Growth of Microbial Cells on Hydrocarbons

Microbial protein feeds from hydrocarbons could be abundant if technological problems were solved.

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The fact that many microorganisms can grow by using hydrocarbons as a sole source of carbon and energy has been known for more than half a century. Recently there has been a great deal of microbiologic and biochemical work on microbial oxidation of hydrocarbons; the mechanisms by which hydrocarbon molecules are attacked and the biochemical pathways by which they are degraded have been investigated. The specificities of hydrocarbon substrates for various microorganisms have been studied. Early work has been well reviewed by Beerstecher (*1*), and Foster's (*2*) review of the general subject of microbial oxidation of hydrocarbons is excellent. Recent work on mechanisms has been reviewed by Van der Linden and Thijsse (*3*) and by McKenna and Kallio (*4*).

Although much research has been done on the manner in which microorganisms utilize hydrocarbons for growth, until very recently little attention had been paid to the microbial cells themselves: the rate at which they grow, the weight of cells obtained from a given amount of hydrocarbon, and the composition of the cells. One reason for this recent interest is the possibility that microbial cells, grown on hydrocarbons, may serve as a source of food for man or domestic animals; cells are rich in essential amino acids and water-soluble vitamins. Production of microbial cells, from raw materials not derived from crops, might increase the world's food supply very significantly. It is technologically possible, by using known processes, to use between 15 and 20 percent of the world's production of petroleum to produce 100 percent of the protein required by the world's inhabitants. Protein food, produced on a large scale by such a process, would today be more expensive than protein from many present sources and would certainly be unacceptable as a major food item to most of the world's population. The possibility of producing this protein, however, does point up the potential of petroleum as a source of food or fodder.

Work in many laboratories, including mine, is directed toward finding the most suitable microorganisms and growth procedures for cell production from various types of hydrocarbons. My purpose now is to describe the present status of these efforts.

Choice of Microorganism

The choice of a microorganism for large-scale growth on hydrocarbons is influenced by many factors. The organism must be able to utilize the hydrocarbon source to be employed, and it must grow rapidly under conditions that make large-scale propagation convenient—for example, it should have no requirements for vitamins or other growth factors, and it should not be mechanically fragile; harvesting, including separation from unused hydrocarbon, should be simple. It should contain a high percentage of essential amino acids, but nothing toxic; it should be readily digestible by animals, and the yield of cells (weight of cells produced from unit weight of substrate) should be as high as possible.

The groups of microorganisms found to include species that grow well on hydrocarbons are bacteria, yeasts, and molds. One cannot make an a priori selection among these groups; the organism selected will depend upon the substrate to be used and the intended use of the cells. It is instructive, however, to compare the groups with each other and with more usual sources of protein.

In comparing analyses of microorganisms, one must take into account the fact that the nitrogen content of microorganisms can be varied two- or threefold by changing growth conditions: cells grown in nitrogen-deficient media are low in protein. Other deficiencies also influence cell composition. However, the amino acid composition of the protein does not change when the amount of the protein changes. Because there are cell constituents, such as nucleic acids and chitinous materials, that contain nitrogen but do not contain essential amino acids, the nitrogen content of the cell is at best only a rough index of the cell's nutritive value as a source of protein. A much better index is the essential amino acid content of the cell. Table 1 gives data on the contents of nitrogen and essential amino acids of a number of sources of protein, including 11 microbial samples; note that the molds have a lower nitrogen content and a definitely lower content of essential amino acids than have yeasts or bacteria. The ratios in which individual essential amino acids occur in various organisms vary, but there are few outstanding differences. Table 2 shows the mean composition of the essential amino acid fraction of the 11 microbial samples of Table 1. The values for standard deviation show that the differences are not large; the largest standard deviation is for histidine, and reflects the fact that bacteria are usually lower in histidine than are yeasts or molds. The methionine content of the microbial-cell protein is lower than that of animal muscle or fish meal. Microbial proteins have in general been found to be somewhat lower in sulfur amino acids than are animal proteins.

