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Expert Working Group Meeting on the
Manufacture of Chemicals by Fermentation
Vienna, 1 - 5 December 1969

DRAFT REPORT OF THE EXPERT WORKING GROUP MEETING ON THE MANUFACTURE OF CHEMICALS BY FERMENTATION 1/

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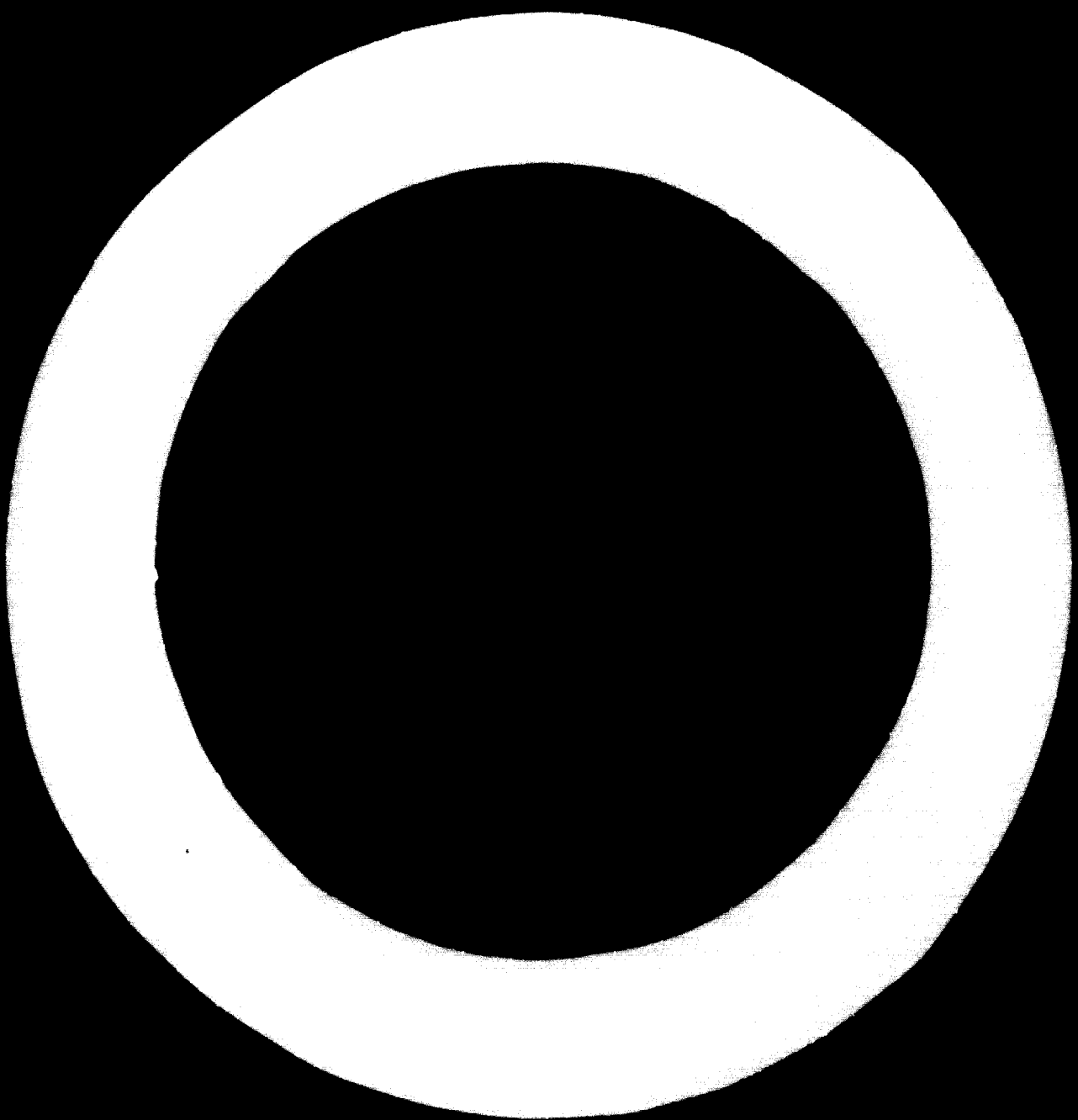


I. INTRODUCTION

The Expert Working Group Meeting on "Manufacture of Chemicals by Fermentation" was held in Vienna, Austria from 1 - 5 December 1969. The various aspects of the fermentation industry were discussed along with the presentation of papers on different specialized subjects in the field. Conclusions and recommendations were drawn up. A visit of a fermentation plant near Vienna was also made by the group during the sessions.

As generally known, fermentation is the earliest process of converting one substance to another and has been used for thousands of years; recently it has become an important branch of the chemical industry. In addition to the conventional products such as ethyl-alcohol, many new products can be produced by fermentation processes such as antibiotics, vitamins, steroid hormones, food ingredients, etc. Great potential exists in many developing countries where plenty sucro - and starchy raw materials are available.

Taking the above into consideration the purpose of the meeting was to promote industrial development in the fermentation sector in the developing countries in general and specifically to examine the possibilities of the application of fermentation processes to the production of different products in the developing countries.

The meeting was opened by Mr. Ibrahim Helmi Abdel-Rahman, Executive Director of UNIDO, who welcomed the participants on behalf of UNIDO and expressed the hope that this working group would recommend concrete measures to be taken by the developing countries themselves, by UNIDO, and by other international organisations such as the World Health Organization, the Food and Agriculture Organization and the International Atomic Energy Agency, to promote the development of the fermentation industry in the developing countries.

UNIDO's introductory remarks were presented by Mr. C.S. Chiang, who gave a brief account of UNIDO's activities in industrial technology, especially in the field of fermentation industry and put forward a few ideas on some of the problems to be discussed in the meeting.

Twenty four participants attended the meeting including ten experts, acting in their personal capacity and not as official representatives of their Governments, one expert from the World Health Organization, and thirteen observers from developed and developing countries. The participants are listed in Appendix II. Professor Elmer Gaden (USA) was elected as Chairman, Dr. C.T. Calam (UK) as Vice-Chairman and Professor J. Meyrath (Austria) as Rapporteur of the meeting.

The agenda of the meeting is given in Appendix I. Presentation of the expert papers was followed by discussion of the topic. Additional remarks were given by some of the observers during the sessions. After consideration of the papers and a general discussion, the participants joined in formulating technical recommendations and recommendations for specific UNIDO action to be taken in order to implement the conclusions arrived at during the meeting.

The present publication includes the report and conclusions of the group resulting from the meeting (part II) and summaries of experts' papers discussed during the meeting (part IV). Papers were presented by experts from Austria, Canada, Federal Republic of Germany, Hungary, Israel, the United Kingdom and the United States, and one by the representative of World Health Organization. A summary of reports from twentyfour countries was also presented in the meeting.

The views expressed in the expert papers are those of the authors and do not necessarily represent the views of the secretariat of UNIDO.

II. GENERAL PRINCIPLES (RECOMMENDATIONS) ON THE POTENTIAL ROLE OF FERMENTATION TECHNOLOGY IN DEVELOPING COUNTRIES

1. The Working Group has outlined certain general circumstances under which fermentation technology is potentially valuable to developing countries.

   These are:

   a) products which can be manufactured by fermentation methods are needed in the local economy and are relatively free from competition (from petrochemicals, for example)

   b) adequate supplies of raw materials (ordinarily carbohydrate) are available in the area.

2. The Working Group also notes that fermentation technology may offer an especially useful means for the introduction of industrialisation into areas which are at a very low level of industrial development. There may therefore be situations in which considerations other than purely technical or economic ones are important. These may justify the local production of a specific chemical product by fermentation even where the import of these same products (perhaps produced synthetically) is less expensive.

3. Finally the Working Group was unanimous in feeling that the separation of chemical production by fermentation from food production by fermentation (especially microbial protein) within UNIDO is not desirable. A single group, or section, is justified because of the essential identity of the technologies involved. In fact there are greater differences between the methods for producing the various industrial chemicals by fermentation than between microbial protein production and certain chemical fermentations.

III. RECOMMENDATIONS TO UNIDO ON PROCEDURES TO BE EMPLOYED FOR EVALUATING THE POTENTIAL FOR FERMENTATION TECHNOLOGY IN DEVELOPING COUNTRIES

The Working Group understands that UNIDO may receive inquiries from developing countries regarding the potential for fermentation technology or may wish to suggest the possibility to specific countries. In either case the Group recommended that UNIDO follow general procedures recognising the need for individual treatment in each case.

1. It was recommended that UNIDO prepare a general document, or report, on the potential for fermentation technology with special emphasis on:
   a) the types of products which can be manufactured, by fermentation;
   b) the kinds of raw materials which can be utilised, including waste or by-products from other technologies (see Addendum VI a).

   This report should then be circulated to appropriate agencies in developing countries, including industrial groups, research institutes, etc.
2. It was also recommended that UNIDO assemble a panel of experts to assist in evaluating inquiries and in advising developing countries. This panel should be made up of individuals with broad experience in the practical aspects of fermentation, economic as well as technical. It is also highly advisable that this panel include representatives from developing countries which have had experience with fermentation technology.
3. When UNIDO receives an inquiry regarding the use of fermentation technology in a particular country or area, UNIDO's staff in conjunction with the panel, can conduct a <u>preliminary review</u> of the proposal. A primary function of this preliminary study will be to guide the inquiring country in the preparation of a formal

request and, especially, to provide the kind of background information, including data on local economic and technical conditions, which is necessary for a complete feasibility study.

