Environmental Health Perspectives
Vol. 55, pp. 149-158, 1984

Intermediary Metabolism of the Lung

by Aron B. Fisher*

The lung is a metabolically active organ that is engaged in secretion, clearance and other maintenance functions that require reducing potential, energy and substrates for biosynthesis. These metabolic requirements are met in part through uptake and catabolism of glucose which represents the major fuel utilized by lung tissues. Gluconeogenesis does not occur, and glycogen stores are limited so that the lung depends on the circulation for its glucose requirement. Other substrates can be metabolized by lung and contribute to the metabolic pool although their role has been less thoroughly studied. Glucose is catabolized in the lung by cytoplasmic and mitochondrial pathways that are responsive to regulatory mechanisms as in other tissues. Activity of the pentose cycle pathway of glucose catabolism is relatively high and generates the NADPH required for biosynthesis of lipid, detoxification reactions, and protection against oxidant stress. The ATP content of the lung is maintained by oxidative metabolism at levels comparable to other metabolically active organs. Alterations in lung intermediary metabolism may depress amine clearance, alter lung permeability, and influence the lung response to oxidant stress.

Although once considered a passive conduit for exchange of gases, it is now recognized that lung tissue carries out important metabolic activity (*1–4*). This realization has led to a flurry of investigation which has greatly increased our knowledge of intermediary metabolism of the lung. Nevertheless, much remains to be accomplished before we gain complete understanding of the relationships between cellular metabolic activity and overall lung function including the mechanisms by which intermediary metabolism is altered in the presence of disease. With the development of effective methods for isolation of individual cell types (*5–10*), it seems likely that major progress in the near future will be toward understanding intermediary metabolism as a function of lung cell type. The present paper will not describe this aspect of lung metabolism but will review the integrated metabolic activity of the lung. The information that will be presented has been obtained primarily with the isolated perfused adult rat lung preparation.

Glucose Utilization and Intermediary Metabolism: Overview

The overall role of intermediary metabolism in cell homeostasis is primarily to generate the requisite energy for cellular functions and to provide the small molecular weight substrates for biosynthetic processes. In lung cells as in most tissues, a variety of substrates derived from protein, lipid and carbohydrate precursors can enter the cellular pool of intermediary metabolites. Thus, lung tissue can oxidize to a variable degree glucose, fatty acids, amino acids, lactate, and glycerol (*11–13*). However, the rate of glucose oxidation is greatest and is not appreciably influenced by added palmitate (*14*), suggesting that glucose serves as the major oxidizable substrate under normal physiological conditions. Therefore, this paper emphasizes glucose metabolism by the lung, including pathways for the utilization of glucose and the role of glucose metabolism in generation of reducing equivalents and energy stores.

Glucose Transport

The initial event in glucose utilization by tissues is its transcellular transport which in most cells occurs by carrier-mediated facilitated diffusion (*15*). However, some epithelia such as renal cortex and intestine accumulate glucose (and other hexoses) against a concentration gradient by an active transport process (*16,17*). Mechanisms of glucose transport can be most easily studied through use of nonmetabolizable glucose analogs so that the transport step can be separated from subsequent metabolic transformations. Recently this approach has been used to evaluate mechanisms of hexose uptake in the perfused lung preparation. 2-Deoxyglucose and 3-*O*-methyl glucose were taken up by facilitated diffusion and did not accumulate against concentration gradients (*18,19*). On the other hand, α-methylglucoside did accumulate against a concentration gradient by a sodium-dependent process, suggesting active transport (*19*). Therefore, there is apparently more than one transport system for hexoses in the lung and both facilitated diffusion and active transport may occur. Glucose itself probably utilizes both systems since this substrate competes for uptake with non-

*Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

metabolizable analogs (*19*). It is possible that multiple uptake mechanisms reflect the contribution of more than one cell type. Although the cell types involved in each of these uptake processes has not yet been determined, analogy with other tissues suggests that epithelium is a most likely site for active transport.

Glucose Utilization

The most direct way to measure glucose utilization is by the rate of disappearance of glucose from the medium during lung perfusion. However, this technique is difficult to apply to lungs because of the normally large perfusate flow rate relative to metabolizing tissue mass. As an alternative method, glycolytic rate can be measured from the rate of generation of ^3H_2O from glucose specifically labeled with tritium (*20*). In the case of glucose labeled in the 5-position, tritium is liberated during glycolysis at the triose phosphate isomerase and enolase catalyzed steps (Fig. 1). The advantage of this method is that the appearance of the radiolabeled metabolic product (H_2O) is easier to measure than is the disappearance of the substrate (glucose).

Utilization of glucose by the lung as indicated by ^3H_2O production varies with perfusate glucose concentration (*21*). The calculated glucose utilization at infinite substrate concentration is 72 μmole/hr/g dry weight or approximately 15 μmole/hr/g wet weight (*21*). Glucose utilization is one-half maximal at a perfusate concentration of 3.4 mM (*21*) to 4.7 mM (*22*). With perfusate glucose concentration of 5.6 mM (the approximate resting physiologic concentration), glucose utilization is 40 to 50 μmole/hr/g dry weight (*20,21*). This rate of glucose utilization is similar on a weight basis to that of other metabolically active organs such as the brain and heart (*3*).

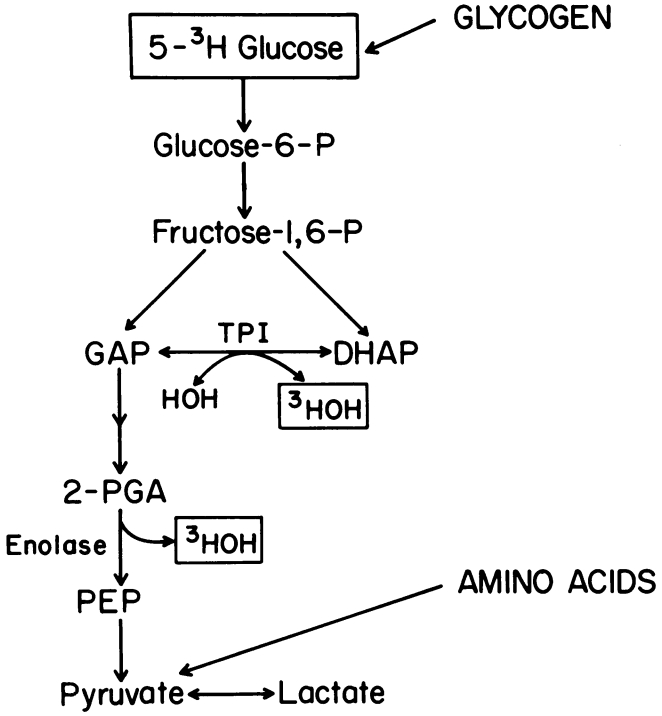

FIGURE 1. Scheme for the glycolytic pathway indicating the sites of ^3H_2O production from glucose labeled with tritium in the 5-position. Also indicated are the sites of entry of carbon from glycogen and amino acids into the glycolytic pathway.