The data of Tables 1 and 2 indicate that, from a nutritional point of view, we should prefer yeasts or bacteria to molds unless there is some other advantage in growing molds. In fact there is an extremely good reason for avoiding molds: when grown on a large scale they are very difficult to aerate; three or four times as much power is needed for aeration and agitation when molds rather than yeasts or bacteria are being grown. A suspension of mold mycelium is likely to resemble a suspension of paper pulp, and rapid transfer of oxygen from air bubbles to cells is difficult to achieve. A choice between

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bacteria and yeasts cannot be made as readily. Bacteria, being smaller than yeast cells, are much harder to harvest by centrifugation—the usual method of recovery for yeasts; other things being equal, a bacterium (1 micron in diameter) sediments in a centrifugal field 25 times more slowly than a yeast cell (5 microns in diameter). Centrifugal harvesting of bacterial cells is expensive, and, unless some other harvesting procedure (flocculation, flotation, or the like) can be substituted, yeasts have an important advantage. Although the useful protein contents of yeasts and bacteria are similar, bacteria have a higher content of nucleic acids, and hence of purines and pyrimidines. If a large part of the protein intake of an animal were to be from microbial sources, a high purine content would be undesirable.

On the other hand, bacteria grow on a much wider variety of hydrocarbon substrates than do yeasts or molds. The only hydrocarbons on which yeasts are known to grow readily are normal alkanes and alkenes, molds grow well on normal alkanes and some slowly utilize branched alkanes, while bacteria grow well on straight- or branched-chain hydrocarbons, aromatic hydrocarbons, or methane.

Cell Yields

If microbial cells are to be grown in quantity on a hydrocarbon substrate, the cell yield (the amount of cell substance produced from a given weight of hydrocarbon) is important. The literature contains few data on yields of microbial cells from hydrocarbons; in some instances yield figures are available only for experiments in which growth conditions did not favor high yields. The information suffices, however, for comparison of yields of yeast and bacterial cells grown on hydrocarbons with yields of the same or similar organisms grown on more conventional substrates.

Yeasts grown on hydrocarbon substrates (*n*-alkanes) are usually members of the genus *Candida,* for which Table 3 lists yields from various carbon sources. The yields are expressed as grams of cells (dry basis) per gram of substrate used, substrate carbon used, and oxygen used. The cell yield based on oxygen used can be regarded as the cell yield on available energy, because synthesis of adenosine triphosphate from most substrates is approximately proportional to the oxygen consumed. The figure for oxygen used is calculated (*5*) from considerations of material balance. It is assumed that the cells produced have "normal" composition, and that no carbon compounds other than cells, and cells and carbon dioxide, are formed. The calculation is based on the fact that the amount of oxygen necessary to burn the utilized substrate, minus the amount of oxygen required to burn the product, must be the amount of oxygen used in conversion of substrate to product. The cell composition assumed was: C, 47 percent; H, 6.5 percent; O, 31 percent; N, 7.5 percent; ash, 8 percent.

All yields in Table 3 were obtained with growth media in which the substrate was the only carbon compound present. The data on yields for glucose, acetic acid, and ethanol (from my laboratory) were obtained in experiments in which the growth conditions were the same for all substrates; they are typical of independent and earlier data. The difference in yield between glucose and acetic acid (which has the same empirical formula as glucose) is striking. The yield on ethanol is better than that from acetate on a weight or on a carbon basis, but the yield from the two two-carbon compounds is about the same on the oxygen basis. The yield from the two-carbon compounds is of interest because, when an alkane is used, it is presumably converted to acetyl coenzyme A; thus, with either two-carbon or alkane substrates, all cell constituents must be synthesized from two-carbon fragments. The yields on alkanes are, on a carbon basis, roughly the same as those from acetate, but are much lower on an oxygen basis. The low cell yields on oxygen, obtained with alkanes and two-carbon compounds, indicate either that available energy (that is, adenosine triphosphate) is not a limiting factor with these substrates, or that more additional energy is needed with these substrates than is calculable from known biosynthetic mechanisms. The weight yields on alkanes (obtained in my laboratory) are in the neighborhood of 80 percent; yields reported by Raymond (*6*) and Takeda *et al.* (*7*) are somewhat lower.

Yeasts have not been reported to attack hydrocarbons other than normal alkanes. Some bacteria are more versatile: members of the genera *Mycobacterium* (and the closely related genus *Nocardia*) and *Pseudomonas* appear to be particularly gifted. Bacteria are known to degrade a wide range of normal, branched, and cyclic alkanes as well as very many aromatic hydrocarbons. Table 4 gives data on cell yields by *Pseudomonas* species on

Table 1. Essential amino acid contents of microorganisms; plant and animal samples are compared. The amino acids are those listed in Table 2.