4. If this preliminary study indicates that there is promise for the application of fermentation technology in the country, UNIDO should arrange for a detailed feasibility study. The Working Group therefore would also recommend that UNIDO compile a list of Government and industrial groups as well as individual consultants who can either assist the UNIDO staff or conduct such feasibility studies under contract. (see Addendum VI b)

5. The Working Group attached great importance to the problem of training of personnel and suggested methods of training to be adopted; this aspect is dealt with in Addendum VI c.

6. It was recommended that consideration be given to the establishment and maintenance of culture collection as stated in Addendum VI d.

IV. SUMMARIES OF PAPERS PRESENTED

Jay V. Beck: Metal Recovery from Low Grade Ores, Sulphur Recovery from Gypsum

The submitted report summarizes the present state of the processes in which microbes affect metal and sulphur production. The role of microbes in the mineral industry is not generally known and appreciated. It is recommended therefore that the submitted report be made available to serve as a preliminary source of information. The bibliography is fairly complete and current and this may be of some value.

The mining industry in developed nations is well aware of the microbial potential in mining operations. This may not be true of developing countries. Distribution should be directed to national agencies, mining bureaus and - due to the applicability on a small scale - to small local mining interests which are involved in metal recovery from sulphide ores. The reworking of waste mine or mill dumps offers a promising source of metals which may be recovered at small capital investment.

The Role of Thiobacillus ferrooxidans
in Mining of Copper and Uranium

I. Copper from sulfide ores of low mineral content.

Introduction
Historical
A typical dump leaching operation
Leaching of various copper minerals
Ore placement for leaching
Leaching solutions
Collection of leach water and copper recovery
Bacteria and dump leaching
Bacterial oxidation of copper sulfide minerals
Physiology of Thiobacillus ferrooxidans
Presence of rare metals in leaching solutions
Conclusion
Bibliography

The mining and recovery of copper by leaching from low grade ores have become significant parts of the copper industry. Studies have shown that the bacterium Thiobacillus ferrooxidans, by rapidly oxidizing and solubilizing sulfide minerals, plays a major role in waste-ore leaching operations. Temperature and oxygen content of gases in the interior of some ore dumps are incompatible with microbial activity, but in low temperature leaching, and even in cases of high temperature, it is suggested that bacterial oxidation and solubilisation are important. Certainly, adjustment of conditions of leaching to more adequately accommodate bacterial growth has greatly increased the efficiency of waste-ore leaching. Further improvements in efficiency may be expected as more knowledge of the bacterium and its activity in leaching systems becomes available.

II. Uranium from its oxides when associated with iron pyrite.

Chemical process for uranium extraction

Thiobacillus ferroxidans in uranium mine water

A proposed bacterial leaching process for uranium

References

A proposed bacterial leaching process for uranium

Although bacterial leaching of uranium is of some economic importance, the process is not rapid enough for general uranium production even in those cases where steps have been taken to increase its efficiency. Recently a reverse flow, six tank continuous system has been proposed as a means of rapid extraction of uranium from its oxide ores by bacterial action. The authors state that the latter process may prove to be economically competitive to the conventional acid-oxidiser method of uranium extraction.

Major economies of bacterial leaching lie in the decreased quantity of acid required and in the lower temperature requirements. Acid leaching requires 60-80 lbs. of sulfuric acid per ton of ore, as compared to 25 lbs./ton in bacterial leaching which of course generates considerable acid from pyrite oxidation. A temperature of 70°C is essential for chemical leaching whereas bacterial leaching occurs at ambient temperatures.

The Role of Bacteria in Sulfur Production

Introduction
Bacterial formation of sulfides from sulfates
Use of domestic and industrial wastes for sulfate reduction
Other materials suitable for use in a sulfate reduction process
Description of the English pilot plant sulfur production process
Conclusion
References

Attempts to use sulfate reducing bacteria for commercial production of sulfur have been made. The most successful of these, to my knowledge, was developed in Britain through a successful pilot plant stage with a daily sulfur production of about 200 lbs. sulfur. This project was abandoned about 10 years ago, but is now being revived.

An interesting and significant aspect of the British project was the use of London raw sewage as the source of the organic substance. It was hoped that the method would prove capable of removing much of the soluble organic matter from domestic sewage and at the same time produce valuable sulfur from inexpensive gypsum.

Large international mining companies and engineering concerns could supply detailed technical information, e.g.,

Anaconda Mining Co.,
Kennecott Mining Co.,
Phelps-Dodge Mining Co.,
Hecla Mining Co.,
Bechtel Associates.

C.T. Calam: **Methods of Industrial Strain Improvement**

The methods used for mutation, isolation and testing of mutants are summarised. Examples are given of the use of different mutagens, including radiations and chemicals. The theory and practice of screening are discussed and reference made to automated methods.

The object of the report is to describe practical methods of working. The general procedure involves (1) mutation, (2) isolation of about 200 cultures, (3) testing of these cultures in single flasks, (4) retesting of the best 50 using 3 - 4 flasks, (5) remutation of the best 5 cultures and repetition of the cycle. Taking the best 5 cultures of remutation has a number of advantages over taking the single best strain.

In discussing techniques, the importance of using reliable, simple methods that give reproducible results is stressed. Success depends on reliability and numbers of isolates screened. The importance of noticing and seizing opportunities and of forestalling difficulties is stressed. Patience and persistence are needed as progress may become slow after a time.

The commonly used mutagens are the following:

U.V. ray
X rays (no longer used to intensify)
fast neutrons
ethylene imine (combined with U.V. rays)
diethyl sulphate
ß-ethoxy caffein
1-methyl-3-nitro-1-nitroso-guanidine
6-mercaptopuric riboside.

It is important that the first screening tests are carried out under conditions which resemble as closely as possible industrial processes to be used.

Following the subjection to the mutative agents the organisms are plated out, tested in single shaker flasks (about 200), the best 50 are then selected of which one carries out further tests in triplicate and keeps the best 5 strains. This cycle is then repeated and with a good team one cycle can be carried out every six weeks.

In many cases the success of the mutation programme can be characterised as follows:

Mutated Population	Frequency of improved mutants	Mean improvement %	Frequency of improved strains by 5%	Frequency of improved strains by 10%
Poor	1/40	2.5	1/2000	1/20 000
Standard	1/20	3.0	1/200	1/3000
Good	1/10	4.9	1/50	1/300

These figures were based on estimates made with penicillin cultures which had already been mutated many times and progress was slow.

Experience has shown that it is far better to isolate and keep the cultures showing moderate improvement and subjecting them to remutation, rather than trying to find very strong improvements after the first mutation programme.

Automatic procedures or combinations of handwork and automated processes can be used successfully.

A section is devoted to hybridisation. The reasons why this method has given rather disappointing results are discussed on a theoretical basis. The comparatively poor success of hybridisation techniques is due to the necessity of a large number of genes being involved in improving the fermentation for a particular product, and the high degree of improbability of finding homozygous cultures in the F_2 generation. Often a limited advance in productivity occurs, after which further progress becomes very difficult or impossible.

Methods, apart from sexual, have included the para-sexual process, transformation and transduction.

Success in both mutation and hybridization depends on the availability of good strains, some strains mutating more readily than others. The possibility that UNIDO could help in obtaining strains is mentioned. This subject is further discussed in Dr. Hesseltine's paper.

E. Codex: Fermentation Plants and Equipment

A. Microbiological processes

1. Characteristics of microbiological process systems which affect design of equipment and plants

2. Microbiological types
   a) biomass production
   b) conversion
   c) metabolite production

3. Process steps
   a) preparation and sterilization of medium
   b) culture development and inoculation
   c) reaction
   d) separation and isolation

4. Process systems
   a) batch
   b) continuous
   c) intermediate

B. Reactor systems for microbiological processes

1. Types
   a) batch
   b) continuous
2. Aeration/agitation systems
3. Heat transfer
4. The standard geometry fermenter
5. Alternatives - including low cost designs for developing countries
6. Materials of construction

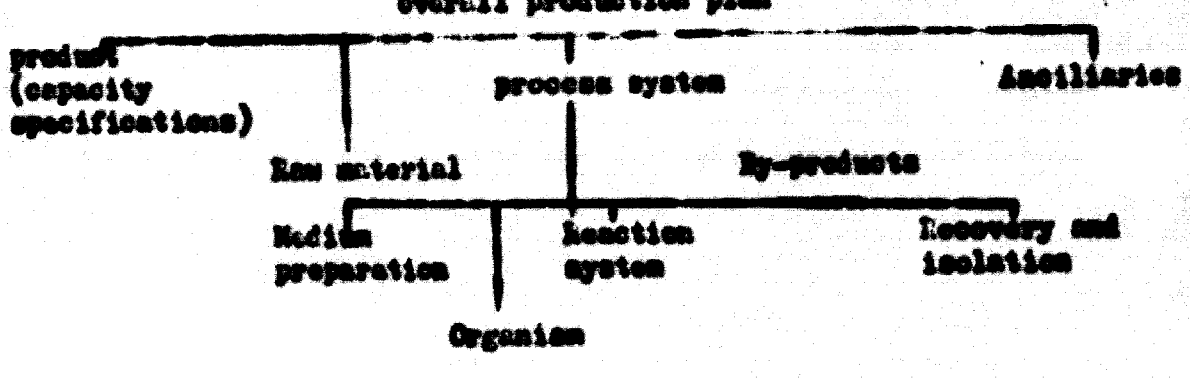
C. Aseptic operation

1. Definitions of "aseptic" operation; pure cultures, etc., concept of "practical" sterility.
2. System integrity
   a) reactor design
   b) medium
   c) inoculum
   d) air
   e) process additions
3. Medium sterilization
   a) batch sterilization processes
   b) continuous sterilization processes
4. Air sterilization

D. Fermentation Process design

1. Background: traditional patterns; dominance of batch processes the "scale-up" approach; lack of flexibility in design (making processes fit existing plants).
2. Chemical process design practice and its application to microbiological processes.
   a) data needed and availability
   b) the flowsheet
   c) equipment sizing
   d) optimization

It is stressed that all processes should be fitted to local needs. Establishment of a plant requires organization at several levels:



Regarding continuous processes it is stressed that even in chemical processes very few are operating truly continuous.