Products of Glucose Metabolism

The major pathways for catabolism of glucose include the glycolytic (Embden-Meyerhof) and pentose phosphate pathways. These reactions produce lactate and CO_2 as major end products and generate glycerol-3-phosphate, pyruvate, and ribose which can be utilized as intermediates for synthesis of lipids and nucleic acids, transamination to amino acids, and oxidation via the Krebs cycle. The catabolism of glucose also generates reduced pyridine nucleotides (NADPH and NADH), reducing potential which is essential in the extramitochondrial compartment for reductive biosynthesis and detoxification reactions and, after transfer into the mitochondria, can be utilized for energy generation via the electron transport chain. Finally, the catabolism of glucose results in synthesis of high energy compounds (ATP). The net ATP gain from glycolysis is relatively small but may be physiologically important. This section discusses the fate of glucose carbons; subsequent sections will describe the role of glucose in generation of reducing equivalents and ATP.

The approximate fate of glucose metabolized by the perfused lung, traced through the use of glucose labeled with ^{14}C, is summarized in Figure 2. The major fraction (40–50%) of glucose carbons is metabolized to the three-carbon compounds lactate and pyruvate (*23*). The distribution between lactate and pyruvate production varies with the redox state of the cell, but under control conditions, lactate production is approximately 10-fold greater (*23*). These three-carbon products of glycolysis readily appear in the lung perfusate. The flux to lactate as a percent of glucose utilized in the aerobic perfused lung is relatively high compared with other organs. For example, lactate production by the perfused rat heart (in the presence of insulin) is only 20 to 25% of glucose utilization (*24*). One possibility to account for the high rate of lactate production is that the relatively large pulmonary perfusion rate might allow relatively greater rates of diffusion of lactate and pyruvate from the cells compared with other organs. As another possibility, some compartments of the lung may be relatively deficient in mitochondrial enzymes with consequent greater dependence on glycolytic pathways. (Ultrastructural examination suggests that membranous epithelium could be such a compartment.) The high lactate production in the normal lung is not due to cellular hypoxia since changes in alveolar PO_2 do not significantly affect lung lactate production until very low levels of PO_2 are attained (*25,26*). Exogenous lactate added to the perfusate can enter the cellular metabolic pool and

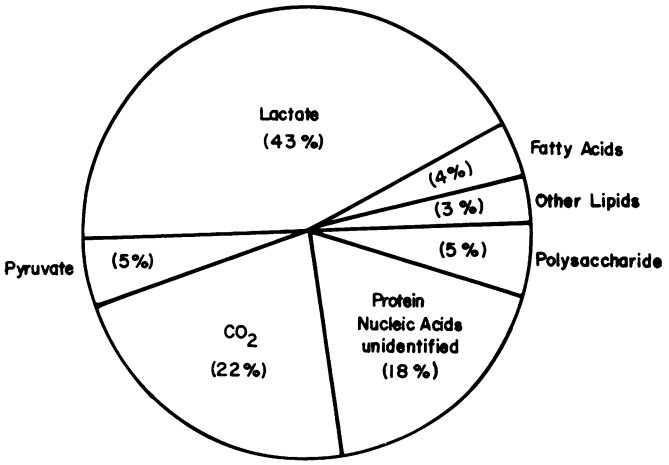

FIGURE 2. Recovery of carbon atoms derived from glucose and products of metabolism during perfusion of the isolated rat lung with 5.5 mM [U-^{14}C] glucose in Krebs bicarbonate solution, pH 7.4, containing 3% bovine serum albumin. The data are represented as percent of total recovery (*20,23,39*).

(after conversion to pyruvate) can be further metabolized via pathways for utilization of three-carbon fragments (*13,22,27*).

Oxidation to CO_2 represents the second major fate of glucose carbons (Fig. 2). The reactions that generate CO_2 include the cytoplasmic pentose shunt pathway of metabolism and mitochondrial reactions catalyzed by pyruvate dehydrogenase and enzymes of the tricarboxylic acid (Krebs) cycle. Of the total CO_2 production by the perfused lung, approximately one-fourth is generated from the pentose shunt, one-fourth from the pyruvate dehydrogenase reaction, and one-half by the tricarboxylic acid cycle (*20*).

The other major fate of glucose carbons is their utilization for biosynthesis of more complex molecules including polysaccharides, proteins, and lipids. Incorporation into polysaccharides probably reflects predominantly synthesis of glycogen. The glycogen stores in the lung (1–3 mg/g wet weight) (*21,28,29*) are markedly less than those of the liver from a well-fed animal, but in the approximate range of other organs that do not specifically store glycogen. The incorporation of glucose carbons into glycogen (*23*) indicates a turnover of approximately 3% of tissue glycogen/hr. The factors responsible for mobilization of glycogen in the lung cells have not been described but the size of this pool appears to be stable during short-term glucose deprivation (*21*) or during 3 days of fasting (*22*).

Glucose carbons are also readily incorporated into protein and nucleoproteins (*23,30*). A major site of entry into the amino acid pool is likely through transamination of pyruvate to produce alanine. Other potential points of interchange of carbon atoms include Krebs cycle intermediates and ribose generated in the pentose cycle. In common with most other tissues, the protein components of the lung are in constant flux with degradation and resynthesis proceeding at variable rates depending on the protein (*31*). Thus, not only are three-carbon intermediates from glycolysis readily incorporated into protein, but alanine and possibly other amino acids from protein degradation enter the metabolic pool where they can appear in the lung perfusion fluid as lactate (*22*). The rate of lactate generation from these nonglucose sources is relatively independent of lactate production from glucose and may account for 25% or more of total lactate production (*21,32*).

Complex lipids are also synthesized by lungs from glucose carbons. Glucose carbons appear in both the fatty acyl moiety, presumably synthesized via acetyl CoA, and the glyceride–glycerol moiety arising from glycerol phosphate (or dihydroxyacetone phosphate) (*33*). Small quantities of glucose carbons may also be incorporated into ethanolamine or other phospholipid side chains. In our studies with the perfused lung, incorporation of glucose carbon into the fatty acyl moiety was about 60% of total incorporation (*34*) although other investigators have suggested that this component may account for only 25 to 40% (*28,35*). The precise distribution of incorporation between the lipid compartments may vary with the availability of fatty acids in the perfusate or nutritional status and age of the animals (*11,36,37*). Thus, adult animals, starvation or the presence of palmitate in the perfusate resulted in increased relative glucose incorporation into the glyceride–glycerol as opposed to fatty acyl moiety.

Gluconeogenesis

Although glucose utilization by lung has been extensively studied, the possibility of gluconeogenesis from two- or three-carbon precursors has not received the same attention. The activity of phosphoenolpyruvate carboxykinase, one of the rate-limiting enzymes in gluconeogenesis, is very low in lung tissue (*38*), suggesting that the gluconeogenic pathway is not of major importance. Therefore, circulating glucose is the probable major source of lung intracellular carbohydrate.