Sample	Content (%)	
	Essential amino acids (dry wt)	Nitrogen
Bacteria		
Staphylococcus aureus (*13*)	21.6	10.75
Escherichia coli (*13*)	33.1	13.19
Bacillus subtilis (*13*)	23.8	10.07
Yeasts		
Saccharomyces cerevisiae, av. (*14*)	17.1–23.8	5.9–8.2
Saccharomyces cerevisiae (*13*)	23.1	8.94
Torula yeast (*15*)	29.5	8.35
Torula yeast (*16*)	24.4	7.47
Molds		
Aspergillus niger (*13*)	9.2	5.21
Penicillium notatum (*13*)	12.8	6.13
Rhizopus nigricans (*13*)	9.6	5.80
Mushroom		
Tricholoma nudum (*17*)	20.8	8.64
Nonmicrobial samples		
Animal muscle, av. (*18*)	48.1	15.4
Fish meal, av. (*16*)	32.1	9.8
Alfalfa meal (*16*)	6.9	2.72

Table 2. Average amino acid distribution of the 11 microbial samples of Table 1, with standard deviation from the average.

Amino acid	Percent of total essential amino acids	Standard deviation
Histidine	7.22	1.05
Arginine	11.18	0.36
Lysine	15.31	1.01
Leucine	16.57	0.53
Isoleucine	11.34	.57
Valine	11.85	.37
Methionine	3.81	.31
Threonine	10.23	.33
Phenylalanine	9.43	.67

various substrates: note that yields on glucose and acetate are a little lower than with yeast, while yields on alkanes are somewhat higher. Yields on methane given by methane-utilizing species are not as high as are given by other species on normal and branched chains; this difference is at least partly attributable to the fact that much less research has been done on cell production from methane than from higher alkanes. There may be another factor: The initial attack by an organism on an alkane molecule is probably an oxidation of a terminal methyl group by a mixed-function oxidase (*5*), in which 1 mole of O_2 is used and no adenosine triphosphate is generated. If a higher alkane is used, only a small percentage of the total oxygen used is consumed in this way; but, if methane utilization involves a mixed-function oxidase, 1 mole of O_2 per mole of methane is used by the oxidase, and the amount of adenosine triphosphate generated is correspondingly less. If the cell yield on methane is 60 percent, on oxygen it is 18.75 percent. If, however, the oxygen presumably consumed by the mixed-function oxidase is omitted from the calculation, the cell yield on oxygen becomes 50 percent—approximately the same as yields, in my laboratory, from higher alkanes.

There are data on cell yields for genera other than *Candida* and *Pseudomonas*. For example, weight yields as high as 83 percent have been obtained (*8*) with *Nocardia* on octadecane; as high as 116 percent, with *Micrococcus* on hexadecane (*9*). In my laboratory yields of 108 to 113 percent have been obtained on octadecane and pristane with *Corynebacterium*. Although cell yields have been studied with only limited numbers of microbial genera and of hydrocarbon substrates, it appears that weight yields of 80 percent can readily be obtained with yeasts; of 100 percent or more with bacteria. Yields from methane, however, are apparently lower.

Choice of a hydrocarbon substrate for production of microbial protein will be dictated largely by cost. The only reasonably pure hydrocarbons that can be called very cheap are methane (less than 2.2 cents per kilogram), and propane and butane (less than 4.4 cents per kilogram). Higher alkanes are usable in liquid fuels and hence command a higher price; and they may need purification before they are used. If the organism to be grown is a yeast, methane apparently cannot be used; no yeasts are known to grow on methane. Bacteria growing on methane are easily isolated and grown; bacteria growing on propane and butane also are well known, but no yield data are yet available. No yeasts have been reported to attack propane and butane, but such may exist; they readily attack higher *n*-paraffins. These alkanes are relatively expensive in purified form, but may be used (as I shall mention) from crude mixtures containing them.

Table 3. Cell yields of cultures of *Candida*, and of one close relation (*Torulopsis*), on various substrates. See text for method of calculating yield per gram of oxygen.