With regards to some newer developments certain drum-type fermentor are shown to be particularly attractive, but being endowed with internal agitators for larger sizes of drum, instead of rotating the drum itself.

In deep tanks sonic nossles are able to give good oxygen transfer rates but poor agitation.

Air lift fermenters have been shown to be of interest for microbial protein production in meshes with low viscosity.

It is also stressed that flexibility of the whole plant should be maintained, and one important aspect in this respect is not to choose the fermenters too large. While the minimum size for most fermentations may be about 40 m^3, the maximal size should not exceed 100 m^3 for aerobic fermenters by too much.

Regarding the material of the fermenters there is usually no reason for choosing stainless steel; for corrosive meshes newer plastictype materials are attractive, such as F.R.P. (fibre glass), and there may also be a future for concrete fermentation equipment.

In aseptic operation the inoculation technique has very often been at fault in the past and not so often the operation system. It is important also that bottom valves should be omitted. Contaminations occur frequently during starting up, when there is water of condensation in many parts of the system, including filters. Mist eliminators are important, and as an insurance membrane filters with pre-filters can be inserted at the entrance to the fermenter.

In the ensuing discussion Dr. Hesseltine reported, that while agreeing with Dr. Gaden, there is still nowadays a use for solid cultures in the production of certain chemicals e.g., certain enzymes (see also the use of bran for production of spores, Vesina). Regarding the reported necessity by Dr. Iyengar for stainless steel in penicillin fermenters, the Chairman (Dr.Gaden) pointed out that the experiments reported may be a reflection of the particular conditionsused, particularly with respect to scale.

Leon Goldstein: Use of Water-Insoluble Enzyme Derivatives in Synthesis and Separation

Water-insoluble enzyme derivatives have been prepared by 1. adsorption on inert carriers or ion-exchange resins; 2. entrapping in gel lattices; 3. covalent binding to insoluble polymeric carriers and 4. covalent crosslinking using bifunctional reagents. The kinetic behaviour of immobilised enzyme systems is dominated by several factors not encountered in the kinetic of free enzymes: a) effects of the chemical nature of the carrier, stemming from the modified environment within which the immobilized enzyme is located, b) steric restrictions imposed by the carrier and c) diffusional control on the rate of substrate penetration. Thus the anomalous pH-rate dependencies and Michaelis constants of several polyelectrolyte-enzyme derivatives could be related to the unequal distribution of ionic species between the charged "solid phase" polyelectrolyte-enzyme particle and the surrounding solution. Proteases bound to polyelectrolyte carriers have been shown to exhibit restricted specificity towards protein substrates. The flow rate at which substrate perfuses through an enzyme column has been shown to affect the degree of conversion of substrate to product, the apparent Michaelis constant and the apparent rate constant. Anomalies in the pH-dependence of activity of papain-collodion membranes could be explained by the generation of local pH-gradients within the membrane due to the liberation of hydrogen ions in the course of hydrolysis of an ester substrate. Kinetic analysis has shown that under stationary state conditions, a membrane-bound enzyme could not attain its maximal activity, except when acting on a poor substrate. Immobilised enzymes have been used to attain better regulation of enzymic processes and for the preparation of enzyme electrodes. Enzyme columns have been utilised in devising automated analytical procedures and in affinity chromatography - for single-step purification procedures of specific inhibitors; reversal of the latter procedure has been employed for the purification of enzymes. Large scale-columns operated continuously on an industrial basis have been shown to be superior to the batch processes utilizing native enzymes.

C.W. Hesseltine and W.C. Haynes: Microorganisms and Their Role in Fermentation

The paper emphasizes the use of microorganisms in fermentations in the developing countries. Inasmuch as the key to success or failure in most fermentation processes is availability of the proper microorganisms, the characteristics of suitable microbial strains are enumerated, and some 20 pages are devoted to listing the industrial collections of the world, their locations, their general holdings and the names of their directors. The attributes of a good culture collection are given. The source of new strains of microorganisms for fermentations are the isolation of new wild strains and isolated from culture collections. Various fermentations in use throughout the world are listed, together with the specific microorganisms used to carry them out. These processes most likely to be useful in developing nations are stressed. The means by which small fermentation plants may acquire suitable microbial strains is discussed as also are the problems of maintaining stable cultures. Considerable space is devoted to the question of shipment of microorganisms in international channels and also to legal problems relating to patents involving microorganisms.

Dr. Hesseltine stressed also the fact that it is unrealistic to maintain culture collections in developing countries.

The following considerations of culture location should be borne in mind:

Considerations of Culture Collection locations

The questions of how many of each of the various kinds of culture collections (general, medical, references, agricultural, etc.) should be sponsored and where in the world they should be located is under study by the Section on Culture Collections of the International Association of Microbiological Societies. Our concern, which overlaps theirs, is the narrower one of where collections of industrial microorganisms should be

situated so that they will be accessible to and do the most good for people in developing nations. Should each nation have its own collection? Do the existing ones suffice? We think the answer to both questions is "No". Because of the scarcity of scientists trained in culture collection science in developing countries, it seems unrealistic to support the idea of national collections of any sort. It seems to us that the source of cultures of microorganisms should be limited to a relative few well-equipped collections located at various places around the world. They need to be adequately staffed and financial support should be assured on a longtime basis. A culture collection in each country would be wholly unrealistic and unworkable. Money spread over so many places would be utterly wasted. On the other hand, public collections that distribute industrial microorganisms are relatively rare and often are located too far from the developing areas to furnish the expert assistance that is needed in handling the cultures. Also, the cost of the cultures is prohibitive because hard currency is hard to come by in many of the developing areas.

These are our conclusions based upon practical experience and on frank discussions with a number of knowledgeable persons from various countries. We think it would be well if regional collections could be set up in strategic places where governmental stability would allow proper development of a collection and where political considerations would not restrict the free flow of cultures and information to fermentologists and other scientists of the service areas. Certainly the existing ones must suffice for now, and in certain regions they can provide satisfactory service. Thus, culture collections in existence

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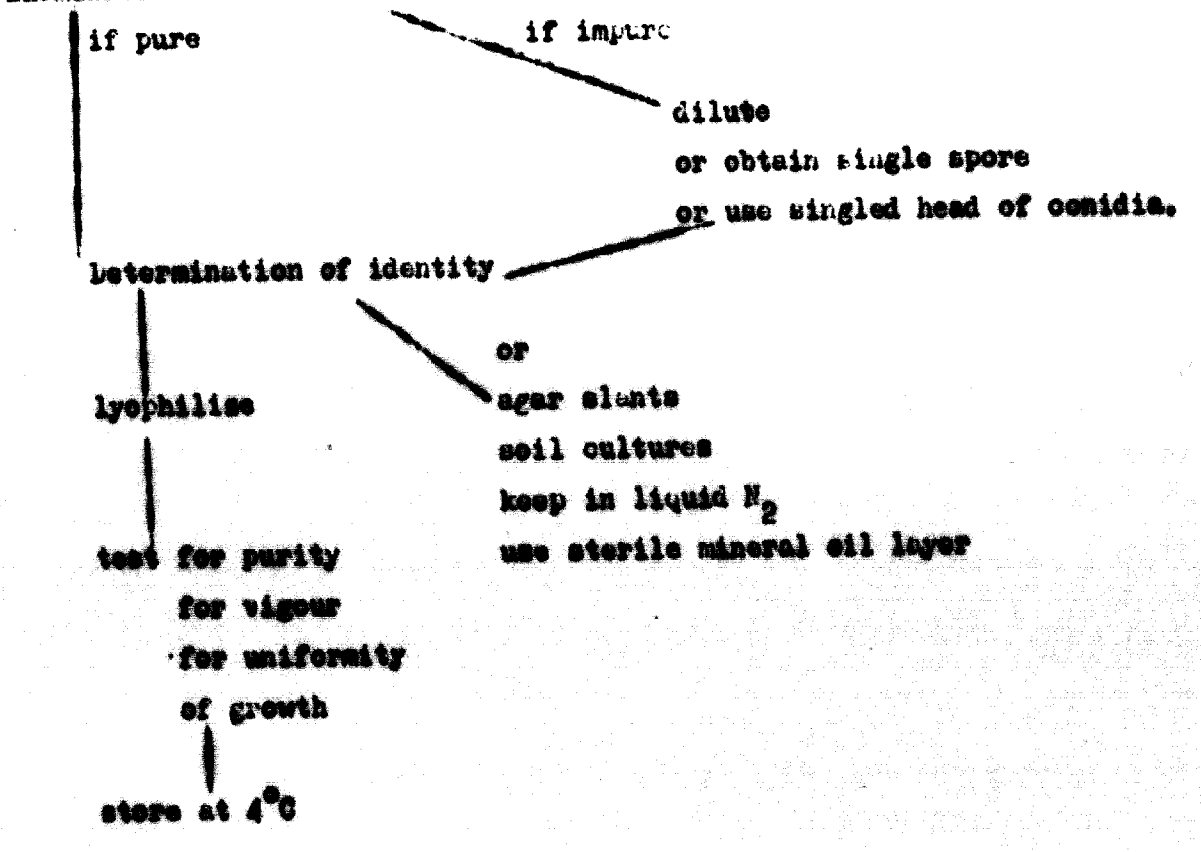
in the U.S., USSR, U.K., Netherlands, Japan, Canada, and South Africa would serve many areas. The excellent Dutch collection would and does fill the needs of Central Europe. The USSR All-Union Collection can adequately meet the requirements of Poland, Romania, Bulgaria, etc. Areas where it seems that well-staffed and financed collections need to be established are (1) South America (perhaps in Brazil or Argentina), (2) India, (3) Central Africa, and (4) the Middle East and North Africa. We do not mean to imply that none exist in these regions but rather to suggest that they need to be enlarged in size, better equipped, and more adequately staffed. We believe that if these proposed collections were established, the fermentation industry in these areas would be adequately backstopped with sources of cultures, culture information, and technical expertise.