Control of Glycolytic Flux

Metabolic control of the glycolytic pathway can be analyzed from the standpoint of agents that exert regulation over the long or over the short term. Long-term regulation occurs chiefly through the effect of hormones and other mediators on the enzymes involved in glucose uptake and metabolism. Short-term control occurs by regulation of enzyme activity through changes in concentration of important reactants and modifiers. Two important glycolytic regulators of the second class are the cellular ATP concentration (or perhaps ATP/ADP or the energy charge of the cell) and the cellular NAD^+ concentration (or the NAD^+/NADH or redox state of the cell). In other tissues, glycolytic flux increases in response to ATP depletion (assuming sufficient ATP for glucose phosphorylation) and decreases as NAD^+ is depleted. Operation of these short-term regu-

lators has been evaluated in the perfused lung by using metabolic inhibitors with different mechanisms of action.

To study the role of ATP, lungs were perfused with dinitrophenol (DNP), an uncoupler of oxidative phosphorylation, or ventilated with carbon monoxide (CO), which inhibits oxidative phosphorylation through competition with O_2 for cytochrome oxidase. DNP significantly decreased the ATP and ATP/ADP (*39*), while CO depressed cellular energy state to an even greater degree (*23*). Both of these metabolic inhibitors stimulated the rate of glycolysis, indicating responsiveness of the system to ATP depletion. The effect of CO is analogous to the classic Pasteur effect, i.e., stimulation of glycolysis secondary to O_2 lack. Thus, lung tissue demonstrates a brisk Pasteur effect with an increase in glycolytic activity of 2.5-fold in response to complete inhibition of mitochondrial oxidations (*23*).

It should be noted that glycolysis was stimulated by CO (Table 1), despite a marked reduction of cytoplasmic pyridine nucleotides (that is, elevated NADH/NAD^+ as reflected by increased lactate/pyruvate). We have recently shown that perfusion with pyruvate to decrease the redox ratio leads to a further stimulation of glycolysis in the presence of CO (*40*). The effect of redox state on glycolysis was further evaluated by perfusion of lungs with phenazine methosulfate (PMS), which can directly oxidize the reduced cytoplasmic pyridine nucleotides. PMS did not affect lung energy status but significantly decreased lactate to pyruvate ratio (indicating shift of cytoplasmic redox state toward oxidation) (Table 1). PMS also stimulated the glycolytic pathway of glucose utilization (*39*). Thus, glycolysis responds to redox state independently of changes in energy status.

The provision of mitochondrial (Krebs cycle) substrate can also have a regulatory effect on glycolysis. Recent observations from our laboratory indicate that glycolysis is inhibited in the presence of 1–2 mM lactate (*40*). Pyruvate is also inhibitory. This effect is not due to alteration of redox ratio but most likely reflects increased citrate synthesis by the mitochondria with subsequent inhibition of cytosolic phosphofructokinase. A similar inhibition by lactate on lung metabolism has been observed for the oxidation of glucose to CO_2 (*13*).

Table 1. Effect of metabolic inhibitors on glucose utilization by the perfused rat lung.[a]

	Glucose utilization, μmole/hr/g dry wt.		Glucose conversion, μmole/hr/g dry wt.		Lact/ Pyr
	Total	Via E-M	To Lact + Pyr	To CO_2	
Control	44.4	39.1	16.5	8.8	10
CO[b]	63.3	62.7	64.5	1.9	53
DNP	79.9	75.7	32.5	17.9	13
PMS	64.3	53.9	21.9	19.1	4

[a] Perfusate contained 5.6 mM glucose plus insulin; DNP = 0.08 mM dinitrophenol; PMS = 8 mM phenazine methosulfate; E-M = Embden-Meyerhof pathway (calculated as total minus pentose pathway).
[b] Lungs ventilated with 0.95 ATA CO; 0.05 ATA CO_2.

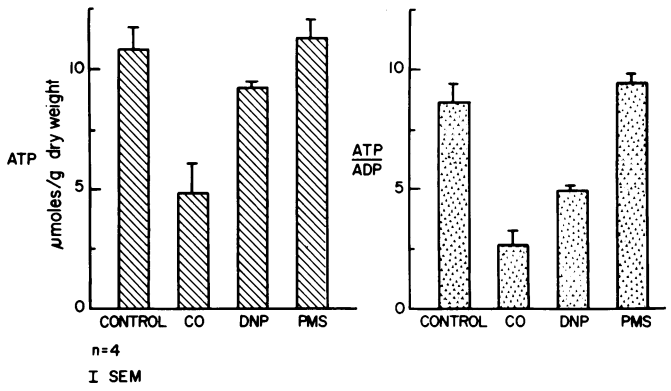

FIGURE 3. ATP content and ATP/ADP ratio in the isolated perfused rat lung: under control conditions, during ventilation with CO, perfusion with dinitrophenol, or perfusion with phenazine methosulfate (*23,39*).

The results with metabolic inhibitors (see Fig. 3 and Table 1) and substrates indicate that regulatory mechanisms for glycolysis in lung cells are qualitatively similar to those in other tissues.

The evidence for hormonal regulation of lung glycolysis is less clear. Most studies in this area have been directed toward the role of insulin. Insulin-specific receptors have been demonstrated in crude membrane preparations from normal lungs (*41*) and insulin may modulate lung lipid synthesis (*35,42*) and proteolysis (*43*). On the other hand, possible effects of added insulin on glycolytic activity have been difficult to confirm in the control perfused lung, perhaps related to the persistence of endogenous insulin already bound to receptors. Lactate production and glucose utilization were stimulated in the presence of insulin (*21,44*) but in one study (*21*) the effect was observed only at a low glucose concentrations. Isolated perfused lungs showed increased uptake of 2-deoxy-D-glucose in the presence of insulin (*18*). Furthermore, lungs from diabetic rats had decreased glucose oxidation and decreased uptake of 2-deoxy-D-glucose (*18,41*). Thus, the studies provide evidence that insulin has a role in regulation of lung glucose utilization, although the currently available data suggest that the effect is not major. Possible regulatory roles of thyroid, adrenal and other hormones that may be predicted to affect glucose utilization have not been adequately evaluated in the lung.

Generation of Reducing Equivalents

In addition to generating carbon substrates for further oxidation or for biosynthetic reactions, the catabolism of glucose generates reducing equivalents which in turn are used for reductive biosynthesis, detoxification reactions, and generation of ATP via the mitochondrial electron transport chain. Cytoplasmic reducing equivalents are generated as NADH during glycolysis and NADPH from the reactions of the pentose shunt pathway. Mitochondrial reducing equivalents, which are

generated as NADH and reduced flavins from reactions including pyruvate dehydrogenase and Krebs cycle, are linked directly to the mitochondrial electron transport chain.

Generation of NADPH

NADPH is the major biological reductant for a wide variety of biosynthetic and detoxification reactions. Reactions that generate NADPH in the cytoplasm include the pentose pathway (glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase), conversion of malate to pyruvate by malic enzyme, and conversion of isocitrate to α-ketoglutarate by isocitric dehydrogenase; since mitochondria also have a $NADP^+$-linked isocitric dehydrogenase, this provides a mechanism by which NADPH generated in the mitochondria can be "shuttled" into the cytoplasm. All of these NADPH-generating enzymes are present in the lung although activity of malic enzyme is low and the quantitative contribution of the isocitric dehydrogenase reaction has not been evaluated (*28,45*). Therefore, the major source of NADPH in the lung cytoplasm is assumed to be the pentose pathway.

