and crew were placed on a large raft (Fig. 1), the intention being that the boats should tow it to shore. But of discipline there was none. After a short distance, those in the boats yielded to selfish terror, abandoned the raft, and made their way safely to shore.

The raft, provisioned only with six casks of wine, two casks of water, and some biscuit, floated helplessly. On the second night the soldiers broached a wine cask, becoming wild with delirium and furiously attacking the officers. Many were killed or thrown into the sea. The water, along with most of the wine, was lost. On the third day, only 60 persons remained, and they began to devour the dead left on the raft. On the fourth day, all the carcasses were cast into the sea but one, which was kept to feed those who "the day before had clasped his trembling hands, vowing him eternal friendship." The fifth day saw 30 persons left alive, half of whom were covered with wounds and almost irrational. The 15 who retained some strength and reason, to save their lives and the bit of wine remaining, threw the others overboard.

A raging thirst, redoubled in the day by the beams of a burning sun, consumed them so that they eagerly moistened their parched lips with urine cooled in little tin cups, which were often stolen for their contents. They tried to quench their thirst by drinking sea water, but all these means failed or diminished thirst only to render it more severe a moment later. Their anguish was inexpressible. On the 13th day, they were rescued by a ship sent from St. Louis to search for them—15 long-bearded men, almost naked, bodies and faces disfigured by the scorching sun, limbs excoriated, eyes hollow and almost wild.

Thus was the shipwreck of the Medusa, famous in the annals of the castaway at sea (Savigny and Corrèard, 1817; Wolf, 1958). There are few such accounts of events in northern or southern latitudes, because few live to give them. Cold is the greatest hazard facing men adrift once they are in a lifeboat (Critchley, 1943; McCance et al., 1956). But in warm regions, on enforced voyages in open boats, lack of fresh water becomes increasingly urgent and an important cause of death. So it was in bygone days before the advent of efficiencies in search and communication. An ancient tradition enjoins men not to drink from the ocean, but, sooner or later, many yield in the exigencies of distress and seem to be led ineluctably to earlier disaster.

Thirsty men adrift or lost on desert shores frequently experiment with drinking sea water—especially after the third day—without harm if only small quantities are taken. But such experimentation is difficult to control, and, when in a group, individuals often drink furiously at night. The fleeting relief it affords gives way to an ever more ardent thirst and more copious drinking. This may be succeeded by silence and apathy. The eyes take on a fixed and glassy expression; the breath, an offensive odor. Then delirium begins—first quiet, later violent—and consciousness is gradually lost. At some time froth appears at the corners of bright, cherry-red lips, and even in non-drinkers the tongue may be covered with an annoying white slime. The victim frequently goes overboard in noisy delirium, on occasion by half-reasoned design or desire; or death comes quietly (Wolf, 1958; Critchley, 1943; Ladell, 1943).

In the face of these facts, we shall consider an outwardly absurd idea, namely, the potability of sea water in mammals.

Sea water drinking, called mariposia, is normal for the bony marine fishes. Their gills serve as excretory organs for salt and help to regulate the salinity of their body fluids. Sea birds, some of which remain away from land for years and are known to drink sea water, may be enabled to do so by means of a special nasal gland. At least it is found that, when an excess of salt is present in the body, this gland secretes a fluid even more salty than sea water. It collects at the tip of the beak and is shaken off by a jerk of the head.
It is with certain mammals, marine and other, that serious doubts about mariposia arise. To be sure, some wild goats and cattle drink from the ocean, although whether to replenish salt or water, or both, is not certain. There is little doubt that seals and whales and their kind swallow some sea water, if only inadvertently, when taking their food. The leopard seal of the Antarctic has been observed to drink large quantities of sea water, but under unusual conditions (Brown, 1952). Yet it is difficult to come by unequivocal reports of “normal” elective drinking of sea water by marine mammals. The largest body of evidence consists of negative or moot observations, e.g., that they have not been seen to drink sea water (although the thirsty seal greedily drinks fresh water), or that the stomach contents of a whale feeding on plankton (“krill”) appear “dry,” or that only traces of magnesium and sulfate, which are appreciably concentrated in sea water (Table 1), are found in rectal washings of seals.

It has been estimated from the chemical composition of herring, one food of seals, that there is enough water available—both preformed in the fish and obtainable as a metabolic product of combustion of its protein and fat—to satisfy all the water requirements of these animals (Irving, Fisher and McIntosh, 1935). Even if this were the case for all of their foods (and this has not been established), and they had no need to drink any fluid, it does not follow that seals and other marine mammals do not drink sea water. Yet many biologists have assumed that they do not. Supposedly buttressing this shaky assumption is an old argument of the physiologists, originally invented in connection with the human organism.

A man, they showed, is unable to produce urine much more concentrated in salts than its equivalent of 2% NaCl. Sea water con-
Physiologists denounced claims that sea water is a potable fluid for and vast human experience, many found. The desert rat is one of few available theory and secure in the empirical certitudes of tradition creature possibly able to drink sea mammals that can produce a urine more concentrated in salt than sea water. Here, it seemed, was a water profitably. And so it was produce urine sufficiently saltier for, the reasoning is that sea water drinking should be proscribed for gm of water from the body. There­ fore, the reasoning is that sea water drinking should be proscribed for gm of sea water were drunk, providing an excess of 3.2 gm of “salt” in the body, then, to eliminate that excess in the urine, it would appear that 160 gm of urine must be excreted, making for an undesirable loss of 60 gm of water from the body. Therefore, the reasoning is that sea water drinking should be proscribed for man. Since a seal is not known to produce urine sufficiently saltier than man's to nullify this, a similar physiologic interdiction was seen for it. The desert rat is one of few mammals that can produce a urine more concentrated in salt than sea water. Here, it seemed, was a creature possibly able to drink sea water profitably. And so it was found.

Fortified with a not obviously assailable theory and secure in the empirical certitudes of tradition and vast human experience, many physiologists denounced claims that sea water is a potable fluid for mammals with unexceptional kidneys.

During World War II, a renewed concern over U-boat victims and others set adrift caused physiologists to reexamine their stock of doctrines on mariposia. W. S. S. Ladell, in England, for instance, took hold of a curious and subtle idea, which can be understood by an illustration.

When a man is deprived of water, his urine output becomes reduced, and its concentration of total solute approaches a “maximum.” Most of this is nitrogenous waste such as urea. Relatively little is salt; for simplicity, let us call its concentration zero. For our purposes solute excretion is best described in terms of osmotic units. Let us take the maximum total solute concentration of a man to be 1.2 osm/liter. If salt had been present and maximally concentrated at ca. 2%, its osmotic concentration would have been about half of the total, i.e., approximately 0.60 osm/liter. Salts of sea water (3.5%) have a concentration of approximately 1.0 osm/liter, a value greater than can be attained by salts in human urine.

The key to Ladell's concept is that, even when a man is deprived of water, his kidneys continue to excrete. If he produces 0.40 liter of maximally concentrated urine per day, his total solute excretion is 0.40 × 1.2 or 0.48 osm/day. If he takes in and excretes an extra 0.48 osm/day in the form of salt, his total solute excretion becomes 0.96 osm/day. Keeping to its maximum concentration, his urine volume would increase to 0.80 liter per day to accommodate the extra salt. This constitutes an undesirable loss of an extra 0.40 liter per day of urinary fluid. However, if this extra salt had been taken as sea water, it would have meant taking 0.48 liter per day of sea water. This fluid intake exceeds the 0.40 liter per day loss of urine conditioned by the salt by 0.08 liter per day. It therefore provides, relatively, a small net gain of fluid to the body. All extra salt would be eliminated, and the urinary salt concentration would be .48/.80 or 0.60 osm/liter, a value not exceeding the concentrating power of the kidney for salt.

This in essence is the theory of “osmotic space” (Fig. 2 and 3). A relatively salt-free, nitrogen-obligated volume of urine accommodates salt which is to be excreted; and a virtually nitrogen-free, salt-obligated increment of urinary volume accommodates nitrogen. Both types of solute are excreted in accord with restrictions imposed by the limited capacities of the kidney to concentrate salt and total solute (Wolf, 1958).

Unfortunately Ladell's experiments to test the theory in men did not come up to expectations, and his idea was subsequently misinterpreted or ignored. The theory seems essentially valid, however, and its “failure” in man was probably no failure at all. Man is a relatively poor urinary concen-

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### TABLE 1
Surface Composition of “Open Ocean” Water.

Individually, bodies of water vary in total dissolved solids not only among themselves, but at different places, depending on relative evaporation rates, proximity to river mouths, etc. Thus, the Mediterranean near Gibraltar is 3.6%; off Syria, 3.9%. The Gulf of Suez is 4.1%; the Black Sea, generally, 1.8%; the Baltic, 0.7%. For 60 to 120 miles off the mouth of the Amazon River the sea surface concentration may be only 1.0% to 1.4%, but it rises rapidly beyond these distances and is “normal” at 200 miles.

<table>
<thead>
<tr>
<th>Major Constituents of Sea Water* (grams per 100 grams of water)</th>
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<tbody>
<tr>
<td><strong>Positive Ions</strong></td>
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<tr>
<td>Sodium</td>
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<tr>
<td>Magnesium</td>
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<tr>
<td>Calcium</td>
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<td>Potassium</td>
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<td>Strontium</td>
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<td><strong>Sub-total</strong></td>
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<tr>
<td><strong>Negative Ions</strong></td>
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<tr>
<td>Chloride</td>
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<tr>
<td>Sulfate</td>
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<tr>
<td>Bicarbonate</td>
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<tr>
<td>Bromide</td>
</tr>
<tr>
<td>Fluoride</td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
</tr>
</tbody>
</table>

Total 3.4455

* Sea water of this composition has a density of 1.024, a freezing point of -1.87°C, an osmolality of 1.01 osm/liter and an osmotic of .550 mM/liter, making it the osmotic equivalent of 3.2% NaCl (Wolf, 1958, 1966).
trator, and more inclusive calculations than given above suggest indeed that, without fresh water, sea water should not be potable in his species, at least in steady state. When we apply this theory to the cat (Fig. 4), a land relative of the seal and also a carnivore, fish lover, and one of the best urinary concentrators in the animal kingdom, quite different predictions are forthcoming (Wolf et al., 1959).

First, a cat (much as a seal, but not a man) ought to be able to obtain all the water it requires from a diet of various fish, without drinking. Such water, derived both from that already preformed in the fish (let us say, 68%) and from the oxidation of fish protein and fat, is sufficient to cover all losses of water from the urine, lungs, feces, and skin. Second, a cat ought not be able to obtain its full water requirement from this same fish from which a third of the water has previously been removed by drying. These two “predictions” have actually been empirical facts for many years. Third, a cat should be able to obtain its full water requirement from this partly desiccated fish plus specified amounts of sea water, and, if this sea water be disallowed, the cat should die. In another way, it should be able to depend for its survival on an admixture of sea water and water-poor fish, neither of which alone will support it. Fourth, the urinary salt concentration of a cat maintaining itself on sea water need not be as high as the salt concentration of sea water, because the urinary fluid, derived from both food and sea water, exceeds in volume the sea water ingested (Fig. 2 and 3). All of these predictions have been verified experimentally (Wolf et al., 1959).