The existing collections which have gained stature over the years each is associated with either a research institute or with a university that is famous for its fermentation studies. For example, the University of Tokyo collection is housed in the Department of Agricultural Chemistry and Applied Microbiology. The famous Dutch collection of yeasts is housed with the Institute of Microbiology at Delft. Governments or organizations establishing new collections should bear this in mind. A culture collection of fermentation microorganisms not placed in close proximity with an active institution of fermentation and applied microbiology research will be like planting a seed on a rock.

The question can then be justly asked what should one do with a small plant producing a given product, say a food product destined for human consumption. In this instance, the development work should be done in some central research laboratory. To insure good reliable inoculum, this should be prepared and supplied as a dry, stable from which the workers in the plant can use to seed the fermentation to the degree that the process will go to completion in spite of contaminants. Thus, in the Bantu beer process, even the larger plants do not keep cultures or prepare inoculum but this is supplied to them in 1-pound packages which a technician uses to inoculate a given quantity of media in full confidence that he can depend on obtaining a certain type of product at a certain

time. Little or no formal microbiology needs to be known by the plant operators. The original starter culture can be kept in a central culture collection and supplied to a company who makes, packages, and distributes the inoculum.

The following procedure for isolation and selection of microorganisms from nature can be used:



It is important that records are made of: number, otherwise references, name, date, source, product formed, publications special requirements, number of tubes available.

In the discussion the importance of collaboration of culture collections with IAMS (International Association of Microbiological Societies) is stressed (Dr. Martin).

István Horvath: Fermentation Processes Employed in the Pharmaceutical Industries and Their Economic Aspects

The discovery of penicillin, the elaboration of its mass production and its introduction into therapy marked the emergence of a new branch of research and a new method of production in pharmaceutical industry, which as a result entered a phase of extremely rapid development. Today, 25 to 30 per cent of pharmaceutical products are produced by this technology, among others the most important antibiotics; vitamin B_{12}, ketosteroids and enzymes are manufactured by sterile fermentation processes. The advance of technology, the isolation of biologically active high-yielding strains reduced the prime costs in the first place, which is demonstrated by the price levels that developed after the patents have expired. This fact ensures that the production of most antibiotics by chemical synthesis will not become economical even in the future. The different fermentation processes used in pharmaceutical industry are summarized in a table which gives the price, the probable cost of production and the patent situation.

Principles for the establishment of an industrial fermentation plant

In a developing country it seems reasonable to start fermentation technology with the production of important antibiotics, first of all penicillin, tetracyclines, and vitamin B_{12}. The raw material required for production are agricultural products or by-products available in every country. Apart from its therapeutical importance it enables the rational development of animal breeding as well. Considering the current market prices the smallest but still economically producing unit is estimated to be of 200 metric tons capacity of fermentation volume. The conditions for raising a fermentation plant of such a volume are the following. /Fermentation technology and the most important microbiological processes are presented and discussed separately./

1. General aspects of planning a fermentation plant.
2. Insurance of appropriate technology that the supply of strains used for production be provided for at least five years. To achieve this the setting up of an international strain bank seems desirable.
3. The training of experts which should include not only engineers and microbiologists but skilled workers as well.
4. To insure the undisturbed operation of a fermentation plant care should be taken that besides raw materials high voltage electricity, steam and adequate cooling be available especially in the tropics.

5. The control of production effectuated by a small experimental plant apart from the routine laboratory control tests. This plant is to adapt the manufacturing procedures to the local supply of raw materials.

The most important fermentation processes used in pharmaceutical industry

In this chapter a brief summary will be presented of the major manufacturing processes, which at the same time gives an account of the requirements for a processing division in a generally adaptable fermentation plant. In connection with the more important processes the main trends of development will be surveyed.

1. Production methods of penicillin G and penicillin V.
2. Production methods of tetracycline group/ oxytetracycline and tetracycline, the therapeutic importance of new tetracycline derivatives.
3. Production methods of basic antibiotics/streptomycin, neomycin. Pharmaceutical importance of substances isolated on the basis of similar technological principles.
4. Production methods of macrolide antibiotics/erythromycin, oleandomycin.
5. Production methods of antifungal antibiotics/nystatin, candicidin, griseofulvin.
6. Technological development in the production of vitamin B_{12}.
7. Technology of the production of enzymes.
8. Utilisation of by-products.

Most important fermentation processes and their economic aspects

Informatory economic calculations for a fermentation plant of the most important products/penicillin, streptomycin, tetracyclines, vitamin B_{12}, etc./ on the scale of a 200 metric tons capacity. A brief summary of the attainable results with other fermentation.

Table 1a

Important products of pharmaceutical industry

Groups of products	Name	Date of Discovery	Comments
A. **Antibiotics**			
I. Antibiotics active against Gram-positive bacteria			
1. Penicillin and cephalosporine derivatives	Penicillin-G	1929	potassium salt, price 12 $ Kg, used for animal feeding
	Penicillin-V	1948	potassium salt, price 20 $ Kg
	6-aminopenicillanic acid	1960	produced of penicillin-G, basic product of semi-synthetic penicillins
	Methicillin	1960	
	Nafcillin	1963	
	Oxacillin	1961	
	Cloxacillin	1961	
	Dicloxacillin	1963	
	Ampicillin	1960	it has wide-range spectrum
	Carbenicillin	1967	" "
	Cephalosporin C	1956	
	Cephaloridine	1961	
	Cephaletin	1962	
	Cephalexin	1968	
2. Macrolides	Erythromycin	1952	Price 180 $ Kg.
	Oleandomycin	1954	
	Carbomycin	1952	
	Leucomycin	1953	
	Spiramycin	1954	

Groups of products	Name	Date of discovery	Comments
VII. Antibiotics applied locally	Tyrothricin	1939	
	Gramicidin	1939	
	Xanthocillin	1953	
VIII. Antibiotics applied for other purposes			
1. Animal feedings	Bacitracin	1945	
	Moenomycin	1964	
2. Plant protecting agents	Blasticidin S	1958	
	Cellocidin	1958	
	Polyoxin	1966	
3. Food-industrial preservatives	Nisin	1946	
	Subtilin	1946	
	Tylosin	1961	
4. Antibiotics used for other purposes	Hygromycin B	1958	
B. Vitamins	Vitamin B_{12}	1949	Price of crystalline vitamin B_{12} 4n3 R.S.
	Vitamin B_2		
	Gibberellic acid		
C. Compounds produced by steroid bio-oxidation	Hydrocortisone	1952	
	Prednisolone	1955	
D. Enzymes	Proteases		
	Amylases		
	Amyloglucosidase		
	Lipases		
	Cellulase		
	Hemicellulase		
	Pectinase		

Groups of products	Name	Date of discovery	comments
3. Other antibiotics	Novobiocin	1955	
	Vancomycin	1956	
	Lincomycin	1962	
	Chlorlincomycin	1967	
	Fusidic acid	1962	
	Pristinamycin	1960	
II. Antibiotics with wide-range spectrum			
1. Tetracyclines	Chlortetracycline	1948	used for animal feeding
	Oxytetracycline	1950	Price 30 $ kg
	Tetracycline	1953	
	Demethylchlor-tetracycline	1956	
	Methacycline		
	Doxacycline		
2. Water-soluble basic antibiotics	Streptomycin and Dihydrostreptomycin	1944	Price 24 $ kg.
	Neomycin	1949	" 28 "
	Paromomycin	1958	" 38 "
	Kanamycin	1959	
	Gentamicin	1963	
III. Antibiotics active against Gram-negative bacteria	Polymyxin B	1947	
	Colistin	1950	
IV. Antibiotics active against TB bacteria	Viomycin	1951	Price 220 $ kg
	Capreomycin	1962	
	Cycloserine	1954	
	Rifamycins		
V. Antifungal antibiotics	Nystatin	1951	Price 53 $ Kgm
	Amphotericin B	1956	
	Candicidin	1953	
	Trichomycin	1952	
	Hamycin	1960	
	Griseofulvin	1939, 1958	Price 80 $ kg
VI. Anticarcinogen antibiotics	Actinomycin D	1953	
	Mitomycin C	1956	
	Chromomycin A_3	1958	
	Olivomycin	1962	
	Streptonigrin	1960	
	Daunomycin	1965	
	Bleomycin	1965	

H. T. Huang: Nutritional Supplements, Vitamins, Amino Acids and Flavouring Agents

The introductory part of this paper reviews the significance and uses of nutritional supplements, i.e., vitamins, amino acids and flavouring agents, in human and animal nutrition.

The major part of the paper deals with specific supplements which are produced commercially by fermentation, i.e., riboflavin, vitamin B12, glutamic acid, and lysine.

Technology of production for each product is discussed in detail in terms of culture selection, fermentation process, mechanism of biosynthesis, process control, product recovery, and economics.

Finally, fermentation processes for other nutritional supplements of interest are described. These include the vitamins, β-carotene and ascorbic acid; the essential amino acids, threonine, trytophan, isoleucine, and valine; and miscellaneous flavour products, mushroom mycelia, oriental fermented foods, and 5'-nucleotides.