The role of the pentose pathway can be evaluated by comparing CO_2 production from glucoses labeled in the 1- and in the 6-position. If glucose utilization is measured simultaneously, pentose shunt activity can be calculated from the Katz and Wood model (*46*). In the perfused rat lung, the ratio of CO_2 production from C-1 and C-6 labels was approximately 4, and calculated activity of the pentose cycle was approximately 12% of total glucose utilization (*20*). CO_2 produced by the pentose cycle was 16 μmole/hr/g dry weight, which represents approximately 25% of total CO_2 production (*20*). Since 2 mole NADPH are produced per mole of CO_2, mean NADPH production from the pentose cycle was approximately 32 μmole/hr/g dry weight. PMS, an agent which interacts with cytoplasmic pyridine nucleotides as discussed above, stimulated pentose cycle activity about 2-fold (Table 2). CO ventilation markedly depressed pentose cycle activity, probably by inhibiting NADPH utilization, while DNP had no effect on NADPH generation. These results provide evidence that this pathway is regulated by the rate of NADPH utilization. An interesting observation was that the pentose pathway estimated from specific yields of C-1 and C-6 glucose in lipids was significantly higher than estimates based on CO_2 (*20*). This result could be interpreted as a manifestation of cellular heterogeneity of distribution of the pentose cycle, possibly reflecting the increased utilization of NADPH by cells actively engaged in lipid synthesis.

Recent experiments have suggested that in addition to the pentose cycle, mitochondrial generation of NADPH may be significant in some situations. Using the perfused lung, we evaluated the conversion of *p*-nitroanisole to *p*-nitrophenol, a mixed function oxidation requiring NADPH. The reaction required the presence of glucose for maximal rate, but mitochondrial substrates (palmitate, pyruvate) were equally effective (*47*). Furthermore, mitochondrial inhibitors significantly decreased the rate of the mixed function oxidation reaction (*47*). These results suggest that the mitochondrial generation of NADPH plays an important role in the lung, at least for the mixed function oxidation reaction. Mitochondrial NADPH could be generated by energy-dependent transhydrogenation from NADH and shuttled to the cytoplasm. However, the precise nature of these pathways in the lung remains speculative.

Table 2. Pentose pathway of the isolated perfused rat lung.[a]

	% of glucose utilization	NADPH generation, μmole/hr/g dry wt.
Control	11.9	32
CO	1.0	4
DNP	5.2	30
PMS	16.1	66

[a] Conditions as in Table 1.

Generation of Cytoplasmic NADH

Glycolysis via the Embden-Meyerhof pathway produces 2 mole NADH for each mole of glucose metabolized to pyruvate. Reoxidation of the cytoplasmic pyridine nucleotide is essential to permit glycolysis to proceed. NAD^+ can be regenerated through utilization of NADH in production of lactate from pyruvate or production of glycerol phosphate from dihydroxyacetone phosphate; incorporation of glycerol phosphate into lipids or efflux of lactate from the lung results in a net removal of glycolytically generated cytoplasmic reducing equivalents. The major additional pathway for removal of cytoplasmic NADH is by oxidation via the mitochondrial electron transport chain. However, mitochondrial membranes are impermeable to NADH which, therefore, must be transferred into the mitochondrial matrix via "hydrogen shuttle" mechanisms.

Data cited above for glucose flux in the isolated perfused lung indicate that glycolysis produces approximately 85 μmole NADH/hr/g dry weight. Of this, approximately 70 μmole/hr/g dry weight appear in the perfusate as lactate but the bulk of the rest (15 μmole/hr/g dry weight) is presumably reoxidized by the mitochondria after transfer by the mitochondrial "hydrogen shuttle."

Activities of the shuttle mechanisms for the transfer of reducing equivalents from cytoplasm to mitochondria have not been directly evaluated in the lung. However, there is evidence that at least two of the shuttles that have been proposed in other tissues could be functional in lung tissue. One such proposed shuttle is the glycerol-3-phosphate pathway in which dihydroxyacetone phosphate is reduced to glycerol-3-phosphate in the cytoplasm and reoxidized in the mitochondria (Fig. 4). Mitochondrial glycerol-3-phosphate dehydrogenase has been identified in lung mitochondria (*48–50*) and

activity of the cytoplasmic enzyme can be presumed from the significant concentrations of glycerol-3-phosphate in lung tissue (*26*). Another proposed "hydrogen shuttle" pathway is the malate-aspartate shuttle which requires influx of malate and efflux of asparate from the mitochondrial space. Operation of this shuttle requires transamination in both the cytoplasmic and mitochondrial spaces. Evidence that this shuttle is operative in the lung was provided by the response to infusion of aminoxyacetic acid, a transaminase inhibitor. This inhibitor resulted in a marked increase in the lactate to pyruvate ratio, suggesting reduction of cytoplasmic pyridine nucleotides due to inhibition of shuttle mechanisms (*26*).

In summary, mechanisms for transfer of reducing equivalents between cytoplasmic and mitochondrial spaces must be present in lung tissue. The enzymatic components necessary for operation of the glycerophosphate shuttle are present in the lung and inhibitor experiments suggest operation of a malate–aspartate shuttle. However, quantitative details of the participation of these or other mechanisms are lacking.

Lung ATP Synthesis and Energy Stores

Although the breathing process requires a significant energy expenditure for the organism, the role of the lungs is essentially passive. Therefore, lung tissue per se is a relatively modest consumer of energy in comparison to muscles of respiration or other working tissues (*1*). Nevertheless, the lung has energy-dependent functions that for the most part have been relatively poorly defined. Some of these energy-requiring functions include lung clearance (phagocytosis and ciliary activity), bronchial gland secretion, contraction of tracheobronchial smooth muscle, surfactant synthesis and secretion, and maintenance of normal transcellular ion gradients. Efficient functioning of these energy-dependent systems requires the maintenance of tissue energy stores.