What does this mean? For one thing, it strongly suggests that we take another look at the question of sea water drinking in marine mammals, untrammeled by the belief that mariposias can profit the water and salt economy of a mam-

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**Fig. 2.—Mechanism for utilization of sea water by a cat or similar carnivore. Osmotic concentration of salts in sea water is taken as 1.00 osm/liter; maximum urinary salt concentration is assumed to be 0.90 osm/liter.**

1. **Water balance (equality of water intake and output) is indicated by scale pointer on 0. Water from food and drink just matches the aqueous requirement for the salt-free diet. End products of metabolism (urea waste, etc.) are in urine, maximally concentrated to 2.50 osm/liter. Extrarenal water represents all fluid loss other than urinary, i.e., from lungs, skin, etc.**

2. **Negative water balance (output exceeds intake), as indicated by scale pointer, and body dehydration are caused by adding 0.05 osm of “dry” salt to the daily diet of (1). In order to excrete this salt load, an extra 0.02 liter of urine must form (total volume, 0.08 liter per day), still maximally concentrated in total solute. Nevertheless, the resulting salt concentration of 0.63 is considerably less than the assumed maximum of 0.90 osm/liter for the animal.**

3. **Instead of adding 0.05 osm of salt “dry,” as in (2), it could have been added as 0.05 liter of sea water, since the concentration of that fluid is 1.00 osm/liter. In this case, both the extra salt and the extra water enter into the urine. By virtue of the latter addition, both salt and total solute are diluted to submaximal concentrations. Being relatively dilute, the urine now contains, in effect, 0.03 liter of “free” water which could be eliminated by despensing with the 0.03 liter of fresh drinking water.**

4. **Thus, without fresh drink, the animal still maintains water and salt balance, but the urine is maximally concentrated, as in (2). In this way three volumes of fresh water requirement would be met by five volumes of sea water, and any part of the fresh water ration could have been replaced (i.e., saved by admixing) by sea water in the same ratio. To the extent that salt is initially present in the food, the available osmotic space for salt in the urine and the permissible intake of sea water are reduced.**
mal only if its urinary salt concentration can exceed that of sea water. For many of these animals it now appears that sea water may be a potable fluid. They may or may not drink it, but it is no longer incumbent upon physiologists to conjure up precious schemes by which, it is imagined, marine mammals must avoid swallowing sea water.

Theory or no, we cannot refrain from considering the claims that the human castaway not only can but should drink sea water when fresh water supplies are exiguous. Some of these claims were made seriously from 1952-1960 and were of an evidential nature (Bombard, 1954; Aury, 1954). Many non-physiologists, unperplexed by theory or doctrine, found them plausible or convincing. In some instances survival policy—the do's and don'ts for those who might be set adrift—and the behavior of castaways were affected by them.

Ignoring special cases where sea water drinking is at least less hazardous, as in the Black Sea with its relatively low salinity (Table 1), we may contemplate three claims.

1. In hot climates much salt is lost through sweating; it should be replaced by drinking sea water. This is a more complicated proposition than meets the eye. The simplest argument against it is that sweat is a rather dilute salt solution, say, 0.2% Its removal from the body, whose fluids contain about 0.9%, therefore tends to concentrate salt in the residual body fluid and engender or exacerbate thirst. Addition of 3.5% salt in the form of sea water should hardly constitute logical therapy. Nevertheless, it is well known that even excessive drinking of plain water in a hot environment may not assuage thirst, whereas the addition of some salt to it—20% to 40% of sea water, as Thor Heyerdahl reported on the *Kon-Tiki* voyage—not only relieves thirst, but actually reduces inroads on the fresh water supply. One neutralizes the force of this point in recognizing that it is only apparently and not actually germane. It is relevant only where fresh water supplies are luxurious, and, thus, does not concern our problem.

2. Ladell, with a large experience in human salt and water metabolism, has soberly presented the view that, if chances of being picked up at all depended on keeping fit and alert for the first week, it might be well to drink some sea water, no more than 250 cc/day, whose effect might be to stave off disabling circulatory failure. If chances of rescue depended on remaining alive for the maximum length of time, he would avoid sea water. Admittedly this is an "iffy" matter, special and unsettled.

3. It has been contended categorically that one can live upon

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Fig. 3—Theoretic utilization of sea water by man. These diagrams parallel those of Figure 2. Major differences are that maximal urinary concentration of total solute in man is only 1.2 osm/liter; of salt, 0.60 osm/liter. Because of his relatively low urinary concentrating ability, man is unable to employ his urinary osmotic space as effectively as the carnivore. Of his fresh water requirement, indicated as 0.90 liter in (1), no more than 0.10 liter could theoretically be replaced by 0.60 liter of sea water, as in (4), with maintenance of water and salt balances. Even this modest possibility has not yet been proved practicable.

No dehydrated animal can improve its water balance by drinking its own urine. Since newly forming urine is always maximally concentrated in total solute, there is no available osmotic space left which could accommodate more of the same solute, and no "free" water can be obtained.

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A. V. WOLF
the provision of the oceanic environment. On May 25, 1952, the French physician, Alain Bombard, to test this conviction, set out with a companion from Monte Carlo, in a small dinghy appropriately called l’Héritique. During an 18-day journey which took them to Minorca, they drank sea water, fish juice (pressed from the flesh of sea perch in a fruit press), and also the pinto of fresh water condensed on the bottom of the boat at night. The raft was shipped to Tangier, from whence Bombard continued his adventure alone, drifting to Casablanca and the Canary Islands. On October 19 he left Las Palmas and for 65 days floated across the Atlantic to Barbados. He subsisted on fish, fish juice, rain water, and some sea water. “...I got there,” he wrote, to the consternation of orthodox physiologists (Bombard, 1954). “I had conquered the menace of thirst at sea.”

Scientifically, Bombard’s achievement is dimmed by the fact that it is impossible to ascertain from his account exactly what and how much he consumed, so that his views remain generally unproved. Neither have they been disproved experimentally, but that is hardly remarkable. On a major point, no real contact has ever been made between those professional physiologists who assert that sea water can never benefit a dehydrated man, and a once pro-Bombard faction which recommended that sea water be taken early, before dehydration sets in, if it is not to be dangerous. This is a complicated issue which cannot be treated further here.

So far as is known, man is among the least adapted of the mammals for physiologic mariposia. Whatever else may be said, and it should be said so that there will be no misapprehension on this important question, it must be stated that no professional physiologist can yet advise the castaway who is at sea or on desert shore, and short of fresh water to drink sea water in order to sustain.* Is there no more? Must we assent to the poet’s “Water, water everywhere, nor any drop to drink” and shut the gates of hope?

There remains one curious question—almost a riddle—connected with sea water drinking: if a castaway at sea has a limited supply of fresh water, is he better off to use it alone or to admit it with some volume of sea water, thereby diluting the sea water and augmenting his total supply of potable fluid? Experimentally this is most difficult to resolve, and various answers have been given on conceptual grounds. The theory of osmotic space suggests that it should be possible to reduce (but not supplant) the fresh water requirement—even of a man—by admixing, but much less effectively in man than in a carnivore (Fig. 2 and 3). However, the actual mixing ratios to use, the permissible intakes of sea water, the degrees of preexisting dehydration and starvation, the mean air temperature (as this affects sweating), and the kind of food (e.g., fish and/or fish juice) available, are considerations which, by their complexity, conspire to preclude solution by theory alone.

But the theory of osmotic space enlarges our perspective and should lead to the design of further experimental tests with some promise of new insights. After all, the prac-

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* In the report prepared on this subject for the World Health Organization (1962), F. W. Baskerville, J. Fabre, H. Laborit, R. A. McCance and A. V. Wolf listed six points of advice to those who may have to abandon ship:

(1) Unless you are in charge of a party, do as you are told. Try to remain cheerful. Discipline and morale count for more than anything else.

(2) If you have a remedy for seasickness, take it.

(3) If the temperature is low, your immediate and most dangerous enemy will be cold, so put on as many woollen clothes as you can. They will help keep you warm in the water or on a covered raft, and even if you are fully clothed your life-jacket will always keep you afloat.

(4) If the temperature is high, avoid sunburn, keep yourself as much as possible in the shade, and keep your clothes moist to reduce sweating and so conserve body water.

(5) Drink no water for the first 24 hours you are adrift. Then take 500 ml (a pint) of fresh water daily until supplies run low, thereafter 100 ml until the water is finished.

(6) Never drink sea water. Never mix sea with fresh water if fresh water is in short supply. Sea water has been used to moisten the mouth, but the temptation to swallow it may be irresistible and it is better not to use it for this purpose. Never drink urine.

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Fig. 4—A terrestrial and an aquatic carnivore, both fish lovers. The cat can profitably drink sea water. Does the seal?
The critical issue for man is not whether a castaway, like a cat, can maintain himself indefinitely on sea water, but whether he can use it to prolong his survival.

To thereby gain an extra day would be to win an extra day toward rescue; an extra day in which rain might fall; or just an extra day.

References


The Use of a Computer in the Diagnosis of Intracranial Tumours

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Experiments in the use of a computer as an aid to diagnosis of intracranial tumours have been started at St. Bartholomew's Hospital in collaboration with The City University. The computer can estimate the probability that a patient has any given type of tumour by comparing the results of tests with those obtained in previous patients whose diagnoses have been established. The computer also determines which is the best investigation, from a statistical point of view, to perform next on the patient in order to confirm the diagnosis.

Literature

Korein, Kricheff, and their co-workers (1965, 1966) have described a means of coding and recording information contained in x-ray reports of neurological patients which does not require changing the information into a code of numbers. They also refer to much useful background work by themselves and others. They now have a considerable store of data, but have not gone far in using this method for prospective diagnosis.

The mathematical and statistical backgrounds for such diagnostic attempts were reviewed by Boyle et al. (1966) in their report of a study on the use of a computer in differential diagnosis between simple goitre, Hashimoto's disease and thyroid cancer. Though Boyle's work was concerned with much more limited data than that required in the diagnosis of cerebral tumours, the theory upon which both his and the work at St. Bartholomew's Hospital and The City University rests is the same and has been covered in papers by Jeffreys (1961), Warner et al. (1961), Kendall and Stuart (1963), and Bailey (1965). His approach has given practical and accurate results. Lodwick (1966) has set down some of the steps required in constructing a model for radiological diagnosis of bone tumours.

Program

Eight physical processes are considered. Each process—plain film or carotid angiography, for instance—corresponds to a comprehensive test, each test itself being divided into basic tests. These total about 400. All the basic tests are individual, defined radiological signs. Plain x-ray examination, for example, provides a total of 88 basic tests, each of which must be considered and then recorded positive or unreadable. Basic tests which are negative are not recorded on the "report form."

Carotid angiography, the second of the comprehensive tests, consists of 68 basic tests. The vast majority of these, again, are small individual signs, but a few of them are of a pantechnicon nature and have a slightly different role in the collection and classification of material.

In the disease classification there are about 172 different entries, this being a topographic as well as a pathological index. There are in all only 19 pathological types. In order to obtain some assistance from clinical signs, the patients are first divided into three groups according to nonradiological evidence. These groups are: (1) perisellar tumours; (2) supratentorial metasellar tumours; and (3) juxta- and infra-tentorial tumours. This simple breakdown is generally accurate and promises greater diagnostic value from individual radiological signs.

The file of information concerning past patients is held on magnetic tape. This consists of the number of patients with each type of tumour on whom each basic test was made and the number that had positive results.

Weighting

Statistical methods of diagnosis have certain limitations. These arise chiefly from the fact that the computer is concerned with the quantities rather than the quality of each basic test. Such limitations may be mitigated by a system of weighting basic tests so that one may be made more important than another.

1. In applying the first statistical model to the diagnosis of new cases, it was at once obvious that, even in Group 1, where most data had been accumulated, the differences in probability separating different diagnoses were very small indeed. An examination of the predictions revealed that this was largely due to the fact that negative results counted equally with
positive results and, of course, far outnumbered them.

Accordingly, it was decided to weight each positive by a factor of 100 as against each negative, thus increasing the effectiveness of positive findings in making a diagnosis. The immediate result of this single first step in weighting was a considerable increase in diagnostic accuracy.

There are other reasons for weighting and different ways of doing it. Two more stages are proposed.

2. Some basic tests, by their nature, must be more significant than others. They are the tests which show the tumour directly, as opposed to those due to secondary displacements of more distant structures. Certain more significant basic tests are therefore given an extra weight. The actual weight to be assigned to these more significant basic tests is now in the process of being calculated.

3. A distinction may be drawn between weighting that is due to the inherent importance of a sign, such as already described, and significance, which may appear unexpectedly due to the frequency with which a distant sign occurs. Because the calculation by the computer upon which a diagnosis is made is a sum of signs, it would be valuable to give extra weight to any sign which appears frequently and exclusively with a particular disease. Such signs will probably not be included among those derived from Stage 2.

The accuracy of a particular basic test in making a diagnosis of a particular disease should be in some way proportional to its exclusiveness to that disease. It should also be proportional to the frequency with which the sign occurs in that disease (due allowance having been made for the number of cases).