Organism	Substrate	Cell yield (g/g)		
		Substrate	Substrate carbon	Oxygen used
C. utilis (*19*)	Glucose	0.51	1.28	1.30
C. utilis (*19*)	Acetic acid	.36	0.90	0.62
C. utilis (*19*)	Ethanol	.68	1.30	.58
C. intermedia (*20*)	*n*-Alkanes (av. C_{14}–C_{18})	.80	0.94	.34
C. intermedia (*10*)	*n*-Alkanes (av. C_{16}–C_{22})	.81	.96	.35
Torulopsis sp. (*7*)	*n*-Alkanes (av. C_{14}–C_{18})	.72	.85	.29
Candida sp. (*6*)	Octadecane	.74	.87	.30

Past Progress

There has been much work on the growth of microorganisms on hydrocarbons, but little of it has been primarily concerned with obtaining high yields of cells from hydrocarbons that are available in bulk. Much more work has concerned production of yeast cells from normal alkanes than the production of bacterial cells from various hydrocarbons; some work on yeasts is summarized in Table 3. In 1964 Miller *et al.* reported from my laboratory that cell yields of about 80 percent were obtainable from several normal alkanes; the organism grew well on the alkanes used. Growth was slowest on the alkane of lowest molecular weight (dodecane) and most rapid on the alkane of highest molecular weight (octadecane). Alkanes lower than dodecane were not tried because their volatility made determination of yield difficult, and alkanes higher than octadecane were not used because they were waxy solids rather than liquids, and difficult to maintain in a dispersed state; if finely dispersed, they rapidly agglommerated during the fermentation. Later it was found practical to dissolve solid hydrocarbons in a branched-chain liquid hydrocarbon that was not significantly attacked by the organisms used—a procedure followed more recently (*10*). A mixed culture comprising two *Candida* species gave better results than did either species alone (Table 5). One may see that the solid alkanes were readily used to give high yields of cells. When solid alkanes were used with pristane, it was necessary to wash the harvested cells with pentane and acetone, thereby reducing their lipid content. Table 5 is intended to show that cells of acceptable nitrogen content can be produced, from a variety of normal alkanes, in yields exceeding 80 percent.

Takeda *et al.* (*7*) have also obtained yields of more than 70 percent by growing yeasts on pure *n*-alkanes, including a yield of 70 percent on a petroleum fraction containing about 76 percent alkanes; they used a small amount of corn steep liquor in their medium. They give no data on cell nitrogen. British Petroleum, Ltd. (*11*), has apparently done a good deal of laboratory and pilot-plant work on growth of *Candida* on alkanes contained in petroleum fractions; the object is to

Table 4. Cell yields of *Pseudomonas* on various substrates. See text for method of calculating yield per gram of oxygen.

Organism	Substrate	Cell yield (g/g)		
		Substrate	Substrate carbon	Oxygen used
P. fluorescens (*19*)	Glucose	0.37	0.93	0.66
P. fluorescens (*19*)	Acetic acid	.28	.70	.40
P. aeruginosa (*21*)	Octadecane	.60	.70	.23
Pseudomonas sp. (*22*)	Octadecane	1.03	1.20	.50
Pseudomonas sp. (*22*)	2, 6, 10, 14-Tetramethylpentadecane (pristane)	0.97	1.13	.46
P. methanica (*23*)	Methane	.56	0.75	.17
Pseudomonas sp. (*24*)	Methane	.60	.80	.19

Table 5. Growth of a mixed *Candida* culture (*C. intermedia* plus *C. lipolytica*) on normal alkanes. Cells were grown on mineral salts medium in an aerated and agitated fermentor at 30°C; *p*H controlled at 5.5. Final cell concentrations were 10 to 14 grams per liter. Liquid alkanes were used alone; solid alkanes were dissolved in 2,6,10,14-tetramethylpentadecane (pristane).

Substrate	Generation time (hr)	Cell (%)		
		Yield on added substrate	N	Lipid
Liquid alkanes				
$C_{15}H_{32}$	4.0	87	7.77	4.6
$C_{16}H_{34}$	4.5	78	7.25	11.2
$C_{17}H_{36}$	5.5	74	7.42	9.2
$C_{18}H_{38}$	5.0	84	6.75	13.4
Solid alkanes				
$C_{20}H_{42}$	3.5	82	8.81	3.2
$C_{22}H_{46}$	3.0	90	8.48	1.9
$C_{24}H_{50}$	4.0	90	8.20	3.6
$C_{28}H_{58}$	8.0	88	8.19	3.7

remove wax (that is, higher normal alkanes) from the petroleum fractions by converting it to microbial cells; dewaxing (normally done by other methods) is thereby accomplished and at the same time yeast cells are produced. British Petroleum is presumably evaluating the economic feasibility of such a process.