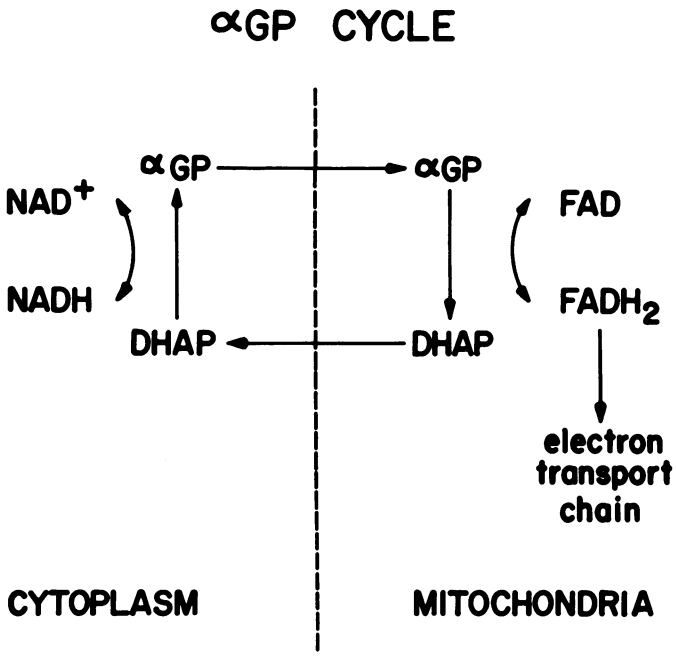

FIGURE 4. Schematic of the glycerol-3-phosphate (αGP) cycle for transfer of reducing equivalents between the cytoplasmic and mitochondrial compartments. Dihydroxyacetone phosphate is reduced with NADH by the cytoplasmic glycerol-3-phosphate dehydrogenase. The product, glycerol-3-phosphate, can enter the mitochondrion where it is oxidized by the flavin-linked mitochondrial glycerol-3-phosphate dehydrogenase. The product, dihydroxyacetone phosphate, can then diffuse into the cytoplasm.

Lung Energy Stores

The ATP content of the normal perfused lung is approximately 2 to 2.5 μmole/g wet weight (*23,39,51*). This value is approximately 50% of that measured in rat heart, but is similar to ATP values for rat brain, liver and kidney (*52*). Since the intracellular water space of the perfused lung is approximately 50% of wet weight, the intracellular ATP concentration is approximately 4 to 5 mM. The ATP/ADP of the lung is approximately 8. The calculated energy charge ([ATP + 0.5 ADP]/[ATP + ADP + AMP]) as defined by Atkinson (*53*) is greater than 0.9. Thus, the normal lung exists in a highly energized state similar to other metabolically active organs (*52*).

ATP Generation

Tissue ATP stores are determined by the balance between rates of ATP generation and utilization. In most metabolically active tissues, the bulk of ATP is generated from mitochondrial oxidation while glycolysis is only supplemental. The contribution of glycolytic and mitochondrial pathways of glucose utilization to ATP generation in the lung can be estimated from the results for glucose utilization described above. Production of lactate or pyruvate generates a equimolar amount of glycolytic ATP. Production of one mole of pyruvate also results in the generation of 3 mole mitochondrial ATP from the oxidation of NADH via the mitochondrial shuttles. Oxidation of glucose generates one-third mole glycolytic ATP and 6 mole mitochondrial ATP/mole of CO_2 produced. Using these relationships for the lung, generation of ATP is approximately 80% mitochondrial and 20% glycolytic under control condition (Table 3). With anoxia produced by CO ventilation, mitochondrial ATP production is essentially abolished while ATP generation by cytosolic pathways approximately doubles. However, the total rate of ATP generation during anoxia is reduced by about 70% and is reflected by a marked decrease in lung ATP content and ATP/ADP (*23*) (see Fig. 3). This result indicates that oxidative metabolism is required in order to maintain the normal energy status of the lung.

Table 3. Estimated ATP generation from metabolism of glucose by the isolated perfused rat lung.[a]

	ATP generation, μmole/hr/g dry wt.		
	Cytosolic	Mitochondrial	Total
Control	62	363	425
CO[b]	124	42	166

[a] Results represent estimates based on recovery of glucose-carbon in catabolic products.
[b] Lungs ventilated with 95% CO, 5% CO_2.

Critical P_{O_2} of the Lung Cells

The oxygen tension at which oxidative metabolism is depressed (critical P_{O_2}) is of some interest in defining control of lung metabolism. It should be noted that diffusion pathways in the lung are extremely short (as required for proper functioning of the organ) compared with other tissues and that alveolar gas represents a large reservoir for oxygen at a relatively constant P_{O_2}. Therefore, alveolar P_{O_2} approximates intracellular P_{O_2}, a relationship that can be strengthened by using the perfused lung preparation under conditions of no net gas exchange.

With the isolated lung preparation, oxidative metabolism as reflected by lactate production, lactate to pyruvate ratio, and ATP content is not affected until estimated intracellular P_{O_2} is approximately 1 mm Hg; complete inhibition of oxidative metabolism requires a P_{O_2} less than 0.04 mm Hg (*25,26*). The ability of the lung tissue to sustain oxidative metabolism in the face of very low P_{O_2} likely accounts for previous observations that the lung is relatively resistant to damage from hypoxia (*54*). It should be noted that the "critical" P_{O_2} for the lung roughly corresponds to that measured for isolated mitochondria from various organs (*55*). We postulate that the measured critical P_{O_2} of the lung is probably similar to the critical intracellular P_{O_2} for most other organs. Major differences between lungs and other organs are that the lung is not dependent upon vascular perfusion for its oxygen needs and has a much more favorable balance between oxygen availability and oxygen utilization.

Isolated Lung Mitochondria

The mitochondrion is the site of oxidative ATP generation; inhibition of the function of this organelle *in situ* results in depletion of lung ATP stores as described above. Evaluation of isolated lung mitochondria is hampered by cellular heterogeneity of the lung and only a limited amount of baseline information has been obtained for these organelles. Intact mitochondria can be isolated from lungs by modification of standard techniques based on tissue homogenization and differential centrifugation (*1,48–50,56,57*). These isolated mitochondria have a full complement of respiratory chain cytochromes and demonstrate respiration that is coupled to ATP synthesis (*49*). Morphologically, isolated lung mitochondria resemble those isolated from liver (*1*) but show considerably fewer cristae than heart mitochondria. Rates of substrate oxidation, degree of coupling (i.e., respiratory control ratio), and content of cytochromes with most preparations have been somewhat less than observed with liver preparations; however, this difference may be related primarily to the greater contamination of lung preparations with nonmitochondrial protein and the greater trauma required to homogenize the lung (*57*).

Lung mitochondria oxidize pyruvate, glycerol-3 phosphate, glutamate, fatty acids, and intermediates of the tricarboxylic acid cycle (*49*). These activities indicate the presence of the pyruvate dehydrogenase complex, glutamate transaminases, glycerol-3 phosphate dehydrogenase, enzymes for beta-oxidation for fatty acids, and the Krebs cycle enzymes. Thus, these isolated lung mitochondria have the usual enzymes necessary for the organelles to carry out their complex oxidative reactions. β-Hydroxybutyrate, a ketone body and product of fatty acid oxidation, is oxidized poorly in comparison with other substrates by mitochondria from the rat (*49,50*) but at a relatively greater rate by mitochondria from the lungs of other species (*48*). Relative rates of oxidation of selected substrates by lung mitochondria from several species are shown in Table 4.

Intermediary Metabolism: Pharmacology and Toxicology

The relationship of intermediary metabolism to lung pathophysiology has been examined in detail for only a limited number of conditions. Studies of this sort are particularly vulnerable to problems with interpretation because of cellular heterogeneity of the normal lung and heterogeneity of cellular response to toxic insults. Conditions of toxicologic interest for which some information is available with respect to involvement of intermediary metabolism include pulmonary uptake of vasoactive hormones, pulmonary edema and the effects of oxidant exposure.