Method of Working

A very simple, duplicated form has been designed. One such form is used for each patient, and the patient is identified at the top by hospital and registry numbers. A patient's diagnosis, when known, is recorded by the code 1, 2, or 3 for supratentorial suprasellar, supratentorial metasellar, and juxta- or infra-tentorial tumours, and, thereafter, by the number which signifies the exact diagnosis. When a new patient is to be assessed, only the clinical group 1, 2, or 3 is put at the top.

The rest of the form consists of divisions, two for each type of examination (here known as Comprehensive Tests 1–8). In one division are written the numbers representing positive basic tests and, in the other, the numbers representing those basic tests which, for one reason or another, have been unrecordable. Unrecordable tests result chiefly from technical failures. The failure of the posterior communicating artery to fill at carotid angiography is one such example.

When each form has been completed, it contains anything from, let us say, 6 to 25 numbers indicating positive observations at plain x-ray and whatever contrast examinations have been completed.

In the computer department of The City University this information is transferred to punch cards. The subsequent operations have already been described up to the point at which an answer is obtained from the computer to the two questions: 1) What is the diagnosis? and 2) What investigation should be performed next in order to confirm this diagnosis?

The answer to the first question is presented as a list, with a figure against each diagnosis indicating probability. Some types of investigation may be inadvisable clinically—for instance, pneumo-encephalography in the presence of raised intracranial pressure. A second choice of investigation is therefore given.

Results

Since completing Stage 1 of the weighting (the operation by which positive signs are given a weight of 100 against negative signs which have a weight of one), the tests on seven new patients have been processed. Five of these patients were in Group 1; two were in Group 2.

The predicted diagnosis was completely correct in five cases and was either a near miss or partly correct in the other two. These results, though far too few to be of real significance, are very encouraging.

Discussion

It may be valuable to repeat certain generalisations about computer-assisted diagnoses.

1. The computer in no way replaces the observer. Each sign in the list must be thought about and assessed as positive, negative or unreadable, and the definition of all the signs must be clear in the mind of the radiologist. This in itself demands a clarification of thought which should go a long way toward improving interpretation.

2. The choice of signs to put in the program in the first instance is made on the basis of previous experience; but it is possible to supplement or subtract from them. In designing the program, an attempt was made to include everything that the radiologist had found useful in the past, while at the same time leaving out not only what was obviously an alternative way of expressing the same anatomical deformity, but also what seemed indefinable.

The list of basic tests will require additions from time to time. It contains almost all that I have found valuable in diagnosis of cerebral tumours without the help of a computer; but without doubt there are many other signs to be elicited, some of them already of established...
value in the hands of other neuroradiologists. It is important, however, to include only that which is reasonably easy to define. Measurements would have been ideal, and yet the use of actual measurements in neuroradiology is disappointing, for the criteria of normality are so wide. The use of a computer does not provide a shortcut. It is only the means towards a more sophisticated appraisal of observations already made.

3. Because information about the margins of an intracranial tumour is so often inadequate, the computer program does not attempt an estimate of size, but does record the fact that the actual margin of the tumour has been determined and by which method of investigation.

4. By its nature, this method cannot recognise the relative incidence of diseases in the general population—at least until a large amount of material has been accumulated and many patients have been investigated.

If the signs in a new case fit two diseases well, though neither perfectly, one of the diseases being rare and one common, the computer will not at present take this factor into account in expressing the diagnostic probability.

In order to manage such patients, the clinician needs to know the answers to two questions. On the basis of signs or symptoms alone: 1) What are the likely diagnoses? 2) What is their probability? Furthermore, he needs to ask: How would the relative incidence of these diseases alter the answers to the preceding questions? Discussion up to now has dealt with the questions of diagnoses and probability. Many more patients must be assessed before the third question can be answered.

Retrospective review of the neuroradiologists' index up to 1964 has given some statistics of groups of diseases falling into the scheme of this study, which, without being detailed enough to provide a full pathological diagnosis, may be of some assistance.

References


Potential Applications of Lasers in Ophthalmology*

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Shortly after Maiman successfully produced the first working model of the ruby laser in 1960, lasers were employed in the field of ophthalmology. Ophthalmology may, therefore, logically lay claim to having introduced this ingenious device as a therapeutic modality into the medical armamentarium. Actually, the discipline of ophthalmology has for almost a century experimented with the idea of using high intensity visible light for the treatment of retinal pathology. This idea became practical with the epochal work of Meyer-Schwickerath (1959) and Littmann (1957) who developed the well-known Zeiss light coagulator. The laser, therefore, may be considered simply another energy source in light coagulation, a light source which, in some instances, may be found superior to the xenon arc and, in other instances, inferior.

The rapid progress of laser development requires constant re-evaluation of its usefulness in the field of medicine and, in particular, the field of ophthalmology.

From the great number of existing lasers today, whether gaseous, liquid or solid state, only five are probably of ophthalmological interest at present. In regard to pulsed lasers, i.e., those emitting light within millisecond ranges, the ruby and neodymium lasers must be looked at critically, while in the CW (continuous wave), the He-Ne (helium-neon) and argon gas lasers are of importance. Special attention should be given to the YAG-Nd (neodymium-doped, yttrium-aluminum-garnet) laser for reasons outlined below.

The advantages, disadvantages, as well as the potentials of these lasers, will now briefly be discussed and compared with the xenon arc as a light source (Fig. 1).

Ruby Laser (694.3 nm)

At present only the ruby laser has been used clinically on a more or less routine basis and here only in the normal pulsed mode, i.e., a pulse duration approximately 200 µsec to a few milliseconds. Extremely short exposure times of nanosecond (10^-9 sec) or even picosecond ranges (10^-12 sec) can physically be achieved; however, they have no place clinically and may be extremely hazardous for the ocular fundus. At these very short exposure times high energies are delivered so fast that effects other than those caused by heat generation take place. For instance, shock waves may be produced which may cause explosion-like disruptions of biological structures with intracocular hemorrhages and retinal detachment.

The principal advantage of the ruby laser clinically is the emitted monochromatic dark red light. This spectral quality prevents photophobia, and the short exposure time allows for ocular treatment without anesthesia in most cases and treatment of areas close to the macula.

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with less of a hazard. Some of the disadvantages, however, have to do with the same two factors which are also classed as advantages. The red light of the ruby laser is not suitable for vascular lesions of the ocular fundus, since the red blood vessels, aneurysms or vascular tumors reflect the light to a great extent where absorption is needed for effective treatment. In addition, the very short exposure times make it necessary for the intended intensity of the exposure beam to be preset. Once the triggering button is pushed, all the energy impinging on the eye will interact with the exposed ocular structures without further adjustments being made during this exposure time. This fact was responsible for severe overexposures with subretinal, intraretinal, and even preretinal hemorrhages when lasers were first used clinically in ophthalmology. Even today this complicating factor may still be a considerable one where the operator is inexperienced. Another disadvantage of the laser burn is that sharply demarcated coagulation spots produced by lasers are at times less desirable clinically than those with a wider reactive zone, decreasing in intensity toward the periphery of the lesion (Geeraets et al., 1965; Geeraets, 1965).

Neodymium Laser (1060 nm)

A theoretical advantage of this laser lies in the fact that the beam is invisible to the eye. Exposure times correspond to those of the ruby laser. Clinically its great disadvantage in ophthalmology is the high absorption of its beam energy within the ocular media (Geeraets and Berry, 1968). The total amount of energy necessary to produce a chorioretinal lesion comparable to that produced by a ruby laser is five to ten times as great as the energy required with the ruby laser (Geeraets, 1967). Investigations on the effect of neodymium and ruby lasers on non-pigmented and pigmented experimental retinal or choroidal tumors indicated that both light sources failed to completely destroy the tumor masses. Tumor cells continued to show undisturbed growth in cell cultures after maximum exposures to these laser light sources (Unpublished data), and most of the cells appeared also histologically unaltered in morphology. This latter observation was also described by Chan, Guerry, and Geeraets (1963) following treatment with the xenon arc as a light source. High intensity exposures with the neodymium laser or fast repetition of such exposures have led to cataract formation and to extensive biomicroscopically visible vitreous clouding and electrophoretically-demonstrable protein changes in the vitreous (Geeraets, 1966; Berry, Lederman and Geeraets, 1968).

He-Ne Laser (632.8 nm)

This laser, which emits a bright red colored light beam, belongs to the CW gas lasers. Its emission appears more intense to the human eye than does the deep red light of the ruby laser. Its greatest advantage lies in the greater variability of possible exposure times. For the production of chorioretinal lesions, exposure times may be chosen from millisecond ranges up to any desired length, thus combining positive features of the ruby laser and the xenon arc. For long exposure times, however, it would be preferable or necessary in most instances to administer retrobulbar anesthesia.

At present, the greatest disadvantage of this laser is the great length and weight of the instrument required to obtain adequate power output if one wishes to achieve the great range of exposure times. Experimentally this has been solved by delicately counterbalancing the instrument. The use of fiber optics, though decreasing the power output, may reduce this disadvantage.

Argon Laser (Major Output at Wave Lengths 488 nm and 515 nm)

This laser emits numerous wave lengths from the ultraviolet region to the blue-green spectrum with the
latter as the most intense emissions. From a theoretical point of view, this laser has a number of advantages. The transmission of these wave lengths through the ocular media is almost 95\%, and they fall in the region of peak absorption by the retinal pigment epithelium and hemoglobin (Geeraets et al., 1962). The output energy of this laser is greater than that of the He-Ne laser, which means that the exposure times can be chosen by the surgeon to fit the optimal needs of a given situation. As of now the greatest disadvantages of this laser for clinical ophthalmological use are its bulkiness and the high purchase price. Experimentally this laser has given promising results. Exposures are best done under retrobulbar anesthesia unless very short exposure times (ms ranges) are used.

**YAG-Nd Laser (1064 nm)**

Though the primary wave length of this solid-state laser is very close to that of the neodymium laser, the YAG-Nd laser seems to be capable, experimentally, of having sufficient energy for its second harmonic is used, i.e., frequency doubling. This can be achieved by passing the primary laser beam through a barium-sodium-niobate crystal (B,Na,NbO₃). In this way the wave length obtained is 532 nm. The exit energy at the 532 nm wave length seems, experimentally, to be sufficiently great to give a flexibility in exposure time selection even greater than that described for the He-Ne and argon lasers. This laser seems to be unique in this respect, since it can be pulse or used in Q-switched fashion similar to the ruby and neodymium lasers as well as on a CW mode similar to most gas lasers.

Its dimensions and weight are significantly less than those of the two gas lasers mentioned above. The emitted wave length of green color would theoretically be somewhat less advantageous than that of the argon laser (about 12\% of the light incident on the cornea is absorbed by the hemoglobin [Geeraets et al., 1962]). However, the other features described lead one to believe that this more recent laser development may present a light source possibly of some potential for use in clinical ophthalmology.

**Xenon High Pressure Light Coagulator (Zeiss—Spectral Range 350-1100 nm)**

This instrument has had universal clinical acceptance with its usefulness documented by the successful treatment of thousands of patients all over the world (Meyerschwickertath, 1959; Guerry, 1968). Its greatest advantage is that of adjustable exposure time. The standard commercially available instrument allows the operator to select exposure times by push-button operation while making it possible to observe the area under treatment as the actual exposure takes place. This permits the operator to terminate the exposure at any time he deems advisable. An optional accessory is a built-in shutter, which allows exposure times down to 20 msec. In most cases retrobulbar anesthesia is advisable.

This factor is really not a disadvantage as has been claimed by some advocates of the ruby laser, for it allows one more easily to manipulate the globe by forceps. This feature is of particular value where the extreme temporal periphery is to be treated or where the globe to be treated is relatively enophthalmic.

A disadvantage claimed by some is that a portion of the emitted spectrum is in the near infrared. Though this spectral range has as high an absorption rate by the ocular media as does the neodymium wave length, one should realize that, in the latter instance, this is the only wave length emitted, while in the xenon light coagulator the greatest spectral portion lies in the visible range with a high transmission through the ocular media up to 95\% (Geeraets et al., 1960, 1962). When properly used, i.e., not too rapid exposure and avoidance of overexposures, this coagulator apparently gives rise to no ill effects attributable to these spectral emission characteristics, a general observation based on more than ten years of experience since its introduction into clinical ophthalmology. If one wishes to eliminate these theoretical disadvantages, a Schott KG III heat-absorbing filter can be inserted within the optical pathway of this coagulator. This eliminates the near infrared beyond 900 nm almost entirely from the exit beam. In some instances, where lesions close to the macula must be treated, shorter exposure times than those obtainable with the Zeiss coagulator would be of advantage. Experimentally this has been achieved by pulsing the xenon high pressure lamp via a capacitor bank (Ham et al., 1963). These short pulses simulate the exposure times of the ruby laser. Broad-base interference filters used with this coagulator also provide a means of comparing the effects of various spectral regions.