Riboflavin can be produced by Eremothecium ashbyi and Ashbyi gossipii, the latter being the most important today. Being plant pathogenes care has to be taken to avoid dissemination during production of riboflavin. Usually substrates consisting of ground lentils and pancreatic digests of gelatine are used. Glycine content is a critical factor. The reproduction costs in U. S. in 1953 were 100 - 130 per kg with yields of 2.5 g/l; nowadays yields of more than 10 g/l are reached. The total production in U. S. A. is about 900 kg p.a. with a total value of about $8 million.

Monosodium glutamate can be produced by special strains of Bacillus megaterium-perexus. There is now already a world-wide production of this flavouring agent while in 1963 there was hardly any outside Japan. Yields of 60 - 80 g/l with conversion coefficients based on sugar of 60% are reached. Biotin content in the medium is very critical in order to obtain high yields. Recovery can be done by acidification when glutamic acid precipitates. In 1953 production costs were about $70 per lb, while today it can be produced at $.45 per lb.

Lysine can be produced by mutants of glutamate-producing cultures with yeilds of 56 g/l in 80 h of fermentation time. In Japan alone 3000 t.p.a. are produced at a price of $1.95 per lb. (1969); the latter, however, seeming a rather overcharged price (Prof. Wagner pointed out that lysine

Table 6.

Cost of production in the case of most important antibiotics and vitamin B_{12}

Product	Fermentation level	cost of one cu.m. broth in $ if fermentation term is 140 hr	Amount of isolated substance/ cu.m. (with a 70% yield)	Production cost
Oxytetracycline or tetracycline	12.000 ug/ml	106	8.4 kg	12.61 $/kg
Penicillin-G Potassium salt	15.000 U/ml	130	10.5 Bou	12.38 $/Bou
Penicillin-V potassium salt	12.000 U/ml	130	8.4 Bou	15.47 $/Bou
Streptomycin base	10.000 ug/ml	110	7.0 kg	15.71 $/kg
Neomycin base	8.000 ug/ml	110	5.6 kg	19.64 $/kg
Erythromycin base	3.000 ug/ml	140	2.1 kg	66.70 $/kg
Nystatin	10.000 U/ml	140	7.0 Bou	20.00 $/Bou
Vitamin B_{12} *	30 ug/ml	60	20 g	3.00 $/kg

* Production cost of vitamin B_{12} may considerably be reduced in easily realisable larger volumes and by simplifying fermentation technique.

could be produced synthetically at $.25 per kg). Biotin content in the medium is critical, and serves to repress accummulation of glutamate.

β-Carotene is not yet produced on industrial scale, but the process seems to be ripe for being taken up by industry.

5'-Nucleotides are important flabouring ingredients and can be used to 1/50 - 1/10 of the amount of monosodium glutamate. They can be obtained from nucleic acids by ion exchange chromatography. Mixtures (1:1 monosodium glutamate and 5'-nucleotides are sold in U. S. A. nowadays at $9.60 per lb. with a strong likelihood that this price is coming down further.

At the discussion Dr. Martin raised the question of Methionin, whereupon Dr. Huang pointed out that the competition by synthesis is very stiff as optically inactive mixtures can be used.

J. Meyrath: **Energetic and Kinetic Aspects of Industrial Fermentation**

The basic aspects of the kinetics of growth and fermentation of microbial cultrues are briefly reviewed. Several proposals to characterise mathematically various phases of culture development are discussed. Some essential (selected) factors are discussed which affect the various phases of growth and fermentation. The special problems of fungal cultures in which the initial phases of culture development are important for the properties at later stages are examined in some detail, and the importance of self-stimulating and self-inhibiting substances is revealed.

Some fundamental questions are reviewed regarding the application and performance of continuous cultivation of micro-organisms, in particular factors determining the choice for single-stage or multi-stage operation.

Energetic aspects of yeast development under aerobic and anaerobic conditions are examined from which results also the more recent procedure of performing continuous alcoholic fermentation with extremely high rate and little surplus yeast production; the yeast requiring virtually no more than maintenance energy to keep up its activity. Besides energetic considerations of biomass production under aerobic conditions from carbohydrate, the particular situation of utilisation of strongly reduced carbonaceous compounds, i.e., hydrocarbon is examined in detail. Explanations are proposed for the rather poor energetic utilisation of this energy source.

D. Posada: The Role of Industrial Fermentations in Cuba

Of the 3 million tons of molasses produced in Cuba the biggest portion is used in animal feeding (together with urea for cattle). The remainder is used for protein biosynthesis and for alcohol production.

In view of the intensively developing use of molasses for feeding purposes, molasses is no longer abundantly available for fermentation processes, and efforts are being made to use all kinds of waste materials.

In the ensuing discussion the author mentioned that 30-50% of the carbohydrate portion is currently being replaced in the fodder diet for calble, and efforts are being made at the same time to increase the protein content of molasses by addition of soy beans. Dr. Martin also mentioned the importance of pelletising essential amino acids (methionin) in the ration for cattle feeding in order to enable the passage of the rumen and the various stomachs.

C. Vezina: Microbial Production of Therapeutic Agents

Introduction

Antibiotics

Currently available antibiotics

The need for new antibiotics

Production of antibiotics - General considerations

Fermentation improvement

Microbial genetics

Role of the environment

In antibiotics production the price of the medium is not as critical as it is in some other fermentations, e.g., citric acid.

In antibiotics production there is usually a rapid growth phase followed by an accumulation phase. Very often it is the extraction procedure which is the more expensive part of the process as is the case in penicillin production.

The search for new antibiotics is justified in view of the development of resistance among sensitive pathogenic microorganisms. In the selection process it is emphasised that the primary screening process should be cheap.

PENICILLIN

Strain Selection

Fermentation Media

Fermentation and Recovery

F. Wagner: Industrial Chemicals: Organic Solvents, Organic Acids Miscellaneous Products, Microbial Insecticides.

1. Organic Solvents.

11. Ethanol

Considering that industrial ethanol can be produced much more cheaply by synthesis means (using ethylene and natural gas as raw materials), this fermentation looses ground steadily. The following table from U.S. Treasury Dept. summarizes this state of affairs:

Table 1 Materials used for ethanol production[a)]

Raw material used	Ethanol produced			
	% of Total		Millions Proof Gal	
	1956	1966	1956	1966
Grain and grain products	1.2	11.54	5.4	80.4
Molasses	25.5	1.59	126.7	11.0
Fruit	0.01	4.07	-	28.3
Sulfite liquors	1.32	0.90	6.5	6.2
Cellulose pulp; chemical and crude alcohol mixtures	0.52	0.12	2.5	0.8
Whey	0.09	0.06	0.4	0.4
From redistillation	2.12	4.11	10.5	28.6
Ethylene gas	9.00	18.29	48.6	127.6
Ethyl sulfate	59.34	59.32	294.4	413.8
Total	100.00	100.00	496.2	689.3

a) US Treasury Dept., Internal Revenue Service, Publication 67, 1956 and 1966

With respect to fermentation techniques it may be mentioned that vessels of 250 m^3 can be used with sugar concentrations of 15 - 20%. Continuous systems on industrial scale have been used with starchy raw materials as well as with molasses. Contamination which may be troublesome in continuous fermentations is counteracted by acidification, or by additions of penicillin or sodium pentachlorophenolate.

Course of Fermentation

Role of Precursors

Biosynthesis

Semi-synthetic Penicillins

OTHER ANTIBIOTICS

SEARCH FOR NEW ANTIBIOTICS

Primary Screen. (in vitro)

Secondary Screen

Microbial Transformations of Steroids

SOURCES OF STEROIDS

PREPARATION OF CORTICOIDS

PREPARATION OF ESTROGENS

TYPES OF TRANSFORMATIONS

MICROBIAL TRANSFORMATION PROCESSES

Conventional Method

Spore process

Production of Spores

Transformation with Spores

In the transformation of steroids the use and re-use of spores (conidia, e.g., Aspergillus ochraceus) at high densities is shown. They are often produced on bran cultures. Up to 2.10^9 spores/ml can be recovered. Procedures are also shown to produce conidia by submerged growth in as short periods as 36 h). Kept in the frozen state they remain active for several years, and in this state they can also be transported to other factories to be used there without further manipulation.

OTHER MICROBIAL METABOLITES OF THERAPEUTIC VALUE

ALKALOIDS

Microbial Production

Microbial transformations

POLYSACCHARIDES

ENZYMES

Fibrinolytic Enzymes

L-Asparaginase

REFERENCES (250)

Concentrations up to 25% sugar are fermented, usually in shallow trays with *A. niger*, requiring incubation periods of 7 - 12 days. Yields range from 70 - 90% based on glucose. Raw materials are molasses or fully hydrolysed starch of various origin, or sucrose.

There are abundant uses of citric acid, mainly in the food industry as an acidulant in various ways.

22. Itaconic Acid.

Aspergillus terreus and *A. itaconicus* are usually used either in surface or submerged fermentation, with cane molasses, raw sugar or cane juice as major raw material. Conversion coefficients of 60% can be obtained, and continuous process has been shown to be possible.

Itaconic acid has some application in the manufacture of certain types of synthetic resins and in detergents.

23. Gluconic Acid

Microbial production of gluconic acid is an important and expanding industry. Annual world production is estimated at 30 - 40 million lb. but considering that gluconic acid is now being used successfully in the concrete industry, there may be a rapid rise in production. Submerged processes with *Aspergillus niger* are comparatively easy; glucose concentrations of 3% - 4% are used with aeration rates of 1.0 - 1.5 vol. air per vol. of mash and min. Fermenters with "contactor agitation" give conversion yields of 95 - 97% with aeration rates of 0.2 to 0.4 vol.
air per vol. and min., and fermentation times of 36 - 40 h.