Uptake of Vasoactive Amines

The lung plays an important role in vasoactive amine homeostasis. Thus, lungs accumulate 5-hydroxytrypt-

Table 4. Relative rates of ADP-stimulated O_2 consumption with selected substrates by isolated lung mitochondria from various species.

	Relative rate[a]			
	Rat	Rabbit	Sheep	Pigeon
Succinate	1	1	1	1
Pyruvate	0.75	0.92	0.82	0.69
α-Ketoglutarate	0.75	1.33	1.00	0.73
β-OH butyrate	0.13	0.88	0.55	0.46
Glycerol-3-phosphate	0.41	0.75	0.45	0.23

[a] Rates are relative to the rate for succinate which is assigned a value of 1 for each species.

amine (serotonin) by a sodium-dependent active transport process (*2,58,59*). This amine is subsequently metabolized to inactive products, thereby helping to regulate its serum concentration. Norepinephrine is handled similarly by the lung (*60*). Uptake of serotonin is depressed in the presence of mitochondrial electron transport chain inhibitors such as KCN or anoxia (*59,61*). Thus, ATP generated by mitochondrial metabolism appears necessary to maintain maximal rates of serotonin uptake.

Further evidence for the link between intermediary metabolism and serotonin uptake by the lung is indicated by a 40% decrease in uptake when glucose and other substrates are eliminated from the perfusate (*61*). Thus, catabolism of protein and other endogenous substrates is not sufficient to maintain control rates of 5-HT uptake. The requirement for substrate was further demonstrated by perfusing lungs with 2-deoxyglucose which not only competes with glucose for glycolytic enzymes but also results in depletion of tissue ATP stores (*62*). Addition of a variety of metabolizable substrates including pyruvate, palmitate, β-hydroxybutyrate, and glycerol essentially reverse the inhibitory effect of deoxyglucose (*62*) indicating that intermediary metabolism plays a key role in the maintenance of normal rates of amine uptake.

Pulmonary Edema

Pulmonary edema represents a common response to a wide range of lung insults. Once established, pulmonary edema could influence lung intermediary metabolism through alteration of substrate availability, interference with end product removal, or other secondary effects. More interesting, though, is the possible influence of altered intermediary metabolism on the genesis of lung edema. Maintenance of the alveolar space in an edema-free condition depends in part on maintenance of normal epithelial permeability. This permeability barrier may in turn reflect cellular metabolic activity although specific information on this point is scanty.

Several studies have indirectly suggested a link between lung metabolism and edema. In one study, isolated rat lungs perfused in the absence of a metabolizable substrate in the perfusate developed gross alveolar edema in approximately 1 hr at physiological flow rates; addition of glucose to the medium prolonged the time that lungs remained edema free by 50% while substitution of a complete nutrient medium extended the time to edema 5-fold (*63*). In another study, lungs stimulated to become edematous showed increased glycolytic activity and reduced lung tissue ATP (*64,65*). In another study, inhibition of the mitochondrial electron transport chain by CO appeared to qualitatively increase the tendency towards edema in the perfused lung although the ATP concentration was decreased significantly while the lungs remained edema free (*23*). These responses suggest that edema formation in some circumstances may be related to altered cellular intermediary metabolism although more extensive studies are obviously required.

Response to Hyperoxia and Other Oxidants

Although all tissues are susceptible to damage from exposure to elevated oxygen tensions, the lung is particularly vulnerable since in most clinical situations it is exposed to the highest P_{O_2} (*66*). The toxicity of oxygen appears to derive from the generation of toxic free radicals subsequent to metabolic reduction of molecular oxygen (*67*). The ultimate elimination of these toxic free radicals by their further reduction to water requires reducing equivalents generated intracellularly from intermediary metabolism.

The major intracellular reductant involved in antioxidant defenses is reduced glutathione, which, once oxidized is restored to the reduced condition with NADPH via the glutathione reductase reaction. NADH may play a limited role in antioxidant defense as, for example, in the reduction of oxidized ascorbate by semidehydroascorbate reductase (*68*). In addition, NADH may contribute to the NADPH pool by a transhydrogenation reaction involving the mitochondria as described above. However, generation of NADPH appears to be of primary importance in protection of the lung tissue against hyperoxic damage.

The role of NADPH generation in antioxidant defense has been demonstrated by perfusing isolated rat lungs during exposure to oxygen at 5 atmospheres absolute (ATA). This maneuver led to an approximate doubling of the rate of NADPH generation via the pentose cycle with no change in the rate of mitochondrial activity (*69*). Thus, the effect of hyperoxia on lung metabolism appears to be a specific stimulation of pentose cycle activity in order to meet the increased demand for cytoplasmic reducing equivalents. Further evidence of the role of pentose cycle in antioxidant defense has been obtained by finding increased glucose-6-phosphate dehydrogenase activity (one of the rate-limiting enzymes of the pentose cycle) in lungs from rats exposed chronically to sublethal levels of hyperoxia (*70*).

Paraquat, an herbicide, is another agent that produces lung toxicity as a major clinical manifestation (*71*) and exerts an effect most likely through generation of toxic free radicals (*72*). The sequence of events appears to be reduction of paraquat by an NADPH-dependent microsomal reductase, followed by autooxidation of the reduced paraquat and consequent generation of superoxide anion. The isolated, perfused lung shows a 2.5- to 3-fold increase in pentose cycle activity in the presence of saturating concentrations of paraquat (*73*). Since paraquat cannot interact directly with cytoplasmic nucleotides, the finding of increased NADPH generation indicates an increased rate of its utilization through the NADPH-cytochrome c reductase and glutathione reductase reactions. Thus, unlike oxygen toxicity,

NADPH in paraquat toxicity acts both in the generation of the toxic species (reduced paraquat) as well as in protection against the subsequent metabolic products. The pentose cycle in this situation, therefore, represents a double-edged sword, since it acts as both activator and protector against the toxic mechanism.

I thank my collaborators through the years who have helped to carry out many of the investigations described in this paper. These include David Bassett, Harry Steinberg, Janet Kerr, John Williamson, Arnost Kleinzeller, and Britton Chance. Original research has been supported by Public Health Service Grants HL 15013, HL 15061, and HL 19737 and an Established Investigatorship Award from the American Heart Association.