**Conclusion**

The continuing evaluation of laser instrumentation is of particular interest to the ophthalmologist. Several lasers now exhibit potential properties which may result in superior clinical instruments in the future.

An important feature of almost all existing lasers, as related to ophthalmology, is the potential hazard of accidental exposure of the eye. This aspect of the laser is certainly as important as its clinical application, and it should be the responsibility of ophthalmologists to work actively to provide recommendations for safety standards and criteria for ocular protection in every field of laser application.
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Mechanisms Controlling the Peripheral Circulation of the Lung with Some Clinical Correlations

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Introduction

Many of my earlier studies on pulmonary morphology employed conventional methods of tissue sectioning and staining. Because of their extreme thinness, tissue sections are often difficult to appreciate as parts of a three-dimensional structure; this is particularly true of the complex lung with its myriad branches and delicate, sponge-like parenchyma. If the lung is permitted to collapse prior to fixation, much distortion occurs; airways, their accompanying vessels, and air spaces are altered in shape and size. Depending upon the fixative solution used and the method by which it is applied, a variable amount of further distortion may occur. Many methods are now available to minimize fixation artifacts and to prepare lungs for various morphometric studies (Krahl, 1956; Blumenthal and Boren, 1959; Pratt and Klugh, 1961; Staub, 1961; Staub and Storey, 1962; Storey and Staub, 1962; Weibel and Vidone, 1961; Weibel, 1963, 1964). Students, especially, but investigators, too, have gained a far better appreciation of lung structure through the study of three-dimensional preparations. Dr. William Snow Miller (1947), among many others, helped us to make the transition from two- to three-dimensional studies through his meticulous and laborious plastic and graphic reconstructions of serially sectioned lungs. Now there are also excellent methods of displaying airways and their accompanying vessels in three dimensions by making plastic injections, followed by acid corrosion (Tompsett, 1956).

Today, as the borderland between structure and function becomes less and less distinct, still other methods are required. Dr. Melvin H. Knisely of The Medical College of South Carolina, the widely acknowledged “Dean of Microcirculation,” impressed upon me quite forcefully the need to study the morphology and physiology of tissues simultaneously; i.e., in vivo, for, as he has often said and written, cells, tissues, and organs live not only in the three dimensions of space, but also in the important and too often neglected dimension of time. A thin, fixed section gives the viewer but a glimpse of a “frozen moment” in a tissue’s long life history, tells little of its past, and nothing whatever of what it might have done at various times in the future.

We can now study virtually every tissue and organ of the body by in vivo techniques (Bourne, 1967). Observation of the living lung, however, has posed special technical problems because of its unique structure and because of the fact that its structure and function are altered profoundly when the chest is opened to expose the lung to view.

In Vivo Studies

In 1961 and 1962 I had the privilege of working for some months in the Cardiopulmonary Laboratory at The University of Colorado Medical Center under the direction of Dr. Giles F. Filley. There I devised a thoracic window which permitted me to make direct observations of the living lung in the closed chest of the rabbit (Krahl et al., 1961; Krahl, 1962, 1963a, b; 1964a, b; 1965a; Bourne, 1967). For the first time I was able to observe normal lung as it lived and breathed, long after any effects of surgical trauma, anesthesia, and other stressful influences had subsided (Krahl, 1962, 1963b, 1964a). Moreover, respiratory gases were transported in a natural manner by the animal’s own thoraco-abdominal bellows mechanism. This prosthesis revealed to me an entirely different organ, a new, dynamic structure which I had never really seen before or even imagined. As a result, I had to begin to learn about the lung all over again.

In some of my publications I have described in detail the design of the thoracic window and the techniques of installing it and have pictured some subpleural alveolar sacs and alveoli with their accompanying vessels which feed the alveolar capillary networks (Krahl,
1962, 1963b, 1964a; Bourne, 1967). The lung is illuminated by oblique, incident light from the focused beam of a Bausch and Lomb six-volt lamp fitted with a heat-filtering glass. Even with the unaided eye, a thoracic window enables one to make interesting and valuable observations on the lung, as I will describe presently. With relatively low magnification one can see and record photographically lung movements, changes in alveolar size and shape, and intravascular phenomena in peripheral pulmonary arterioles. These vessels taper rapidly; hence, they are readily plugged by thrombi or red cell aggregates ("sludge") which are known to form following burns, accidental and surgical trauma, and in a host of diseases (Knisely, 1965). W. H. and M. H. Knisely (1954) have described the catch-trap architecture of these arterioles. The vessels deserve much further experimental, in vivo study of their dynamic responses, in thromboembolism, not only to various gas mixtures at ambient and hyperbaric pressures, but to administration of a variety of vasoactive drugs. The thoracic window technique is recommended as a most useful experimental tool in these and other potentially fruitful investigations.

**Observations**

When I watched the lung through a thoracic window in unanesthetized, nonsedated, lightly restrained rabbits, I sometimes noted that certain polygonal areas (bases of secondary lobules) became a paler pink than those adjacent to them. Later, these took on the bright pink hue of well-perfused lung, or paler areas appeared elsewhere in the field. This suggested that some mechanism was altering the capillary perfusion of the lung on a lobular basis.

Upon sacrificing one of my rabbits, I injected a 1:1 mixture of India ink and physiological saline into the right heart and found that the lung became a mosaic of lobules which were either black, pink, or grayish pink. Following removal of the lungs and fixation by tracheal instillation of Zenker-formol solution (Krahl et al., 1959), I removed blocks of lung tissue containing adjacent ink-stained and ink-free lobules for sectioning. Microscopic study of the adjacent pink and black lobules revealed that the ink-blood mixture had perfused peripheral arterioles in all areas of the lung. However, while ink had filled alveolar capillaries in the black lobules, it had not passed through the last, right-angled, short feeders of the capillary networks in the pink lobules. A careful histologic examination of the origins of the right-angled arteriolar branches showed that they were encircled by smooth muscle cells. These sphincter-like structures were evidently able to regulate the perfusion of nearby capillary beds. Whether they were under sympathetic or parasympathetic (vagal) control remained to be seen.

Recalling that vagal motor fibers induce contraction of smooth muscle of the airways (sympathomimetic drugs are used for dilation), my associates and I surmised that vagal stimulation might also constrict the precapillary arteriolar sphincters in the lung. We, therefore, sectioned the rabbit's right cervical vagus nerve, stimulated it electrically, and then injected the ink-saline mixture. As the last drops of ink entered the right side of the heart, we increased the current in order to induce cardiac arrest. When the vagally stimulated, right lung was removed, it was predominantly pink, whereas the left lung showed a general mottingling, characteristic of ink-injected, normal lungs. Histologic examination of the lungs showed well-perfused alveolar capillaries in the grossly black areas. The ink-blood mixture, however, had not passed through the last, right-angled arterioles leading to alveolar capillaries in the grossly pink areas.

These results suggested that peripheral pulmonary arteriolar dilatation should occur during a period of sympathetic predominance. It seemed likely that if a rabbit were to become so excited that it breathed maximally, then adrenergic influences should overcome the vagus and permit optimal alveolar capillary perfusion. Therefore, rabbits were bunted 100 times in a large cardboard carton requiring vigorous contraction of all their antigravity muscles upon each descent in order to break their fall. When cardiac and respiratory rates seemed maximal, the India ink-saline mixture was injected into the right heart through the chest wall. The lungs, when exposed, were almost entirely blackened by the ink; virtually no pulmonary reserve remained, as evidenced by a few pink, poorly perfused lobules of lung tissue.

Having learned that the vagus, a cholinergic nerve, could markedly reduce flow through alveolar capillaries, we decided to inject a dosage of .01 mg/kg acetylcholine into the right heart and, after an interval of 15 seconds, inject a mixture of India ink, physiological saline, and a few crystals of KCl. When the KCl arrived in the left heart and the coronary arteries, there was a prompt cardiac arrest. This left the ink-blood mixture in the pulmonary vascular units which had been well-perfused at the moment of the last systole. The lungs of rabbits, treated in this way, were predominantly of a pink hue, although a few dusky areas suggested that ink was present somewhere in deeper vessels, having bypassed the peripheral alveolar capillaries.

When, on the other hand, .01 mg/kg of epinephrine was injected into the right heart and followed 15 seconds later by the ink-saline-KCl mixture, the exposed lungs became coal black—that is, maximally perfused.

Repetitions of these experiments
in a series of animals confirmed the results just described. It is evident, therefore, that the precapillary, arteriolar, smooth muscular sphincters of the lung contract upon cholinergic stimulation but dilate with conditions of stress (sympathetic predominance) or after the administration of epinephrine.

Clinical Correlations

Pulmonary Embolism

I have previously discussed the lung as a target organ in thromboembolism (Krahl, 1965b) and emphasized that the rapidly tapering peripheral pulmonary arterioles serve as catch-traps (Knisely and Knisely, 1954) in which even small emboli may easily be impacted.

Clinicians have observed both marked elevation of pulmonary arterial pressure and pulmonary resistance when a small shower of emboli have lodged in the pulmonary vasculature. Now, a few small emboli plugging a small proportion of the thousands of peripheral pulmonary arterioles could not directly account for this increase in pressure. However, if receptors in these vessels were stimulated by the impactation of a few emboli and, thereby, initiated a burst of vagal afferent impulses, then a resultant widespread vagal motor discharge might well close large numbers of precapillary arteriolar sphincters. The vagus nerve contributes both sensory and motor fibers to the pulmonary plexuses; hence, one may envision a vago-vagal neuronal mechanism through which a relatively small shower of emboli to the lung could, reflexively, bring about a widespread shutdown of precapillary arteriolar sphincters. This could account for the observed increase in pulmonary arterial pressure in such cases (see Addenda).

Primary Pulmonary Hypertension

The very use of the term “primary” or “idiopathic” pulmonary hypertension infers that its etiology is obscure. In any fluid-conducting system, be it the plumbing in a house or the vasculature of the human body, a narrowing of the lumens of the conducting tubes requires increased pressure if flow is to remain constant. With time, pulmonary arteries under elevated pressures undergo medial hypertrophy. Once this has occurred, vasodilator substances may no longer be effective. However, if the pulmonary hypertension is, in fact, a consequence of generalized contraction of pulmonary vascular smooth musculature under vagal control, and if the contraction can be attributed to a hyperactive dorsal motor nucleus of the vagus nerve, then one can anticipate a reduction in pulmonary arterial pressure following the administration of antivagal agents. Such puzzling disorders as primary pulmonary hypertension obviously require much further study. I should like to suggest to internists trying to solve such puzzles that the vagus nerve may well be involved. If it is, and the condition is detected in its early stages—that is, prior to medial hypertrophy—it is reasonable to expect antivagal therapy to be effective.

Primary Pulmonary Vascular Obstruction

In recent years, increasing attention has been given to a serious pediatric problem—namely, primary pulmonary vascular obstruction (PPVO). Thus far, the etiology of the disease has not been discovered, and no effective therapy has been found. The victims usually succumb before reaching the age of two years. The disease is characterized by an elevated pulmonary arterial pressure, the cause of which is said to lie at the pulmonary arteriolar level (Thilenius, Nadas, and Jockin, 1965). As mentioned previously the sphincters of peripheral pulmonary arterioles receive their motor innervation from pulmonary branches of the vagus nerve. Preliminary investigations in which we have given intracardiac injections of atropine, followed by an india ink-saline-KCl mixture, have shown that atropine relaxes smooth muscular sphincters of pulmonary arterioles; there is a prompt improvement of alveolar capillary perfusion, as evidenced by a uniform blackening of the lung. In the light of these findings, it is tempting to consider a possible autonomic imbalance in cases of PPVO. Certainly in other organ systems when there is vagal hyperactivity, e.g. gastric ulcers, vagotomy or anti-vagal medication can be of some value. If there is a hyperactivity of the vagus nerve in PPVO, perhaps the administration of atropine or some other anti-vagal drug should be considered as a means of improving peripheral pulmonary blood flow and reducing pulmonary arterial pressure.