Miscellaneous Products

31. Dihydroxy acetone.

There are some uses of this product in the pharmaceutical industry (as sun-tanning agent). Raw material is usually glycerol, and the conversion agent various members of the genus *Acetobacter*.

32. Sorbose, Fructose

Sorbose is used quite extensively in the synthesis of ascorbic acid, and is produced by selected strains of *Acetobacter* on sorbitol in concentrations of 20 - 30%, and nearly quantitative conversions can take place at 30°C in 45 h.

12. Butanol and Acetone

Competition from chemical synthesis is extremely severe as in the case of ethanol. In the fermentation process 60% of the production costs are taken in by (comparatively expensive) raw materials (molasses) and 15 - 20% by fuel and energy.

With regard to the process itself, contaminations are very troublesome, particularly by phage. The sugar concentration is usually not higher than 4%, with conversion coefficients for solvents of up to 33%. The continuous process proved to be advantageous on laboratory scale.

13. 2,3-Butanediol.

The organisms potentially useful for this fermentation are Aerobacter aerogenes and Bacillus polymyxa, with citrus press juice, citrus molasses, blackstrap molasses, beet molasses and sulfite waste liquor as possible raw materials.

A. aerogenes can ferment higher concentrations of sugar than B. polymyxa, while the latter has the advantage of having diastatic activity.

The major technical problems involved are the recovery of the product, due to its very high boiling point (180 - 184°C). Counter current extraction methods are possible.

14. Polyhydric alcohols.

Besides glycerol, erythritol, arebitol and mannitol can be produced by osmophibic yeasts, where up to 0.6 g polyols per g glucose utilised can be formed. There may be a chance that production of glycerol by osmophibic yeasts is economically feasible, rather than the old sulphite fermentation process, but so far very little glycerol is prepared by fermentation. Small amounts can easily be obtained by saponification of fats; large scale production by synthetic means is based on the use of allylchloride, acrolein and propylene oxide.

2. Organic Acids

21. Citric Acid.

Annual world production predominantly by fermentation; very little by extraction from fruits) is estimated at 200 - 220 million lb.

Mannitol can be almost quantitatively converted to fructose with selected strains of Acetobacter, the final concentration of fructose could be as high as 35%. Another possibility for fructose production is from a mixture of glucose and fructose by fermenting glucose to gluconic acid and having fructose intact. There are important medical applications of fructose (parenteral injections) and is used also as a sweetening agent.

3. Polysaccharides.

Dextran is currently produced by strains of Leuconostoc on sucrose with fructose as by-product. In order to produce dextrans with a higher degree of chain-length standardisation, enzyme conversion with the isolated dextran sucrase can be carried out.

Xanthan gum, which may be of value in the pharmaceutical, cosmetic, food and textile industries, can be produced with Xanthomonas campestris using glucose, sucrose or other carbohydrate sources as raw material.

4. Microbial insecticides.

Bacteria pathogenic to insects are currently being produced and used in practice. Bacillus thuringiensis, the causative agent of fatal diseases in many lepidopterous insects, is produced by conventional fermentation. Bacillus popilliae, pathogenic to the Japanese beetle is propagated only in larvae of this insect.

P.A. Stevens, WHO: Fermentation and Wastes Disposal

Amongst the residues of human life and activity are many fermentable substances and the wastes of fermentation industries. Wasted substances are naturally assimilated into the environment by various processes, including fermentation. Natural assimilation is limited, and when it is exceeded, nuisances and health hazards invariably result.

Protection of the public health requires as a minimum that wastes be safely confined and disposed of, and in some cases that they be suitably treated to prevent pollution of the enviornment. The wastes of the fermentation industries are in general amenable to biological treatment. Economic and social considerations lead to efforts to recover usable materials or to prevent wastes. Wastes management in developing countries involves planning simple, adequate facilities, geared to present and possibly changing requirements. Industries must bear a fair share of the responsibility and cost of waste treatment and disposal.

WHO has been actively assisting member states to carry out relevant studies and to form competent staff and institutions. An International Reference Centre for Wastes Disposal was set up in 1968.

V. SUMMARY OF THE COUNTRY REPORTS

Twenty-four country reports have been received by UNIDO. In the following summary information has been compiled with respect to those details which were most common to all reports. The units have been standardised and re-calculated as far as was practicable.

General Information on Fermentation Industries in Various Countries[1]

Country	Main raw materials[2] type	amount ($*.10^{-3}$) utilised	Fermentation products[3] type	amount	Number of companies
Argentine	molasses cereals	300	ethanol	90	18
			butanol	2.8	3
			acetone	1.4	
			lactic acid (80%)	0.2	1
			citric acid	1.3	1
			gluconic acid (50%)	0.13	1
			antibiotics vit. B12 dextran	4.5m	5
Australia	molasses		ethanol	135	3
Barbados	molasses		rum	1.5	
Ceylon	molasses		ethanol	5.2	12
	palm infli-rescences		arrack	1.63	
			vinegar[4]	0.54	10
China (Thaiwan)	molasses		fodder yeast	8	
	cassova		ethanol	25	
	soya beans		acetic acid		
	rice		Na-glutamate	10	
	other cereals		citric acid	0.3	
			chlortetracycline	18	
			soy sauce	80	
			soy cheese		

Country	Main raw materials[2] type	amount ($\cdot 10^{-3}$) utilized	Fermentation products[3] type	amount	Number of companies
Colombia	molasses	50%	ethanol	29.5	12
	virgin honey	19%	baker's yeast		
	raw brown sugar	28%	solid	1.7	
			dry	0.5	
			liquid	6.7	
			citric acid	0.9	
			acetic acid	1.5	
Congo	molasses		ethanol	0.36	
			carbon dioxide	1.0	
Czechoslovakia	molasses		ethanol	60	10
	sulphite waste liquor				
	fruits		alcoholic drinks	500	
			fodder yeast	7.5	
			baker's yeast	26	8
			vinegar	32	29
			citric acid	10	2
			lactic acid	0.25	1
India	molasses	900	ethanol	130	63
	dry bagasse	3065	yeast (fodder)	1.1	
			penicillin	122	3
			streptomycin	126	2
			tetracyclines	18.1	3
			chloramphenicol	24.7	3
			amylases (bacterial)		

Country	Main raw materials[2] type	amount ($+.10^{-3}$) utilized	Fermentation products[3] type	amount	Number of companies
Ireland	barley		alcoholic drinks	8.2	
	potatoes		ethanol	3.0	2
	molasses (imp.)				
	raw sugar (imp.)		sugar simps		
	maize (imp.)		vinegar		
Israel	beet molasses		baker's yeast	2.5	
	sugar		ethanol	5.1	4
	citrus fruit and grape wastes		vinegar	1.5	
			citric acid	2	
Laos	rice		ethanol[5]	1.95	
	sorghum				
	wheat				
	sugar				
Mauritius	molasses		ethanol	1.5	
			vinegar		
Malaysia	molasses		ethanol	0.11	3
	tapioca				
	soya beans		fodder yeast	1.2	1
	rice		Na-glutamate	1.7	2
			soya sauce		130
			vinegar		15
Nigeria	cereals		alcoholic drinks	[illegible]	

Country	Main raw materials[2] type	amount ($+.10^{-3}$) utilized	Fermentation products[3] type	amount	Number of companies
Norway	potatoes		baker's yeast		
	sulphite		ethanol		
	waste liq.		vinegar		
	fruits		neomycin		
			bacitracin		
Singapore	molasses		ethanol	2.25	
	raw sugar				
	rice				
	bowlieng				
South Africa	molasses	283	ethanol	7.5	
			butanol		
			acetone		
			yeast		
			carbon dioxide		
			tetracyclines (cap)	11	2
Spain	bagasse of		ethanol	130	many
	grapes		citric acid	1.5	1
	molasses		lactic acid		3
	sulphite waste		90%	0.35	
	liquor		80%	0.09	
			gluconic acid	0.03	1
			vit. B12	30	1
			antibiotics		4
			penicillin	54.12	
			streptomycin	47	
			tetracyclines	19	
			enzymes	104	
			baker's yeast	.	2
			fodder yeast	2.5	1

Country	Main raw materials[2] type	amount (+.10^{-3}) utilized	Fermentation products[3] type	amount	Number of companies
Sudan	molasses	38	ethanol	0.5	3
	dates	39			
	sorghum		alcoholic drinks	2.1	
			baker's yeast	0.2	
			citric acid	0.02	
Sweden	grains		ethanol(ind.)	67.5	12
	potatoes		alcoholic drinks	430	50
	sulphite		baker's yeast		
	waste liquor		solid	14.6	2
	molasses		dried (active)	0.03	
			fodder yeast	0.66	
			vinegar	4.8	
			antibiotics		2
			1 enzymes	0.5	2
			streptolinase		
			galactose oxidase		
			cellulase		
			1 dextran		1
Thailand	molasses		ethanol	9	1
	tapioca		acetic acid		
			Na-glutamate	5 (exp.)	4
Uruguay	molasses		ethanol (total	)	
			alcoholic drinks	90	
			vinegar		
			bacterial amylase securing enzymes (hides)		1
			yeast		2

Country	Main raw materials[2] type	amount ($+.10^{-3}$) utilized	Fermentation products[3] type	amount	Number of companies
Vietnam	molasses		ethanol	8-9	
	manioc		Na-glutamate	2	
	rice				
	brewer's rice				
	red maise				

1) The figures given are the most recent ones available; usually they refer to the years 1966 - 1967; sometimes also 1968.

2) If percent are indicated, they refer to the relative extent of utilisation of the particular raw material as compared to all types of raw material.