REFERENCES

1. Fisher, A. B. Oxygen utilization and energy production. In: The Biochemical Basis of Lung Function (R. G. Crystal, Ed.), Marcel Dekker, New York, 1976, pp. 75–104.
2. Fisher, A. B., Steinberg, H., and Bassett, D. Energy utilization by the lung. Am. J. Med. 57: 437–446 (1974).
3. Tierney, D. F. Lung metabolism and biochemistry. Ann. Rev. Physiol. 36: 209–231 (1974).
4. Tierney, D. F., and Levy, S. E. Glucose metabolism. In: The Biochemical Basis of Pulmonary Function (R. G. Crystal, Ed.), Marcel Dekker, New York, 1976, pp. 105–125.
5. Devereux, T. R., Serabit-Singh, C. J., Slaughter, S. R., Wolf, C. R., Philpot, R. M., and Fouts, J. R. Identification of cytochrome P-450 isozymes in non-ciliated bronchiolar epithelial (Clara) and alveolar type II cells isolated from rabbit lung. Exptl. Lung Res. 2: 221–230 (1981).
6. Fisher, A. B., Furia, L., and Berman, H. Metabolism of rat granular pneumocytes isolated in primary culture. J. Appl. Physiol. 49: 743–750 (1980).
7. Habliston, D. L., Whitaker, C., Hart, M. A., Ryan, U. S., and Ryan, J. W. Isolation and culture of endothelial cells from the lungs of small animals. Am. Rev. Respir. Dis. 119: 853–868 (1979).
8. Kikkawa, Y., and Yoneda, K. The type II epithelial cell of the lung I. Method of isolation. Lab. Invest. 30: 76–84 (1974).
9. Mason, R. J., Williams, M. C., Greenleaf, R. D., and Clements, J. A. Isolation and properties of type II alveolar cells from rat lung. Am. Rev. Respir. Dis. 115: 1015–1026 (1977).
10. Picciano, P., and Rosenbaum, R. M. The type I alveolar lining cells of the mammalian lung. I. Isolation and enrichment from dissociated adult rabbit lung. Am. J. Pathol. 90: 99–122 (1978).
11. Bassett, D. J. P., Hamosh, M., Hamosh, P., and Rabinowitz, J. Pathways of palmitate metabolism in the isolated rat lung. Exp. Lung Res. 2: 37–47 (1981).
12. Rhoades, R. A. Net uptake of glucose, glycerol, and fatty acids by the isolated perfused rat lung. Am. J. Physiol. 226: 144–149 (1974).
13. Wolfe, R. R., Hochachka, P. W., Trelstad, R. L., and Burke, J. F. Lactate metabolism in perfused rat lung. Am. J. Physiol. 236: E276–282 (1979).
14. Shaw, M. E., and Rhoades, R. A. Substrate metabolism in the perfused lung: response to changes in circulating glucose and palmitate levels. Lipids 12: 930–935 (1977).
15. Le Fevre, P. G. Transport of carbohydrates by animal cells. Metabolic pathways. In: Metabolic Transport, VI (L. E. Hokin, Ed.), Academic Press, New York, 1972, pp. 385–454.
16. Landau, B. R., Bernstein, L., and Wilson, T. H. W. Hexose transport by hamster intestine *in vitro*. Am. J. Physiol. 203: 237–240 (1962).
17. Ullrich, K. J. Sugar, amino acid and Na^+ cotransport in the proximal tubule. Ann. Rev. Physiol. 41: 181–195 (1979).
18. Fricke, R. F., and Longmore, W. J. Effects of insulin and diabetes on 2-deoxy-D-glucose uptake by the isolated perfused rat lung. J. Biol. Chem. 254: 5092–5098 (1979).
19. Kerr, J. S., Fisher, A. B., and Kleinzeller, A. Transport of glucose analogues in rat lung. Am. J. Physiol. 241: E191–195 (1981).
20. Bassett, D. J. P., and Fisher, A. B. Pentose cycle activity of the isolated perfused rat lung. Am. J. Physiol. 231: 1527–1532 (1976).
21. Kerr, J. S., Baker, N. J., Bassett, D. J. P., and Fisher, A. B. Effect of perfusate glucose concentration on rat lung glycolysis. Am. J. Physiol. 236: E229–233 (1979).
22. Rhoades, R. A., Shaw, M. E., Eskew, M. L., and Wali, S. Lactate metabolism in perfused rat lung. Am. J. Physiol. 235: E619–623 (1978).
23. Bassett, D. J. P., and Fisher, A. B. Metabolic response to carbon monoxide by isolated rat lungs. Am. J. Physiol. 230: 658–663 (1976).
24. Williamson, J. R. Glycolytic control mechanisms. I. Inhibition of glycolysis by acetate and pyruvate in the isolated, perfused rat heart. J. Biol. Chem. 240: 2308–2321 (1965).
25. Fisher, A. B., and Dodia, C. The lung as a model for evaluation of critical intracellular P_O and P_{CO}. Am. J. Physiol. 241: E47–50 (1981).
26. Fisher, A. B., Furia, L., and Chance, B. Evaluation of redox state of the isolated rat lung. Am. J. Physiol. 230: 1198–1204 (1976).
27. Wallace, H. W., Stein, T. P., and Liquori, E. M. Lactate and lung metabolism. J. Thor. Cardiovasc. Surg. 68: 810–814 (1974).
28. Scholz, R. W., and Rhoades, R. A. Lipid metabolism by rat lung in vitro. Effect of starvation and refeeding on utilization of [U-^{14}C] glucose by lung slices. Biochem. J. 124: 257–264 (1971).
29. Yeager, H., Jr., and Hicks, P. S. Glucose metabolism in lung slices of late fetal, newborn, and adult rats. Proc. Soc. Exptl. Biol. Med. 141: 1–3 (1972).
30. Yeager, H., Jr., and Massaro, D. Glucose metabolism and glyco-protein synthesis by lung slices. J. Appl. Physiol. 32: 477–482 (1972).
31. Chiang, M. J., Whitney, P., Jr., and Massaro, D. Protein metabolism in lung: use of isolated perfused lung to study protein degradation. J. Appl. Physiol. 47: 72–78 (1979).
32. Longmore, W. J., and Mourning, J. T. Lactate production in the isolated perfused rat lung. Am. J. Physiol. 231: 351–354 (1976).
33. Fisher, A. B., Huber, G. A., Furia, L., Bassett, D., and Rabinowitz, J. L. Evidence for lipid synthesis by the dihydroxyacetone phosphate pathway in rabbit lung subcellular fractions. J. Lab. Clin. Med. 87: 1033–1040 (1976).
34. Bassett, D. J. P., Fisher, A. B., and Rabinowitz, J. L. Effect of hypoxia on glucose incorporation into lipids by isolated rat lung. Am. J. Physiol. 227: 1103–1108 (1974).
35. Buechler, K. F., and Rhoades, R. A. Fatty acid synthesis in the perfused rat lung. Biochim. Biophys. Acta 619: 186–195 (1980).
36. Hamosh, M., Shechter, Y., and Hamosh, P. Metabolic activity of developing rabbit lung. Pediatr. Res. 12: 95–100 (1978).
37. Rhoades, R. A. Influence of starvation on the lung: effect on glucose and palmitate utilization. J. Appl. Physiol. 38: 513–516 (1975).
38. Scholz, R. W. Lipid metabolism by rat lung in vitro: utilization of citrate by normal and starved rats. Biochem. J. 126: 1219–1224 (1972).
39. Bassett, D. J. P., and Fisher, A. B. Stimulation of rat lung metabolism with 2,4-dinitrophenol and phenazine methosulfate. Am. J. Physiol. 321: 898–902 (1976).
40. Fisher, A. B. and Dodia, C. Lactate and regulation of lung glycolytic rate. Am. J. Physiol., in press.
41. Morishige, W. K., Uetake, C. A., Greenwood, F. C., and Akaka, J. A. Pulmonary insulin responsivity: *in vitro* effects of insulin on the diabetic rat lung and specific insulin binding to lung receptors in normal rats. Endocrinology 100: 1710–1722 (1977).
42. Moxley, M. A., and Longmore, W. J. Effect of experimental diabetes and insulin on lipid metabolism in the isolated perfused rat lung. Biochim. Biophys. Acta 488: 218–244 (1977).
43. Thet, L. A., Delaney, M. D., Gregorio, C. A., and Massaro, D. Protein metabolism by rat lung: influence of fasting, glucose, and insulin. J. Appl. Physiol. 43: 463–467 (1977).
44. Stubbs, W. A., Morgan, I., Lloyd, B., and Alberti, K. B. M. M.