Respiratory Distress Syndrome of the Newborn (Pulmonary Hypoperfusion Syndrome)

The preceding information which I have given on the regulation of pulmonary vascular perfusion seems pertinent to the successful management of our “Number-One Baby Killer,” respiratory distress syndrome of the newborn (RDS). Recently, Chu and her associates (1965) have renamed RDS pulmonary hypoperfusion syndrome (PHS). I believe that this new term is an excellent one, for my own observations have convinced me that the basic deficit in RDS or PHS is an inadequate perfusion of pulmonary alveolar capillaries. Henceforth, I shall use the term PHS.

The problem of PHS is comparable to a large, difficult jigsaw puzzle containing many pieces which have been roughly shaped and provided by many basic scientists and clinical investigators, working independently. This, in itself, makes the puzzle difficult to
assemble correctly. The familiar commercial puzzle is simply stamped out by machine and, when reassembled, reconstitutes the entire picture story. However, the PHS puzzle picture which has emerged from the literature of the past 50 years is a confusing montage of many themes, reflecting widely varying opinions regarding the etiology and management of the disease. Its many and distorted pieces make it difficult, indeed, to assemble and view as a meaningful picture.

The pathologist, for whom the hallmark of PHS is the presence of the so-called hyaline membranes in the air spaces of infant lungs, has focused attention upon this piece of the puzzle. Some clinicians have tried in various ways (lavage, enzymes, etc.) to remove the membranes, hoping thereby to improve gaseous diffusion across the air-blood pathway. It should be realized, however, that the hyaline membrane is a post-fixation representation of proteinaceous, fibrinous exudate from pulmonary vessels and is, in reality, a fluid prior to the death of the victim. Nevertheless, some authors have considered the presence of hyaline-like membranes to be the sole cause of death, assuming they were made of some impermeable substance preventing alveolo-capillary gas transfer. Membranes are present only as by-products of capillary hypoxia resulting from hypoperfusion. Even if it were possible, in some safe manner, to remove the membrane-producing material in the infant suffering from PHS, more exudate would promptly leak from the still hypoxic capillaries.

Other scientists, concerned with the infant's cyanosis, have attempted to assist his respiration by intermittent positive pressure breathing (IPPB) with air or with air-oxygen mixtures. Assuming that one could effectively and safely ventilate all of the unstable alveoli of the victim's lungs, it would seem to be of little avail if pulmonary capillaries are not transmitting CO2-laden blood to the alveoli or carrying O2 away to the body's hypoxic tissues. I am convinced by the appearance of specimens in my collection of PHS lungs that excessive use of IPPB has, in some cases, hastened the demise of infants in respiratory distress by producing an overwhelming interstitial pulmonary emphysema. There is good evidence that breathing high concentrations of O2 may actually impair pulmonary alveolar capillary perfusion; the lungs are known to be among the prime target organs in O2 toxicity. A number of writers (Bruns and Shields, 1954; Tran-Dinh-De and Anderson, 1954; Berfenstam, Edlund, and Zettergren, 1958) have reported pulmonary lesions quite like those of PHS in animals exposed to 100% O2 for several days. Potter (1952) noted that all of a group of infants whose lungs showed hyaline membranes had been kept in incubators under atmospheres rich in O2 for some time before death. Tran-Dinh-De and Anderson (1954) reported that O2 poisoning actually produced hyaline membranes in adult guinea pigs and rats. In newborn animals, O2 produced the membranes plus atelectasis. In my own in vivo studies of rabbit lungs, even 15-20 minutes exposure to 100% O2 has been followed by several days of extreme hyperemia in the peripheral vasculature of the lung, with marked engorgement of alveolar capillary networks. Thus, the use of high concentrations of O2 with or without IPPB, may actually compound the problem by diminishing an already scanty alveolar capillary perfusion.

In recent years, pediatricians have administered bicarbonate or various buffers in attempts to correct the metabolic acidosis which often accompanies PHS. The change of pH is another by-product of the underlying capillary hypoperfusion and, while correction of pH is considered helpful by some, it does not appear to modify the ultimate cause of the infant's hypoxia. There is still an inadequate oxygenation of mixed venous blood and an inadequate removal of CO2 while precapillary arterioles remain closed and right-to-left shunting continues through thousands of open arteriovenous anastomoses.

From the relatively vast literature on PHS there has come little agreement on the etiology of the disease or a reliable, uniformly effective method of treating it. For further discussion of this controversial subject and an excellent survey of the recent literature, the works of Silverman (1961) and Avery (1964) are highly recommended.

Through the excellent cooperation of pathologists in Baltimore hospitals, I now have a sizable and well-documented collection of lungs of premature infants who succumbed to PHS. While the so-called hyaline membranes were present in all the lungs of this series and have some diagnostic significance, I have accorded to them only slight importance, as they are only a consequence of alveolar capillary hypoxia and could not be the "sole cause of death," as some believe (Latham, Nesbitt, and Anderson, 1955). Other features of these lungs, seldom mentioned by pediatricians and pathologists, appear to be of far greater importance as guides in solving the PHS puzzle.

1) Of primary significance is the presence in all PHS lungs of a generalized constriction of precapillary arterioles with lumens so markedly or completely occluded as to retard or even halt blood flow through alveolar capillaries. Some of the precapillary vessels, seen in serial, 10µ sections, are present in only one section of a series and have no discernible lumens; thus, in such a state of constriction, they could not possibly have been transmitting red blood cells of 7.5µ diameters to the capillary beds. (Fig. 1 and 2).
V. E. KRAHL

Fig. 1—Salient features in lungs of infants who died of pulmonary hypoperfusion syndrome (PHS). Upper left: Arteriole, cut in cross-section (near center), provides a precapillary arteriole which is too constricted to have carried blood to adjacent parenchyma. Alveoli, retaining original cuboidal epithelium, are only partially expanded. Extravasated blood cells lie above arteriolar sheath; at immediate right is an autonomic nerve twig. H & E, X 114. Upper right: At center, contracted arteriole’s side-branch to parenchyma has no visible lumen and is not seen in adjacent sections of the series; therefore, it was unable to perfuse alveolar capillaries. Note proteinaceous coagulum in air spaces. H & E, X 248. Lower left: Blood-filled arteriole could not have perfused adjacent alveolar capillaries because of constriction of its various side-branches. Note widened lymphatic vessels and accumulation of blood cells in the upper right-hand corner. H & E, X 114. Lower right: Strikingly similar picture in another infant’s lung in which distributing arteriole (off-center) shows four contracted branches. H & E, X 114.

2) There is evidence of hemococoncentration in the relatively wide pulmonary alveolar capillaries, as fluid leakage leaves blood cells tightly packed in these vessels. Potter (1952) is one of the few authors who remarks about the obvious capillary engorgement in lungs of infants who have died of PHS. She states that intense capillary engorgement is responsible for the color and increased weight of the lungs and is one of the most striking findings on histologic examination. On the other hand, Avery (1964) writes that such lungs are not significantly heavier than lungs of most infants at autopsy, although she adds that control data are lacking on lung weights of infants who succumbed to non-pulmonary diseases.

3) Many of the lungs show a spilling of blood cells into air spaces and connective tissue planes from fragile subpleural venules and from alveolar capillaries (Fig. 3). Extravasation of blood cells into the connective tissue sheaths of peripheral pulmonary arterioles may, thus, impair by compression an already diminished flow (Fig. 4). Pulmonary vessels may become exceptionally fragile when they are hypoxic, although there is ample evidence that cerebral vessels may also rupture in PHS (Blystad, 1951; Ambrus et al., 1963). In a series of autopsied infants with proven PHS, Ambrus et al. (1963) reported that 67% had cerebral hemorrhage and 53% had pulmonary or visceral hemorrhages. Avery (1964) suggests that such cerebral hemorrhages may be associated with profound tissue hypoxia, depression of clotting factors, or an elevation of cerebral venous pressure consequent to the vigorous respiratory struggles of the infant. Hutchison (1965), citing Inall et al. (1965), stated that an as yet unexplained finding in their cases was a statistically significant lowering of the hematocrit in babies with respiratory distress syndrome (PHS). I should like to suggest here a
plausible explanation for the observed lowering of the hematocrit. Not only is there a trapping of millions of blood cells in the rapidly tapering pulmonary arterioles (Knisely and Knisely, 1954) proximal to the muscular precapillary sphincters, but there is a stasis of millions more in the engorged capillaries seen in PHS (Potter, 1952) and in filled but non-perfused post-capillary venules. This could, at once, account for the increased weight of the lungs in PHS observed by Potter and the lowered hematocrits observed by Hutchison (1965) and Inall et al. (1965).

4) Postcapillary venules were well filled in my PHS lung series, but the next-larger venules into which they emptied had few or no blood cells in them (Fig. 5). This, I feel, is not an artifactual loss of cells during processing; for cells should then have been lost from all vessels, but were not. Rather, this indicates stasis of blood in the alveolar capillaries and their post-capillary venules. The radiographic studies of Lauweryns (1966, 1968) confirm the present findings of precapillary constriction and venular emptiness. In lungs of PHS infants injected with a barium suspension via the pulmonary arteries, Lauweryns (1966) showed the peripheral pulmonary arterioles as having a pruned or “winter tree” appearance. On the other hand, the opposite lungs, injected with barium via the pulmonary veins, showed a complete filling, giving a “summer tree” appearance (Lauweryns, 1968). The constricted pulmonary precapillary arterioles would not transmit the barium mixture, but the empty, postcapillary venules accepted it readily (Lauweryns, 1968).

5) There is a marked engorgement of all pulmonary lymphatics in PHS. This is rarely noted by those interested in PHS but is a significant finding in lungs of PHS victims (Lauweryns, 1965a, b; Lauweryns, Claessens, and Boussauw, 1968). This filling of lymphatic

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**Fig. 2**—Upper left: Constricted orifice of arteriole’s side-branch prevented perfusion of adjacent alveolar capillaries. H & E, × 248. **Upper right:** Arteriole accompanying the bronchiole (below) gives off a constricted or occluded precapillary arteriole. Note hyaline material at upper left and lymphatic vessel arching over sheath of arteriole. H & E, × 248. **Lower left:** Well-filled distributing arteriole (top) shows a constriction of orifice of its side-branch (note thickened musculature), preventing perfusion of adjacent parenchyma. Note extravasated red blood cells in connective sheath of arteriole. H & E, × 248. **Lower right:** Arteriole, cut longitudinally through its lumen, gives off side-branch (bottom) which is seen in cross-section. Constriction of vessels and protrusion of endothelial cells narrow the lumen to less than the diameter of red cells (above). H & E, × 568.
vessels should not be surprising, for fluid leaks in large quantities not only into alveoli and airways from hypoxic capillaries, but also into the various connective tissue planes and sheaths of the lung. Furthermore, Drinker (1945) has shown in dog experiments that lymph does not flow from cannulated thoracic ducts of animals supported on positive pressure insufflation as it does during normal breathing. The rapid, vigorous, but ineffectual respiratory efforts of the infant suffering from PHS are evidently unable to propel the gathering excess of fluid in the lung through the many valved lymphatic vessels which lie in the subpleural connective tissue and in the plexuses which accompany pulmonary arteries, veins, and bronchi. The effects of higher than normal intrapulmonary pressures upon lymph transport, such as occur in IPPB, certainly deserve much further study. Many of the lungs of PHS victims, as received from pathologists, have engorged networks of subpleural lymphatic vessels which are readily seen with the aid of a hand lens or a dissecting microscope. Upon sectioning, such lungs show a majority of lymphatic vessels distended by a coagulum of proteinaceous fluid in which many blood cells are frequently suspended (Fig. 6).

Figure 7 is intended to re-emphasize some of the dominant features of PHS lungs, such as precapillary arteriolar constriction, loosening of bronchiolar epithelium by hyaline material, persistence of primary atelectasis, and extravasation of blood cells.