Detailed data on the removal of normal alkanes from petroleum fractions by *Candida* have recently been given by Miller and Johnson (Table 6; *10*); most of the *n*-alkanes containing from 15 to 30 carbon atoms were removed by the yeast. Cell yields varied from 73 to 96 percent, calculated on the alkane used, from petroleum fractions containing from 6.5 to 18 percent *n*-alkanes, which were the only hydrocarbons used by the yeast. Table 6 serves to demonstrate that yeasts can readily grow on crude petroleum fractions at the expense of the *n*-alkanes contained.

Hydrocarbon-oxidizing bacteria are not rare. Genera comprising many hydrocarbon-oxidizing species include *Pseudomonas, Mycobacterium, Nocardia, Corynebacterium,* and *Micrococcus.* Some data on *Pseudomonas* are quoted in Table 4. Esso Research and Engineering Co. (*9*) has studied the production of cells of *Micrococcus cerificans* on petroleum fractions rich in paraffinic hydrocarbons. Takeda *et al.* (*7*) report an 80-percent yield of *Pseudomonas* cells on a kerosene fraction containing 84 percent paraffins.

Economic Feasibility

The scanty work done thus far on production of microbial cells from hydrocarbons suffices to demonstrate the scientific feasibility of producing useful animal feeds, and to make clear some of the economic difficulties that must be overcome if such feeds are to become practical.

In the United States the cheapest source of good protein for animal feeds is soybean meal, which sells for about 11 cents a kilogram and has roughly the same protein content as yeast or bacteria. The cheapest microbially produced feed in the United States is now torula yeast made from sulfite waste liquor; it sells for about 21 cents a kilogram, commanding a higher price than does soybean meal because of its content of B vitamins. If the yeast became a major protein constituent of a feed, however, this price differential would disappear. Microbial cells to be used in animal feed would have to sell at about 11 cents a kilogram. The price of torula yeast has never been less than 17.6 cents, and the cost of producing it (reckoning the price of sulfite liquor at zero) is probably not greatly below this figure.

It may appear that production of microbial cells from hydrocarbons would now be economically feasible, given the savings attainable by very large-scale production; but there are a number of difficulties. The most serious is the problem of oxygen transfer. When 1 gram of microbial cells are grown on carbohydrate, 1 gram or less of oxygen is used. Table 4 makes it evident that growth of bacteria on alkanes requires about 2 grams of oxygen per gram of cells produced. When cells are grown on methane, with yields currently obtained, about 5 grams of oxygen are required per gram of cells.

Aerobic microorganisms grown on a large scale are grown in a medium that is rapidly and efficiently aerated, generally with the help of suitable agitation. In every well-designed process, almost all oxygen that can be transferred from the gas to the liquid phase is used by the organisms; that is, the microbial population is kept high enough to utilize the full oxygen-transferring capacity of the fermentor. If we increase by a factor of 3 the amount of oxygen necessary to produce a gram of cells, we obviously reduce by the same factor the number of grams of cells per day that can be grown in a given fermentor, thereby increasing by a similar factor operating cost of the fermentor. The most important costs of production are for raw materials (hydrocarbon and inorganic salts), fermentation, and drying. By use of methane, the cheapest hydrocarbon, raw-material costs are reduced but fermentation costs are increased because of the higher requirement for oxygen. The simplest way to reduce the oxygen requirement is to increase the cell yield, so that more hydrocarbon is converted to cells and less to carbon dioxide. Further work is needed on improvement of yield.