The effect of insulin on lung metabolism in the rat. Clin. Endocrinol. 7: 181–184 (1977).
45. Scholz, R. W., and Evans, R. M. Pulmonary fatty acid synthesis II. Amino acids as fatty acid precursors in rat lung. Am. J. Physiol. 232: E364–369 (1977).
46. Katz, J., and Wood, H. G. The use of $^{14}CO_2$ yields from glucose-1- and -6-C^{14} for the evaluation of the pathways of glucose metabolism. J. Biol. Chem. 238: 517–523 (1963).
47. Fisher, A. B., Itakura, N., Dodia, C., and Thurman, R. G. Pulmonary mixed-function oxidation: stimulation by glucose and the effects of metabolic inhibitors. Biochem. Pharmacol. 30: 379–383 (1981).
48. Fisher, A. B., Huber, G. A., and Bassett, D. J. P. Oxidation of alpha-glycerophosphate by mitochondria from lungs of rabbits, sheep, and pigeons. Comp. Biochem. Physiol. 50B: 5–8 (1975).
49. Fisher, A. B., Scarpa, A., LaNoue, K. F., Bassett, D., and Williamson, J. R. Respiration of rat lung mitochondria and the influence of Ca^{2+} on substrate utilization. Biochemistry 12: 1438–1445 (1973).
50. Mustafa, M. G., and Cross, C. E. Lung cell mitochondria: rapid oxidation of glycerol-1-phosphate but slow oxidation of 3-hydroxybutyrate. Am. Rev. Respir. Dis. 109: 301–303 (1974).
51. Fisher, A. B. Energy status of the rat lung after exposure to elevated P_{O_2}. J. Appl. Physiol. 45: 56–59 (1978).
52. Williamson, J. R., and Corkey, B. E. Assays of intermediates of the citric acid cycle and related compounds by fluorometric enzyme methods. Methods in Enzymology 13: 434–513 (1969).
53. Atkinson, D. E., Walton, G. M. Adenosine triphosphate conservation in metabolic regulation. J. Biol. Chem. 242: 3239–3241 (1967).
54. Fisher, A. B., Hyde, R. W., and Reif, J. S. Insensitivity of the alveolar septum to local hypoxia. Am. J. Physiol. 223: 770–776 (1972).
55. Chance, B. Reaction of oxygen with the respiratory chain in cells and tissues. J. Gen. Physiol. 49: 163–188 (1965).
56. Reiss, O. K. Studies in lung metabolism I. Isolation and properties of subcellular fractions from rabbit lung. J. Cell Biol. 30: 45–57 (1966).
57. Spear, R. K., and Lumeng, L. A method for isolating lung mitochondria from rabbits, rats, and mice with improved respiratory characteristics. Anal. Biochem. 90: 211–219 (1978).
58. Fisher, A. B., Block, E. R., and Pietra, G. G. Environmental influence on uptake of serotonin and other amines. Environ. Health Perspect. 35: 191–198 (1980).
59. Junod, A. F. Uptake, metabolism and efflux of ^{14}C-5-hydroxytryptamine in isolated perfused rat lungs. J. Pharmacol. Exptl. Therap. 183: 341–355 (1973).
60. Iwasawa, Y., and Gillis, C. N. Pharmacological analysis of norepinephrine and 5-hydroxytryptamine removal from the pulmonary circulation: differentiation of uptake sites for each amine. J. Pharm. Exptl. Therap. 183: 341–355 (1973).
61. Steinberg, H., Bassett, D. J. P., and Fisher, A. B. Depression of pulmonary 5-hydroxy-tryptamine uptake by metabolic inhibitors. Am. J. Physiol. 228: 1298–1303 (1975).
62. Fisher, A. B., Steinberg, H., and Dodia, C. Reversal of 2-deoxyglucose inhibition of serotonin uptake in isolated guinea pig lung. J. Appl. Physiol. 46: 447–450 (1979).
63. Fisher, A. B., Dodia, C., and Linask, J. Perfusate composition and edema formation in isolated rat lungs. Exptl. Lung. Res. 1: 13–22 (1980).
64. Postlethwait, E. M., and Young, S. L. Alteration of rat lung adenine nucleotide content after pulmonary edema. Lung 157: 165–177 (1980).
65. Young, S. L., O'Neil, J. J., Kasuyama, R. S., and Tierney, D. F. Glucose utilization by edematous rat lungs. Lung 157: 165–177 (1980).
66. Clark, J. M., and Lambertsen, C. J. Pulmonary oxygen toxicity: a review. Pharmacol. Rev. 23: 37–133 (1971).
67. Fisher, A. B., Bassett, D. J. P., and Forman, H. J. Oxygen toxicity of the lung: Biochemical aspects. In: Pulmonary Edema (A. Fishman and E. Renkin, Eds.), Am. Physiol. Soc., Bethesda, MD, 1979, pp. 207–216.
68. Forman, H. J., and Fisher, A. B. Anti-oxidant defense. In: Oxygen and Living Processes (D. L. Gilbert, Ed.), Springer-Verlag, New York, 1981, pp. 235–249.
69. Bassett, D. J. P., and Fisher, A. B. Glucose metabolism in rat lung during exposure to hyperbaric O_2. J. Appl. Physiol. 46: 943–949 (1979).
70. Tierney, D., Ayers, L., Herzog, S., and Yang, J. Pentose pathway and production of reduced nicotinamide adenine dinucleotide phosphate. A mechanism that may protect lungs from oxidants. Am. Rev. Resp. Dis. 108: 1348–1351 (1973).
71. Fisher, H. K., Clements, J. A., and Wright, R. R. Enhancement of oxygen toxicity by the herbicide paraquat. Am. Rev. Resp. Dis. 107: 246–252 (1973).
72. Bus, J. S., Aust, S. D., and Gibson, J. E. Superoxide and singlet oxygen-catalyzed lipid peroxidation as a possible mechanism for paraquat (methyl viologen) toxicity. Biochem. Biophys. Res. Comm. 58: 749–755 (1974).
73. Bassett, D. J. P., and Fisher, A. B. Alterations of glucose metabolism during perfusion of rat lung with paraquat. Am. J. Physiol. 234: E653–E659 (1978).