I have observed at autopsy and shortly after fixation a number of lungs of infants who died having shown all of the well-known clinical features of PHS. In each case, gross and low-power microscopic examinations of the whole lungs have enabled me to accurately predict which of the specimens would later show all of the characteristic features of PHS when sectioned, stained, and examined at higher magnifications. The lungs are heavy for their size; dark, purplish-red, because of capillary engorgement; airless (atelectatic); and readily sink in water or the fixing solution. Superficial lymphatic vessels are distended and, in places, show opacities representing coagulated proteinaceous contents, as do many of the subpleural alveoli under low magnification—especially with oblique, incident illumination. Reddish or pink specks later prove to be areas of minute hemorrhages into alveoli. Although lungs become exsanguinated to a variable degree during their removal at autopsy, some blood usually remains in the peripheral arterioles. Thus, under low magnification using incident illumination, the arterioles are rendered visible by their contents and are seen even more clearly with light transmitted through the thin edges of the lungs. In infants who die of PHS, the branching pattern is always that of the winter tree (Lauweryns, 1966). Hence, one can be reasonably certain of the final diagnosis.
even before the lungs are processed further for microscopic study by the pathologist.

**Experimental Production of Pulmonary Hypoperfusion Syndrome**

A number of workers have attempted to produce hyaline membrane disease in experimental animals and have claimed to have done so. Most of them have given as evidence of their success the presence of eosinophilic deposits in alveoli and peripheral airways. No attempt will be made here to review the literature on such experiments (see Tran-Dinh-De and Anderson, 1953, for review), but various substances, such as amniotic fluid plus HCl or other irritants, have been introduced into the lungs of experimental animals. Some investigators have done vagotomies, induced O₂ or CO₂ poisoning, or administered heavy doses of radiation; following such treatments, hyaline membranes have often been demonstrated. Actually, hyaline membranes may be produced in many different ways, but if a common factor exists in all of these studies, it is that the end result of the treatment has been the production of alveolar capillary hypoxia, which is all that is required to produce membranes following fixation. In their experimental production of hyaline-like membranes, Tran-Dinh-De and Anderson (1954) added the requirement that there should also be atelectasis. In my view, one should not be satisfied that the syndrome which occurs in certain premature infants has been reproduced unless one has not only caused eosinophilic membranes and atelectasis, but has also caused a widespread constriction of precapillary arterioles; stasis and engorgement of blood cells in alveolar capillaries and post-capillary venules; and intra-alveolar hemorrhages and lymphatic engorgement. All these characteristics are present.

Fig. 4—Blood cells are often extravasated into connective tissue planes of PHS lungs, possibly impeding flow of lymph and venous blood by compression. *Left:* Note lymphatic channels and empty venule with many blood cells in the surrounding connective tissue. Some air spaces contain hyaline substance; many alveoli are atelectatic. H & E, × 118. *Right:* Similar conditions in subpleural lobules of another PHS victim's lung. Valve is seen in uppermost lymph vessel. H & E, × 118.

Fig. 5—Commonly seen in PHS lungs are well-filled postcapillary venules (upper left) but, because of stasis of blood in capillaries, the next larger venules are poorly filled or empty. H & E, × 183.
in lungs of infants who succumb to PHS and, therefore, must be considered in reproducing the syndrome. Prior to the death of the experimental animal, there should also have been obvious respiratory distress, an elevation of systemic arterial PCO₂, and a lowered PO₂ and pH. To my knowledge, such results have neither been obtained by others nor published thus far.

Recently a group of freshman medical students and I designed an experiment intended to produce in the adult rabbit all of the antemortem and postmortem phenomena which are seen in PHS in the human infant. The experiment was based upon the assumption that the basic, etiologic factor in PHS is a hyperactive vagus nerve. Rather than attempt the technical problems of maintaining a chronic electrical stimulation of the cervical vagus or the infusion of higher than physiologic levels of acetylcholine (small amounts would be rapidly inactivated by the cholinesterase present in the lung), we elected to infuse small amounts of eserine sulfate (physostigmine), as required, to bind the animal’s pulmonary acetylcholinesterase. This permitted vagally-produced acetylcholine to accumulate and, at vagal terminals, act upon precapillary arteriolar sphincters in order to mimic vagal hyperactivity.

Through a polyethylene catheter advanced from the rabbit’s femoral vein to a position in the inferior vena cava near the heart, we infused small amounts of eserine sulfate (physostigmine), as required, to bind the animal’s pulmonary acetylcholinesterase. This permitted vagally-produced acetylcholine to accumulate and, at vagal terminals, act upon precapillary arteriolar sphincters in order to mimic vagal hyperactivity.

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those weighing less than 2,500 gm. This was suggestive of cell exhaustion arising from excessive activity. Thus, arteriolar constriction, in turn, would reduce or halt the flow of blood through alveolar capillaries.

Capillary hypoxia can be held accountable for the leakage of proteinaceous, fibrinous exudate into alveoli and connective tissue areas of the lung. Following fixation some of the fluid forms the eosinophilic, so-called hyaline membranes in peripheral alveoli and airways. Fluid containing protein and blood cells also distends vast numbers of pulmonary lymphatic vessels (Lauweryns, 1965a, b; Lauweryns et al., 1968), which are poorly drained because of the infant’s abnormal respiratory mechanics.

Stasis of blood in pulmonary alveolar and other peripheral capillary beds deprives the epithelial cell "factories" of the raw materials required for production of the critically important surfactant film necessary for normal alveolar stability. Its deficiency in the lungs of PHS infants accounts for the stiff, noncompliant lungs which are so difficult for the infant and the inhalation therapist to inflate. Widespread alveolar collapse eventuates in the airless, liver-like lungs seen at autopsy. Stasis of blood in pulmonary alveolar capillary networks also explains why there is insufficient *vis a tergo* to propel blood through postcapillary venules onward into the larger venules and pulmonary veins.

If the picture of PHS as I have portrayed it here is the correct one, and the experimental evidence which I have submitted appears to support this, then I feel that there is now a rational basis for treating PHS by anti-vagal therapy when the very first symptoms appear rather than as a last resort. Atropine or other effective anti-vagal agents should be infused via the umbilical vein, as required, to alleviate the clinical symptoms and adjust pH and blood levels of O₂.

Fig. 7—Fluid exudate in PHS lungs loosens and disrupts epithelial linings of peripheral air spaces. *Upper:* Note clumps of bronchiolar epithelial cells lifted by band of hyaline material. *Lower:* Cuboidal alveolar epithelium is loosened at lower left. Precapillary arterioles in both photomicrographs have obliterated lumens as a result of vigorous constriction. H & E, × 340.
and CO₂ toward normal values. Once perfused, alveolar capillaries should stop leaking, respiratory gases should cross alveolocapillary membranes, and alveolar (bronchial?) epithelial cells should begin to produce sufficient quantities of the stabilizing surfactant film. With increased pulmonary compliance, respiratory struggles, sternal retraction, and expiratory grunting should subside. Oxygen therapy and IPPB, with their attendant hazards, would no longer be required. Metabolic acidosis should soon be corrected with adequate O₂ uptake and CO₂ removal from tissues and mixed venous blood.

In recent months, two of my former students in Baltimore and a clinical friend in North Carolina have pioneered in the use of umbilical infusions of atropine sulfate solution in infants who appeared to be dying of PHS. The dramatic initial successes in this small group of babies encourages me to suggest that atropine or other anti-vagal agents might now be tried in PHS cases by other pediatricians conducting prospective and double-blind studies.

Summary

I have described my in vivo studies of mammalian lungs, focusing on the peripheral pulmonary arterioles. These observations led to my current concept that peripheral pulmonary perfusion is regulated on a lobular basis by motor fibers of the vagus nerve.

Besides having purely academic interest, vagal regulation of pulmonary alveolar capillary perfusion has practical implications for clinical problems such as pulmonary embolism, primary pulmonary hypertension, primary pulmonary vascular obstruction and, particularly, PHS.

Supported by experimental evidence, I have presented the thesis that there is a stasis of blood in alveolar capillaries caused by a generalized constriction of precapillary arteriolar sphincters produced by vagal hyperactivity. This, alone, can be held accountable for every clinical and histopathological feature of the syndrome. Evidence adduced from my own and other studies supports the idea of vagal predominance in PHS. A rational basis for a simple and, hopefully, a generally successful treatment of PHS by anti-vagal agents such as atropine has been outlined.

Addenda

After the completion of this manuscript, the following chapter came to my attention: “Pulmonary Circulation in Pathological States” by A. M. Rudolph in Paediatric Cardiology, H. Watson (ed.). London: Lloyd-Luke, 1968, pp. 57–62. This excellent work brings together recent information regarding the pathologic physiology in PHS and the influences of hypoxia and acidosis on pulmonary circulation. It also emphasizes the clinical features, radiologic characteristics, and biochemical changes in PHS. No attempt is made here to summarize Rudolph’s paper; it is simply highly recommended for those who wish an introduction to the complexity of the PHS problem, a statement of current methods of therapy, and an up-to-date bibliography on PHS and other types of pulmonary pathology.

While this paper was in press, I was reminded by Dr. W. H. Knisely that the question of whether pulmonary hypertension actually does follow a relatively small shower of emboli is quite controversial. Through discussion of this question and citation of all the pertinent literature cannot be included here. The reader is referred to an excellent book by R. Marshall: Pulmonary Embolism. Mechanism and Management. Springfield, Ill.: C. C. Thomas, 1965 (includes 484 bibliographic references).

Acknowledgement

In their freshman research project at The University of Maryland School of Medicine, R. Bardow, T. Detrich, A. Steele, and N. J. Wilson undertook the experimental production of PHS in the rabbit. Their findings, mentioned in this paper, are significant. It is a pleasure to acknowledge these contributions resulting from their enthusiastic efforts. A paper describing and illustrating their results in detail is in preparation.

The experimental studies described here were supported, in part, by USPHS Grants HE-2454 (5-12), Career Research Award HE-14191 (2-6) from the National Heart Institute, and USPHS training grants HTS-5450 and HTS-5450 (S1).

References


5-Fluorouracil, A Tool in the Treatment of Skin Cancer and Keratoses*

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Recently interest has arisen in the topical use of chemotherapeutic agents for the treatment of skin cancers and keratoses. Dr. Edmund Klein and his group at the Roswell Park Memorial Institute in Buffalo, New York, carried out extensive work in the study of the following drugs: Actinomycin D, Methotrexate, Spiramycin, Nitrogen Mustard, 5-Mercaptouracil, Dimethylurethimine and 5-Fluorouracil in an acid mantle cream. The results showed that many of these chemotherapeutic agents were able to attack the altered cell of keratosis and skin cancer and produce a destruction of the lesion.

The results showed that 20% 5-Fluorouracil in an acid mantle cream proved to be the most effective agent in the treatment of solar keratoses and skin cancer.

Preparation of Ointment

The 20% 5-Fluorouracil ointment is prepared as follows: The 5-Fluorouracil crystalline powder is micronized in a high speed grinder and sieved through a #100 mesh screen so that the particles are less than 150μ in size. The powder is then intimately levigated with a small amount of base using a triple roller ointment mill. This is then diluted to the desired concentration of 20% and is then mixed for at least one hour using a large Hobart mixer. The vehicle is Acid Mantle Creme of Dome Laboratories.

Protocol

Over two years ago a protocol was set up in Memorial Sloan-Kettering Cancer Center to study the effect of 20% 5-Fluorouracil in an acid mantle cream base in the treatment of patients with keratoses and skin cancers.

The patients who have been treated have had the disease for 5 to 30 years, and all have had the usual modalities of treatment—surgery, x-ray, dessication and scraping. They frequently are able themselves to detect new lesions before their own physician finds them, and they are willing to try any form of treatment which can hold out some promise to them.

Each new patient had the nature of the disease and the form of treatment carefully discussed with him. As the drug is Federal Drug Administration controlled, he was asked to sign a release which stated that he realized this was an investigative project. If possible, a biopsy was obtained, or the biopsy report from his referring doctor was accepted. The area to be treated was photographed. The patient was instructed to apply the ointment twice a day and to wash it off gently before reapplying it. However, this was only possible during the early stages of the treatment.

Treatment

When the patient presented himself with an entire face covered with keratoses and skin cancers, the usual anatomical sections of the face, such as the forehead, half the face, the nose, etc., were treated separately.