3) Units:

ethanol in million litres per year

butanol, acetone } in million kg (thousand tons) per year

lactic acid, citric acid, gluconic acid } in million kg (thousand tons) per year

vinegar as 10% cone. in million litres

rum, arrack } in million proof wine gal.

other alcoholic drinks in 1000 hl.

yeast in million kg.

liquid yeast in million l.

Na-glutamate in million kg.

antibiotics in 1000 kg if no standard units of activity are used.

3) penicillin in M.M.U.
soy sauce in million l.
carbon dioxide in million kg.
vitamin B_{12} in kg.
enzymes in tons (1000 kg.)

4) conc. not indicated.

5) potable alcohol 40 - 50°

VI. a. ADDENDUM

A Consideration of the Major Fermentation Products which may be envisaged to be produced by developing countries

1. Organic Solvents and other Neutral Compounds

a) Ethanol

Ethanol for industrial purposes can be produced more cheaply by chemical synthesis than by fermentation when it is to be produced on large scale. UNIDO will advise country concerned whether it can meet best the local demand including any possible export at the moment and for the coming 10-15 years by fermentation or by chemical synthesis. If marketing and export organisation is sufficiently good and if the necessary capital is available a chemical plant will be envisaged.

Raw materials: molasses, cereals, potatoes, cassava, camote, sulphite waste liquor.

By-products: carbon dioxide (e.g., soft drink manufacture), fusel oil (solvent)

Technology: anaerobic fermentation; starchy substrates require hydrolysis; amylase production plant necessary or amylo process; in the latter saccharification is carried out with a growing mould (Rhizopus) rather than an amylase preparation.

Waste products: slops

Necessary experience required: low; plant usually not suitable for butanol-acetone, as the latter requires high degree of aseptic work.

b) Butanol-Acetone

(see general remarks for ethanol)

Raw materials: as for ethanol

By-products: CO_2, H_2, Riboflavin

Technology: as for ethanol

Reliable sterilisation and prevention of contamination absolutely necessary

Waste products: slops

Necessary experience required: requires considerable microbiological experience particularly for manufacture control; qualified workers in the plant to carry out sterilisation, inoculations and transfers

Plant flexibility: relatively low; fermentation part suitable for anaerobic processes only.

c) 2, 3 - Butanediol

use to developing country unlikely.

d) Glycerol

can be obtained more cheaply from saponification or splitting of fats

e) Erythritol, arabitol, mannitol

or no use to developing country.

2. Organic acids

a) Acetic acid

While industrial acetic acid can be made more cheaply by synthesis, a smaller demand can be met by fermentation.

Raw materials: as for ethanol, including distilled ethanol itself, adjusted to concentration up to about 1%, supplemented with nutrients.

By-products: none

Technology: Preferably submerged fermentation, rather than percolating process. Alcoholic washes from yeast fermentation can be fermented directly if an extraction procedure is used for acetic acid.

Necessary experience: reliable personnel to control fermenters.

Plant flexibility: relatively low, unless stirrers and agitators are specifically adapted; percolating process not usable for other processes.

b) Lactic acid

See acetic acid

Raw materials: as for ethanol including whey; preferably pure raw materials such as glucose are to be used.

By-products: lactic acid bacteria cultures, serving as a regulator of intestinal flora.

Technology: fermentation process comparatively easy; recovery costs high class steel or plastics in recovery stage

Necessary experience required: relatively low with regards to fermentation; some chemical engineering ability in recovery stage.

Plant flexibility: low; fermentation plant can be used for ethanol fermentation; but scales are wholly different.

c) Butyric and Propionic acids

no use for developing country

d) Citric acid

Raw materials: molasses, sucrose, starchy materials

By-products: mycelium as fertiliser

Technology: submerged process and surface fermentation possible. Extremely difficult technology, process unreliable unless all factors under very careful control. Surface fermentation less subject to variation, but nevertheless of all fermentations the most hazardous one.

The use of starchy materials requires enzymic saccharification with -amylase plus amylo-glucosidase.

Necessary experience required: extremely high

e) Itaconic acid

Of hardly any use to developing nations

f) Gluconic acid

Raw materials: Glucose

By-products: Glucose oxidase (to serve as oxygen-removing agent)
Mycelium as fertiliser

Technology: submerged aerobic process
Glucose production from starchy material requires enzymic saccharification with -amylase and amyloglucosidase

Necessary experience required: reliable workers to maintain cultures, prepare inocula, carry out sterilization, inoculations and transfers.

Plant flexibility: good; suitable for other aerobic fermentations.

3. Miscellaneous simple and carbohydrate compounds

a) Dihydroxyacetone, Sorbose: of hardly any use in developing country; vitamin-C (derived from sorbose) should be available in sufficient quantities in developing countries (mainly tropical with usually large supply of fruits).

b) Fructose: Production of this may be justified for parenteral solutions for intravenous infusion of shock patients; relatively small amounts needed.

Raw material: Sucrose, Mannitol, Starch

4. Microbial insecticides

Production not recommended as too difficult to apply product at the right time.

5. Penicillin G and Penicillin V

Uses: antibiotics, active mostly against gram positive bacteria.

Raw materials: lactose, corn steep liquor or peanut meal.

Process: aerobic, fully aseptic

Technology-difficulty/Availability: technology established and available; considerable knowledge and experience required.

Comments: Active derivatives from Penicillin can be obtained chemically and enzymatically.

6. Tetracyclines

Uses: antibiotics (wide range)

Raw materials: soy bean meal, peanut meal; yeast extract; corn steep liquor; starch, sucrose.

Process: aerobic, fully aseptic

Technology-Difficulty/Availability: technology established and available a good deal of knowledge and experience required.

7. Riboflavin

Uses: Food and feed supplement

Basic raw materials required: ground lentils and pancreatic digest of gelatin; molasses or sucrose. Glycine = critical ingredient

Process: Aerobic process gives highest yields; fully aseptic operation

Technology-Difficulty/Availability: Rather difficult; technology available

8. Lysine

Uses: Food and feed supplement (upgrading of vegetable protein)

Basic raw materials: carbohydrate sources; biotin; corn steep liquor.

Process: Aerobic; fully aseptic

Technology-Difficulty/Availability: Not easily available

Comments: Competition by chemical synthesis is likely to develop.

9. 5'-Nucleotides

Uses: Flavouring Agent

Basic raw materials: carbohydrate sources

Process: aerobic; fully aseptic

Technology-Difficulty/Availability: Developing technology, not easily available.

10. Monosodium glutamate

Uses: Flavouring agent

Raw materials: carbohydrate sources; biotin

Process: aerobic, fully aseptic operation.

Difficulty: Careful control; technology developing, not easily available.

Comments: Competition by chemical synthesis is likely to develop.

11. Vitamin B_{12}

Uses: feed and feed supplement

Raw materials: carbohydrate sources (molasses).

Process: aerobic and anaerobic, fully aseptic.

Technology-Difficulty/Availability: technology established; comparatively easy.

12. Enzymes

Amylases

Necessary fermentation products if starchy material to be fermented;

Raw materials: bran of various grains, starch, potatoes

By-products: none (from bran), or mycelium

Technology: In developing countries amylase used in saccharification of starchy materials for alcoholic fermentation is best produced on loose solid cultures on bran.

Necessary experience: requires careful control in inoculum preparation. Submerged process more difficult, is usually used for production of amyloglucosidase.

Plant flexibility: low, particularly due to small size required.

Other enzymes usually not attractive for developing countries.

Multipurpose Plants:

1. Aerobic processes.

Antibiotics

Vitamines

Gluconic acid

Citric acid

L-sorbose (for Vit. C.)

M.S.G.

2. Anaerobic processes.

Ethanol)

Butanol)

Lactic acid) interconvertible if fully aseptic work

Vit. B 12 (by anaerobic bacteria) possible.

VI b. SOURCES OF TECHNICAL ASSISTANCE AND ADVICE

A. Suggestions for membership on the UNIDO advisory panel

(1) Members of the working group (see Appendix II)

(2) Dr. Arthur Murray
6 Wych Lane
Adlington, Macclesfield, Cheshire
UNITED KINGDOM

(3) Dr. Zdenek Fencl
Department of Technical Microbiology
Czechoslovak Academy of Sciences
Budejovicka 1083
Praha 4 - Krc
CZECHOSLOVAKIA

(4) Prof. C. Terui
Department of Industrial Microbiology
Osaka University
Osaka
JAPAN

(5) Prof. E.B. Chain
Department of Biochemistry
Imperial College of Science and Technology
London, SW 8
UNITED KINGDOM

(6) Prof. Helge Cyllenberg
Department of Microbiology
University of Helsinki
Helsinki
FINLAND

(7) Prof. A.E. Humphrey
School of Chemical Engineering
University of Pennsylvania
Philadelphia, Pa. 19104
USA

(8) Prof. Daniel Wang
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts
USA

(9) Prof. Shuichi Aiba
Institute for Applied Microbiology
University of Tokyo
Bunkyo-ku
Tokyo
JAPAN

(10) Prof. A. Sanchez-Marroquin
Miami-18
Mexico, D.F.
MEXICO

(11) Dr. David Perlman
College of Pharmacy
University of Wisconsin
Madison, Wisconsin
USA

(12) Prof. Dr. H.G. Schlegel
Institut für Mikrobiologie
Göttingen
FEDERAL REPUBLIC OF GERMANY

(13) Prof. Dr. F. Wagner
Gesellschaft für Molekularbiologische Forschung
Stöckheim/Braunschweig
FEDERAL REPUBLIC OF GERMANY

B. Institutes, Consulting Corporations, etc.

(1) Research Institute for Antibiotics and Biotransformations
Roztoky nr. Praha
CZECHOSLOVAKIA

(2) Department of Technical Microbiology
Czechoslovak Academy of Sciences
Vlnitejovicka 1083
Praha 4 - Krc
CZECHOSLOVAKIA

(3) Vogelbusch G.m.b.H.
Reutner Markhof-gasse 40
1110 Wien
AUSTRIA

(4) Battelle Memorial Institute
101 King Avenue
Columbus, Ohio
USA

(5) Biochemical Processes, Inc.
666 Third Avenue
New York, N.Y. 10022
USA

(6) Research Institute for Pharmaceutical Chemistry
Budapest
HUNGARY

(7) Antibiotics Research Institute
Warsawa
POLAND

(8) All-Union Research Institute for Antibiotics
Moscow
USSR

(9) Friedrich Uhde G.m.b.H.