In a practical process for cell production, continuous propagation would be used. The fermentor would be continuously fed with fresh medium, and cell suspension would be withdrawn continually. Cost considerations would prohibit aseptic operation. The environmental conditions would be such that only the desired organism or organisms would be present in appreciable numbers. Such ecological control of microbial population in continuous propagators has been successful in producing yeast from sulfite waste liquor or from wood sugar (*12*), but is difficult to achieve in yeast production from cane molasses; it is apparently being used in pilot-plant production of yeast from petroleum fractions (*11*). One should not assume as a matter of course that contamination by other organisms will cause no difficulties, especially when

Table 6. Growth of *Candida* on petroleum fractions. Each value is the average for two experiments. The culture was mixed, as for Table 5. Abbreviations: FB, furnace-boiling; IB, intermediate-boiling; CCU, from catalytic cracking unit; HB, high-boiling.

Gas oil used	*n*-Paraffin		Generation time (hr)	Cell (%)		
	Content (wt %)	Used (% of total)		Yield on paraffin used	N	Lipid
Virgin gas oil, FB range	18.1	96	4.0	73	9.02	1.9
Virgin gas oil, IB range	13.2	90	4.3	90	9.09	1.5
Gas oil CCU	12.7	97	5.5	76	8.77	2.2
Waxy distillate	10.7	94	6.0	79	9.28	2.3
Viscous HB fraction	6.5	72	9.3	96	8.83	7.2

bacteria are grown: bacteriophage may be a problem, and, with the slow growth rates currently attainable on methane, protozoa may be troublesome predators. Contamination problems will probably not be too difficult to solve, but certainly cannot be ignored.

Consideration of the economic factors involved in the production of protein from hydrocarbons makes it clear that research is needed on yield improvement, on the isolation of cultures of the highest-possible nutritive value, and on comparison of various practical hydrocarbon sources. Engineering research is needed on methods for harvesting bacterial cells, and on the design of fermentors of high capacity to transfer oxygen.

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NEWS AND COMMENT

Medical Costs: Rapid Rise Causing Government Concern

After several months of study and research the Department of Health, Education, and Welfare has come up with a report* that confirms what everyone who has been paying medical bills knows without being told—that medical costs are rising, and rising fast. The government's interest in this condition arises from the fact that, with the passage of Medicare, Medicaid, and a number of other new programs, it is increasingly a bill-paying participant in the process of medical care and not, as in the past, merely an interested onlooker. The report is a trifle weak on recommendations and is frankly gloomy in its forecast that continued increases are inevitable. It does not say very much that experts on medical economics and critics of American medicine have not been saying for years. But it is a remarkably lucid, sensible, and straightforward summary of what is ailing our medical economy, and its appearance as a government document marks a high point in governmental perception of what the problems are.

The facts seem to be simple enough. According to the HEW report, doctors' fees, which had been rising at a rate of less than 3 percent per year, rose almost 8 percent during 1966. Hospital room rates rose about 16.5 percent, and are now about $45 a day. Drug prices have not contributed significantly to recent overall increases in costs, according to HEW's analysis, but they do contribute significantly to the high cost of medical care in general.

The essential reason for the rise in doctors' fees, according to the report, is "a substantial and sustained increase in demand without a corresponding increase in supply." Recent growth in demand is attributed to many factors, beginning with the simple 28-percent increase in population between 1950 and 1965. In addition, the report says that changes in the internal character of the population have enlarged the groups that tend to seek medical care—there are more women, more city dwellers, more educated people, more children, and more elderly. The expansion of insurance coverage has also played a role, as has the public's conviction that medical care has become more effective, hence more desirable.

During the same period (1950–65) the number of physicians increased by 33 percent. But the proportion of physicians in private practice declined from 72 to 62 percent; the remainder work in hospitals, medical schools, and so forth. And there was a numerical decline in the total number of family physicians—pediatricians, internists, and general practitioners—as more doctors entered specialties.

The doctors responded to this situation partly by increasing their productivity—seeing more patients per week, shifting from house to office visits, increasing their staffs, acquiring complex equipment, and entering into new organizational forms such as group practice and partnership. But they increased their fees as well, and they increased them far faster than the general rise in the Consumer Price Index.

Hospital Costs

As far as hospitals costs are concerned, they are affected by the same increase in demand and by the same increase in insurance coverage that affect the doctors. But HEW says that the major reason for the price rise is the rise in wages, which account for two-thirds of the costs of hospital care. Since the report notes that as recently as 1963 there were ironers in Memphis, for example, earning less than 45 cents an hour, it would seem that any changes

**Medical Care Prices* (Superintendent of Documents, Government Printing Office, Washington, D.C. 20402; 20 cents).