The usual sequence of treatment is as follows: By the fourth to seventh day, an area of erythema appears. This occurs not only around those areas which were clinically suspicious, but also in other areas which the examiner may not have noted. It is thus believed that the drug has an affinity to find and attack the altered cell. From the seventh to 21st days the erythema increases. There will be some superficial ulceration, and crusting will start. Treatment is continued to 30 days. When areas of the face are being treated, they are left open to the air. In areas normally covered by clothes, a simple 4” x 4” dressing with paper tape is applied. When occlusive dressing is used, the reaction is much more marked. At the end of 30 days, treatment is discontinued. The crust is allowed to separate, and a pink surface remains which is quite similar to that produced by superficial abrasion.

There have been no systemic complications whatsoever. Blood counts which were studied in the early cases showed no alteration. The patients have complained of pain and a burning sensation. The simultaneous application of 20% Cortisone preparation has lessened this problem. Occasionally there will be marked edema around the eyes, which can be controlled by antihistamines. The most difficult problem is the appearance of the patient. Those who have a severe...
facial reaction, especially men, whose beards tend to grow through the crust, will look frightful. However, the patient’s weekly visit serves as a time to reassure him.

Upon completion of one area, a period of time is allowed for evaluation. Then, usually, with the patient freely giving his opinion, we are able to determine whether he chooses to go on and have another area treated. It is to be noted that the skin, after treatment, is softer, and many fine lines also disappear. This is rather encouraging to the women patients, but this is only temporary edema, and with time the fine lines again return. Most of the patients who need further treatment are anxious to go on, as they were pleased with the results.

When a second course of treatment is given, the response is quicker and more severe. The erythema will be produced by the second and third day, and ulceration and crusting will start by the seventh to tenth day. The patient has probably been made sensitive to the drug by the first treatment, and the second treatment elicits a much quicker response. In the future we will be able to take advantage of this reaction by reducing the length of time of the treatment or, possibly, by reducing the concentration of the ointment. In those cases which we have now given a third course of treatment, the reaction is even more accelerated. The ointment has an affinity for the altered cell and does not attack normal skin. When placed over an entire area, such as the forehead, the appearance is one of mottling with areas of erythema, and normal skin remains untouched in between.

We have advised the patients to keep the ointment away from the mucous membranes of the eyes, mouth, and nose. However, I know that on a number of occasions the patients have gotten the ointment on the various mucous membrane surfaces, and there has been no untoward reaction. We do not feel that the ointment should be used over bare cartilage or bone.

In the beginning we were hesitant in using 5-FU in the treatment of radiation dermatitis and radiation-induced cancer. To date we have treated three patients with the disease and find a remarkably good response.

Results

In over 100 cases now treated at Memorial Sloan-Kettering Cancer Center, the response has been excellent. However, these are patients who for many years have developed new lesions. The ointment is only able to remove keratoses and basal cell carcinomas which are present. It does not alter the fundamental makeup of the skin, and it must be expected that the patient will go on and develop new lesions. However, the patients who have undergone the treatment are extremely grateful for being freed of their problem for a period of time, whether this be a year, or two, or longer. The treatment can be repeated any time that new lesions appear.

The individual basal cell cancer can still best be treated by surgical excision. It is when one is presented with the multicentric basal cell problem and where surgery becomes an almost impossible task that 5-FU becomes a useful tool.

Summary

1. 20% 5-Fluorouracil ointment in an acid mantle cream base is a useful tool for the treatment of multiple basal cell carcinomas and keratoses.

2. The method of treatment to date is application twice a day for a period of 30 days.

3. A second course of treatment can be applied to the same area or to other areas. A more severe reaction occurs with the second and third course of treatment.

4. The treatment removes the lesions which are present but in
Relationship Between Fertility and Elevated Cholesterol Levels in Rats

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Introduction

It is well known that in rats estrogen and testosterone influence the cholesterol concentration in blood and tissues, and that blood cholesterol levels are higher in young adult females than in males of the same age. At birth there is no difference in the blood cholesterol levels between the sexes, but differences begin to appear at approximately 21 days of age and gradually increase with age.

Experiments by Fillios et al. in 1958, in which blood cholesterol levels were measured during the several phases of the rat menstrual cycle, verified the existence of higher cholesterol concentrations during the preovulatory and ovulatory phases, as identified by vaginal smears, when estrogenic activity is higher. The two phases coincide with the time of greatest activity of the ovarian follicles. When this activity increases, the blood cholesterol concentration rises. The authors also observed that injection of testosterone in females with ovarian activity decreased the blood cholesterol levels. Therefore, they believed the biosynthesis of endogenous cholesterol in rats to be stimulated by estrogen and depressed by testosterone.

Studying two groups of rats that received a high-cholesterol and a low-cholesterol diet, respectively, Morris and Chaikoff observed in 1959 that testicular cholesterol was of endogenous origin. In liver, small intestine and adrenals, this endogenous origin of cholesterol was not completely suppressed, even in those animals that received prolonged rations of a high-cholesterol diet.

In previous work with rabbits on high-cholesterol and on high-cholesterol plus triparanol diets, I observed that no offspring were produced, even though the animals were not carefully separated by sex. Consequently, it seemed advisable, as the main purpose, to re-examine the possibility that a diet high in cholesterol, with or without triparanol, might affect reproduction. In this study rats were used instead of rabbits. Since triparanol inhibits the conversion of desmosterol to cholesterol, it seemed advisable to study the effect of triparanol on blood and tissue cholesterol itself. It also seemed of interest to study the distribution of cholesterol in various tissues.

Materials and Methods

Three groups of young adult Wistar white rats, averaging 154 gm in weight, were divided into the following groups.

Group A: 26 rats—13 males and 13 females. They received a daily diet of 18 gm rat chow containing 0.27 gm of pure cholesterol plus 0.01 gm of an inhibitor of cholesterol synthesis (triparanol) in addition to the normal daily supplement of vitamins, mineral salts, etc., which was totally eaten.

Group B: Same number of animals as in the previous group, with equal numbers of either sex. They received a daily diet of 18 gm rat chow, which was totally eaten.

Group C: Same number of animals as in the previous group, with equal numbers of either sex. These rats received only a high-cholesterol diet with a daily ration of 18
gm rat chow containing 0.27 gm of pure cholesterol plus vitamins, mineral salts, etc.

Group C: 16 rats—eight males and eight females. They received a daily normal diet of 18 gm standard rat chow and served as the control group.

The animals were kept in individual cages and received their rations in two stages at 12-hour intervals. The whole amount given was eaten.

Before the experiment started, two animals from both sexes were sacrificed, and the cholesterol and desmosterol concentrations were determined in both blood and tissues. These animals were on ordinary diet and were later included in Group C as control animals.

After one month on the diet, four animals from each group were killed and cholesterol and desmosterol levels were determined in their blood and tissues.

Desmosterol was determined indirectly by measuring the color developed with Liebermann-Burchard reagent at 400µ and 620µ according to the procedure of Abell et al., (1952). It is possible that other non-cholesterol sterols besides desmosterol are included in the desmosterol values.

After two months, we placed the remaining animals in pairs within their own groups and observed them for three months.

**Results and Discussion**

There was weight gain in the three groups, the average weight in Groups A and B being 160 gm; in Group C, 158 gm.

Table 1 shows that the blood cholesterol of animals on high cholesterol diet (Group B) increased, while the desmosterol level decreased. In the animals on high cholesterol plus triparanol diet (Group A), the cholesterol level was higher than in the control group but lower than in Group B, and the desmosterol level in Group A was higher than in the other groups.

In the rats from Group B, the cholesterol level in the heart was higher than in the other two groups that showed similar values for both cholesterol and desmosterol levels. However, the desmosterol levels in Group A and in Group C were higher than in Group B. Similar changes were seen in the aorta, but the values were higher.

In the spleen, the high cholesterol diet was associated with increased endogenous cholesterol.

The adrenals were very sensitive to the diets. With the high cholesterol diet, the synthesis of cholesterol seemed to be completely abolished, because desmosterol was absent. With the cholesterol plus triparanol diet, desmosterol was again present in higher levels than in Group C.

An interesting result was observed in the testicles, where the highest level of endogenous cholesterol was found. In the control group, for example, a 93 mg/10 gm level of desmosterol and a 140 mg/10 gm level of cholesterol were observed, indicating high cholesterol biosynthesis activity. This was the highest desmosterol level found in tissues. In Group A, the levels of both cholesterol and desmosterol decreased in comparison to Group C. In Group B, the desmosterol level dropped and the cholesterol level rose.

---

**TABLE 1**

Cholesterol, Desmosterol, and Total Steroid Concentration of Serum and Tissues.*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Group A High Cholesterol Diet + Triparanol</th>
<th>Group B High Cholesterol Diet</th>
<th>Group C Normal Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>0.62 ± 1.0 mg/ml serum mg/gm wet tissue</td>
<td>0.13 ± 0.7 mg/ml serum mg/gm wet tissue</td>
<td>0.76 ± 0.9 mg/ml serum mg/gm wet tissue</td>
</tr>
<tr>
<td>Heart</td>
<td>9.9 ± 0.9 mg/ml serum mg/gm wet tissue</td>
<td>2.5 ± 0.9 mg/ml serum mg/gm wet tissue</td>
<td>15.7 ± 1.0 mg/ml serum mg/gm wet tissue</td>
</tr>
<tr>
<td>Aorta</td>
<td>20 ± 0.8 mg/ml serum mg/gm wet tissue</td>
<td>1.8 ± 0.7 mg/ml serum mg/gm wet tissue</td>
<td>55.9 ± 1.2 mg/ml serum mg/gm wet tissue</td>
</tr>
<tr>
<td>Spleen</td>
<td>47.1 ± 1.1 mg/ml serum mg/gm wet tissue</td>
<td>1.7 ± 0.9 mg/ml serum mg/gm wet tissue</td>
<td>26.6 ± 0.8 mg/ml serum mg/gm wet tissue</td>
</tr>
<tr>
<td>Adrenals</td>
<td>113 ± 1.0 mg/ml serum mg/gm wet tissue</td>
<td>6.5 ± 1.0 mg/ml serum mg/gm wet tissue</td>
<td>119.5 ± 1.0 mg/ml serum mg/gm wet tissue</td>
</tr>
<tr>
<td>Testicles</td>
<td>11 ± 0.9 mg/ml serum mg/gm wet tissue</td>
<td>6.9 ± 1.0 mg/ml serum mg/gm wet tissue</td>
<td>17.9 ± 0.9 mg/ml serum mg/gm wet tissue</td>
</tr>
</tbody>
</table>

* 10 gm from each of these organs were used in homogenized solution. The figures given are average values ± standard errors of the means. Standard deviation in the method used was 1.03 mg/10gm.
The puzzling results observed in the testicles led to histological sections of these organs being made from animals of the three groups (Fig. 1, 2, 3). At the same time, the remaining animals were bred within their own groups and observed for three months.

The control group, with four males and four females, had normal offspring and were considered to be 100% fertile.

Eleven pairs from Group A mated normally but produced fewer offspring than Group C. They were 63% fertile, and their babies had little or no possibility of survival, as they showed a high incidence of malformation such as phocomelia and sirenomelia. Four of them had almost complete organic agenesia. The abdominal cavity of one of these babies appeared empty (Fig. 4). In the chest cavity, there was only the heart and rudiments of lungs. The posterior portion of the body was not formed, and the lower limbs and the tail were missing. Seven pairs had 21 babies. Nineteen of these babies had malformations, as shown in Table 2, and all 21 died before three days of life. One of the mothers from this group died of uterine hemorrhage immediately after delivery of five dead malformed babies. Three of them had organic agenesia.

The rats from Group B were 100% sterile. In view of the complete sterility found in the pairs from this group, there was considerable interest in determining whether the male, the female, or both were at fault. Continuing to submit all the animals to the same diets, they were cross-mated as follows:

a) Males from Group B were coupled with control females for two months and continued sterile.

b) Control males were coupled with females from Group B for the same time and had normal offspring.

c) Males from Group B were mated with females from Group A and continued sterile.

d) Males from Group A were mated with females from Group B. Sixty-seven per cent of the matings resulted in offspring with a 20% lower incidence of malformations than in pairs from Group B.

Naturally, it was thought that only the males from Group B became sterile with the high cholesterol diet. Attempts were then made to determine the type of lesion and its location.

The diets in the study groups were discontinued, and all the animals received the same normal meals as in Group C. After one month on this diet, all the groups

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tbody>
<tr>
<td>Results of Breeding of Group A</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Pair</th>
<th>No. of babies</th>
<th>Normal</th>
<th>Types of Malformations</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phocomelia</td>
<td>Sirenomelia</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<td>2</td>
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<tr>
<td>6</td>
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<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>2/9.5%</td>
<td>5/23.8%</td>
<td>4/19.1%</td>
</tr>
</tbody>
</table>
were again cross-mated, as before. All the animals then had normal offspring, except the males from Group B that remained sterile.

Histological sections from testicles of animals from Groups A and B were performed during the special diets and three months after these diets were discontinued. Comparative studies with testicles of rats from the control group were also done. The following results were obtained.

Group A: There were some changes in the testicular tissue while on the diet. These changes resembled fat degeneration but were not severe. There was no atrophy, and apparently spermatogenesis was not seriously affected. Only lower numbers of sperm were seen. When the diet was discontinued, these changes disappeared (Fig. 3).

Group B: There were serious and irreversible lesions, which definitely blocked spermatogenesis. These lesions were fat degeneration and complete atrophy of testicular tissue; they suggested somewhat the changes seen in inanition (Fig. 2). However, the rats were well nourished, with a good supply of vitamins and mineral salts in their diets.

It should be emphasized that the sterility of males from Group B did not have any relation to impotence, since there was no difference between the sexual activity of these males and the males from other groups.

Summary and Conclusions

Several conclusions were drawn from these experiments.

1. Desmosterol levels were higher in the testicles of animals on a normal diet, and lower in animals that became sterile on a high cholesterol diet. This suggested that desmosterol, in addition to being a precursor of cholesterol, could also be a direct precursor of a male hormone (or hormones) which controls or influences spermatogenesis.

Fig. 1—Normal testicular tissue, with normal spermatogenesis from animals of the control group. X 400 (Trichrome staining technique).

Fig. 2—Severe degeneration of the testicular tissue, with spermatogenesis blocked, as seen in animals from Group B with high cholesterol diet.
genesis. However, this remains hypothetical.

2. The sterility induced in males on a high cholesterol diet could not be reversed by the discontinuation of the diet.

3. The cholesterol concentrations in the adrenals increased to the highest levels found in the two studied groups, and desmosterol was absent in Group B. No anatomical or histological changes were seen.

4. Cholesterol and desmosterol levels in serum of animals from the three groups are compatible with the hypothesis that triparanol inhibits the synthesis of cholesterol in its last stage.

It is my hypothesis that the higher cholesterol and lower desmosterol levels in the heart and aorta of animals from Group B probably mean that the endogenous cholesterol was replaced by the cholesterol from the diet.

The fat degeneration and complete atrophy of testicular tissue in animals from Group B were probably due to the poor nutrition of the testicular tissue provoked by diet.

References


BOOK REVIEW


One of the most perplexing problems to teachers, psychiatrists, and neuropathologists is that presented by the child with specific language-learning difficulty. Children who find it impossible to keep up with classmates in reading, spelling, and penmanship are frustrated, and as a result they often become emotionally upset. Published observations of children with this disorder are difficult to find. For 30 years Mrs. Margaret Rawson directed a program to detect and correct developmental language disabilities at The School in Rose Valley, Moylan, Pennsylvania. She followed the academic progress and the adult achievement of her students. This monograph is a report of her observations.

The School in Rose Valley was founded and operated through the initiative of a small group of parents in Moylan during the late 1920's. On the whole, these parents were well-educated and fairly prosperous. There were 56 dyslexic and non-dyslexic boys who entered the school between the years 1930 and 1947 and had attended long enough to be considered valid subjects for this study. The dyslexic child has a partial disability in the areas of reading, spelling, and penmanship. It is possible that only one area may be affected. More accurately, the term applied to this deficit should be “the dyslexias,” and the present tendency to refer to all children with reading difficulties as “dyslexic” should be abandoned. The true dyslexic presents a picture of confusion with reversals, inability to sequence syllables, and general linguistic disorganization. Other non-readers may have emotional blocks, lack of family motivation, or any number of problems which interfere with reading progress.

For the purposes of this study, the boys were categorized as having Low, Medium, or High Language Facility. The diagnostic criteria employed by Mrs. Rawson to identify the dyslexic boys included: initial failure to read; poor oral reading and word memory; reversals of orientation and sequence; poor response to special language teaching; persistence of characteristic spelling inadequacies; speech delays and inadequacies; poor motor skills often reflected in poor penmanship; difficulties in word finding; immature grammar; auditory and visual perception problems; and lack of strong lateral dominance. Each boy was placed in a category through assessment of his individual learning pattern. The nature and degree of his difficulty was compared with those of others in the study.

Individual language therapy was given as indicated by the diagnostic criteria. Stress was placed upon simultaneous use of the senses of sight, hearing, and muscular awareness in such admonitions as, “Sound it out while you trace it as you look; your ears and your muscles will help your eyes to get it—or to get it back if you’ve forgotten.”

Results of the study show that those with Low Language Facility ultimately attained more “years worth” in colleges and universities and achieved a larger number of academic degrees than those with High Language Facility. The author feels that it is possible to explain this by chance alone, but perhaps it was the effect of the “sustained, systematic effort they are called upon to make.” The adult career accomplishments of the dyslexic boys are cause for all who wrestle with the problem to take heart. Dyslexics are found to have made average and sometimes superior achievement.

Mrs. Rawson has carefully examined the boys’ family influences, their general scholastic abilities, their siblings, their speech and language patterns, and their adult achievement. She has included pertinent information which could be of use to others wishing to research in the same area. Review of the literature is thorough.

One thing noted in reading this book was that the subjects were fairly homogeneous. They were from unusually understanding and knowledgeable families. The results obtained at The School in Rose Valley present to the reader irrefutable proof that the dyslexic child need not be “lost” academically. However, a like expectation of progress by the child from the indifferent home background with a degree of cultural deprivation would be unrealistic. In short, this volume demonstrates what can be done to educate the dyslexic child under excellent circumstances. It challenges workers in the field to find new methods of dealing with reading failures and with those whose language learning ability is deficient. It is well worth the reading, particularly for those who have felt the dyslexic child is extremely limited in his chances for progress.

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Associate Professor
Department of Otolaryngology
Medical College of Virginia
Grimaldo Carvalho (Relationship Between Fertility and Elevated Cholesterol Levels in Rats) is assistant professor of cytology and vice-director of the school of cytology at the Medical College of Virginia. Born in Brazil, he received his medical degree from the Escola de Medicina Cirurgia do Rio de Janeiro, after which he served in general practice at the Santa Casa da Misericordia of that city. He then completed three years as scientist and cytologist in cancer research at Roswell Park Memorial Institute in Buffalo, N.Y. Before coming to MCV, he was head of the cytology department at the Hospital Moncorvo Filho in Rio de Janeiro. The author of a textbook on vaginal cytology, Dr. Carvalho served as president of the Third Brazilian Congress of Cytology held in May of 1968.

G. H. du Boulay (The Use of a Computer in the Diagnosis of Intracranial Tumours) is consultant radiologist at St. Bartholomew’s Hospital and The National Hospital for Nervous Diseases, Queen Square, London. He has been engaged in clinical neuroradiology for the past 17 years and for the past four years has run the research x-ray department at the London Zoo. Dr. du Boulay is also an associate research fellow at The Nuffield Institute of Comparative Medicine, Zoological Society of London.

Walter J. Geeraets (Potential Applications of Lasers in Ophthalmology), professor of ophthalmology and associate professor of biophysics at the Medical College of Virginia, was born in M. Gladbach, Germany. He obtained a doctor’s degree in medicine from the University of Bonn, later serving as a research fellow at the Radiation Institute of that university and as the chief assistant of the surgical clinics at Bochum, Germany. In 1957 he came to MCV with appointments in the departments of ophthalmology and biophysics. Dr. Geeraets is currently director of ophthalmic research and coordinator of the NIH ophthalmic resident training program at MCV.

David E. Green (Mechanism of Energy Transformations in Biological Membranes) is one of the pioneers in the field of enzyme chemistry. He first became interested in the subject in 1930, after graduating from New York University. As a summer student at the Marine Biological Laboratory in Woods Hole, Massachusetts, he learned of the work being done on enzymes in England and decided to attend the University of Cambridge. After earning his Ph.D., he remained there as a research fellow for seven years. He later spent a year in research at Harvard University and then became head of the Enzyme Laboratory of the College of Physicians and Surgeons of Columbia University. In 1948 he became professor of enzyme chemistry at the Institute for Enzyme Research of the University of Wisconsin. He is now co-director of that Institute. Dr. Green’s career has centered on the description of the activities and organization of particulate enzyme systems.
Vernon E. Krahl (Mechanisms Controlling the Peripheral Circulation of the Lung with Some Clinical Correlations) is professor of anatomy at the University of Maryland School of Medicine. A Pittsburgher, he holds B.S. and M.S. degrees from the University of Pittsburgh and a Ph.D. from the University of Maryland. With the exception of one year spent at Wayne University in Detroit, Dr. Krahl has taught anatomy at Maryland from 1941 until the present. Although his research interests have included gross and comparative anatomy, physical anthropology, cardiology, and chemoreceptor mechanisms, he is probably best known for his work in pulmonary morphology and physiology. He is a recipient of an NIH Career Research Award.

Richard W. Schayer (Histamine and a Possible Unity of Autonomous Microcircular Dilator Responses) is principal research scientist, Research Center, Rockland State Hospital, Orangeburg, New York. He has a Ph.D. in biochemistry from Columbia University and was formerly on the staffs of the Merck Institute for Therapeutic Research, Rahway, New Jersey, and the Rheumatic Fever Research Institute, Chicago, Illinois.

Reuven K. Snyderman (5-Fluorouracil, A Tool in the Treatment of Skin Cancer and Keratoses) is attending surgeon in plastic surgery at the New York Hospital and associate attending surgeon in plastic and reconstructive surgery at Memorial Hospital. He received his A.B. and M.D. degrees from the University of Pennsylvania, completing his internship at the U.S. Naval Hospital in Philadelphia and his surgical service at the U.S. Naval Hospital in Bethesda. Dr. Snyderman holds teaching and research appointments at the Cornell University Medical College and the Sloan-Kettering Institute.

Arnold V. Wolf (The Potability of Sea Water) is head of the department of physiology at the University of Illinois College of Medicine. He received a B.S. degree from City College, New York, and a Ph.D. from The University of Rochester. He was formerly on the staff of Albany Medical College, Albany Hospital, and the Walter Reed Army Institute for Research. Dr. Wolf's research has been concerned with water and electrolyte metabolism, thirst, and properties of body fluids.
the “spasm reactor” in your practice
The Machine Age man still possesses a Stone Age stomach; sometimes the job of merely coping with today’s environmental stress may prove too much. For some (the “spasm reactors” in your practice), tension, anxiety and worry may find expression through the voice of gastrointestinal or other smooth muscle spasm. To treat these patients with antispasmodics alone is often to miss the point of origin of their disturbance; to rely solely on tranquilizers often proves discouragingly slow or ineffective in relieving spasm and pain.

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<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Each Tablet/Capsule or 5 cc. Elixir</th>
<th>Extentab®</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyoscyamine sulfate</td>
<td>0.1037 mg.</td>
<td>0.3111 mg.</td>
</tr>
<tr>
<td>atropine sulfate</td>
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<tr>
<td>phenobarbital</td>
<td>(½ gr.) 16.2 mg.</td>
<td>(½ gr.) 48.6 mg.</td>
</tr>
<tr>
<td>(warning: may be habit forming)</td>
<td></td>
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</tbody>
</table>
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Librium®
(chlordiazepoxide HCl)

Quickly relieves anxiety—Helps improve response in psychophysiological disorders—Seldom impairs mental acuity or physical coordination, on proper dosage—Has wide margin of safety.

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**Indications:** Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

**Contraindications:** Patients with known hypersensitivity to the drug.

**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

**Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxic reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

**Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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