(10) Instituto Superiore di Sanita
Roma
ITALY

(11) Interacid
Ghar
SUDAN

(12) International Minerals and Chemical Corp.
Libertyville
Illinois 60015
USA

(13) Firma Fringe
Bonn
GERMANY

(14) AG für Biologische Verfahrenstechnik
Bonsel
SCHWEIZ

(15) Alembic Chemicals
Baroda 3
Gujarat
INDIA

(16) Indian Chemical Manufacturer's Association
Nithalidas Chambers
Apollo Street
Bombay 1
INDIA

(17) The Delhi Cloth and General Mills Co., Ltd.
Sugar and Alcohol Division
Swastriti Bhawan
Jhandewalan
New Delhi
INDIA

(18) All India Distiller's Association
M-37 Connaught Circus
New Delhi
INDIA

(19) Northern Utilisation Research and Development Division
U.S. Department of Agriculture
1819 University Avenue
Peoria
Illinois
USA

(20) The British Chemical Plant Manufacturers Association
16 Suffolk Street
London S.W.1.
UK

(21) C.J.B. (Projects Ltd.)
Vickers House
Millbank
London, W.C.2
UK

(22) Badger Ltd.
Aldwych House
Aldwych
London, W.C.2
UK

(23) The Lummus Co. Ltd.
58 Monmouth House
City Road
London, E.C.1
UK

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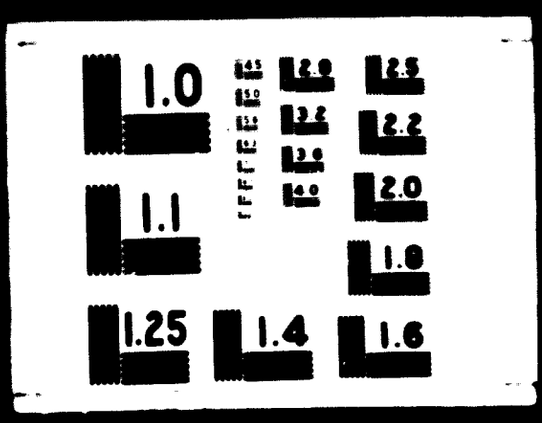

(24) Lightnin Mixer Ltd.
Poynton
Stockport
Cheshire
UK

(25) Taylor Rustless Fittings Ltd.
King Road
Lower Wortley
Leeds
UK

(26) George Kent and Co, Ltd.
Luton, Bedfordshire
UK

(27) Elliott Process Automation Ltd.
Abbey Road
Park Royal, London, N.W.10
UK

(28) Burnett and Rolfe Ltd.
Rochester, Kent
UK

(29) Metal Propellers
74 Purley Way
Croydon, Surrey
UK

(30) A.P.V. Ltd.
Manor Royal
Crawley, Sussex
UK

(31) Halfics - Head Wrightson
P.O. Box No.11
Northwich, Cheshire
UK

(32) Simon Hartley Ltd.
Biochemical Engineering Division
Stoke-on-Trent, ENGLAND

VI c. TRAINING

A. Needs

The experts which are sent out to the developing countries will make a careful assessment of the needs for training, when particular consideration should be given also to the training needs at lower (technician, craftsman) level. It is also felt that the technologists and engineers who may be involved in setting up the plant and operating it should really have practical experience in this field.

This Working Group feels that the guaranteed availability of trained personnel over the long term is a condition sine qua non.

B. Methods

One of the primary methods of training is on the job training while the contractor is setting up the plants and operating this scheme over the specified period of time: the contractor should be responsible for this.

Considering that fermentation technology is a good means of introducing industrialization at many different levels, the existing fermentation plants and those newly erected should provide extensive facilities for training technicians and craftsmen which would then enable them to move out to other industries. In other cases the existing industry may be of a different kind, such as sugar refineries from where may then come trained personnel for the first fermentation plants as well as for other industries. In fact a fermentation plant may be set up with dual purposes or several purposes in mind, when personnel is being trained for one type of fermentation product while the production is going on for another.

It is emphasized that the academic persons should have practical experience of the work in a plant and should never find it beneath their dignity to show the technical staff how it should be done.

It is recommended that UNIDO should seek co-operation with other agencies of the United Nations family who are already operating such training schemes. UNIDO should also seek co-operation with other agencies in various countries such as British Council who also operate training schemes on various levels. UNIDO should furthermore seek co-operation with a variety of research and development institutes located in various countries.

VI 4. <u>CULTURE COLLECTIONS</u>

1) A few regional culture collections should be established which would be sources of cultures, culture information and technical expertise. These should be located near to a fermentation plant or a University doing applied fermentation research. Staff members should be available for microbiological trouble shooting in the plants in their region. These centres might even supply inoculum to plants in the region. Here also would be a good place to train technicians in routine production control, techniques (determination of pH, product stability, etc). Training would be no more than one year. Probably the only centres actually needed would be in India, Central Africa, the Middle East, North Africa and South America.

2) The Section on Culture Collections of the International Association of Microbiological Societies invites the participation of international agencies, such as UNIDO, in its programmes. It would also welcome suggestions from such organisations as to means by which it might aid science and technology in developing countries.

Appendix I

Agenda

Monday, 1 December 1969:	**Morning Session**	
09:00-10:00	Registration of participants and observers Distribution of documents	
10:00-10:45	Formal opening of the meeting Election of Chairman, Vice-Chairman and Rapporteur Adoption of Agenda	
Break		
11:15-11:30	Introductory Remarks	
	C.K.H. Chieng	WHO STAFF
11:30-12:00	A talk on the Austrian Fermentation Industry and Technology	
	J. Meyrath	AUSTRIA
	Afternoon Session	
14:30-15:00	Fermentation and Waste Disposal	
	P.A. Stevens	WHO STAFF
15:00-15:30	Discussion on above paper	
	A talk on "Biological Treatment of Wastes from Antibiotic and Related Industries"	
	K.S. Iyengar	INDIA
Break		
16:00-16:30	Manufacture of Industrial Chemicals by Fermentation: Industrial Alcohol; Organic Solvents (acetone, butanol, glycerol); Organic Acids (acetic acid, citric acid), Microbial Insecticides, etc.	
	F. Wagner	FRG
16:30-17:00	Discussion on above paper	

Tuesday, 2 December 1969:

Morning Session

09:30-10:00 — Nutritional Supplements: Vitamins, Amino Acids, and Flavouring Agents
H.T. Huang — USA

10:00-10:30 — Discussion on above paper

Break

11:00-11:30 — Fermentation Processes employed in the Pharmaceutical Industries and their Economic Aspects
L. Horvath — HUNGARY

11:30-12:00 — Discussion on above paper

Afternoon Session

14:00-14:30 — Microbial Production of Therapeutic Agents
G. Vezina — CANADA

14:30-15:00 — Discussion on above paper

Break

15:30-16:00 — Energetic and Kinetic Aspects of Industrial Fermentation
L. Novrath — AUSTRIA

16:00-16:30 — Discussion on above paper

16:30-17:00 — General Discussion: Prospects for Fermentation Technology in Developing Countries

Wednesday, 3 December 1969:

Morning Session

09:30-10:00 — Micro-organisms and their Role in Fermentation
Carl Hesseltine — USA

10:00-10:30 — Discussion on above paper

Break

10:50-11:00 — A talk on "Use of Radiation in the Genetic Improvement of Industrial Micro-organisms"
B. Mukherjee — IAEA STAFF

11:00-11:30	Problems of Culture Improvement in Industrial Microbiology
	C.T. Calam UK
11:30-12:00	Discussion on above paper
	Afternoon Session
14:00-14:30	Fermentation Plant and Equipment
	L.L. Caden, Jr. USA
14:30-15:00	Discussion on above paper
15:00-15:10	A talk on "Antibiotic Fermentations: Problems in Translation of Laboratory and Pilot Scale Results to Large Scale Practice"
	K.S. Iyengar INDIA
Break	
15:30-16:00	Metal Recovery from Low-grade Ores, Sulphur Recovery from Gypsum
	J.V. Beck USA
16:00-16:30	Discussion on above paper
16:30-17:00	General discussion: Technological and Training Needs of Developing Countries
Thursday, 4 December 1969:	Morning Session
09:30-10:00	Use of Water-Insoluble Enzymes Derivatives in Synthesis and Separation
	L. Goldstein ISRAEL
10:00-10:30	Discussion on above paper
Break	
11:00-12:00	General discussion on conclusions, specific problems arising from session, adoption of procedure for the preparation of the Expert Working Group Report, report of the Rapporteur, etc.
	Rapporteur: J. Meyrath AUSTRIA
	Afternoon Session
14:30-17:30	Plant visit: Fermentation plants of the Vereinigte Hefner Markhof'sche Presshefe Fabriken, Simmeringer Hauptstrasse 101, Vienna.

Friday, 5 December 1969:

09:30-12:00 — Morning Session

Preparation of recommendations for the report

14:00-17:00 — Afternoon Session

Adoption of recommendation, closing of meeting.

Appendix II

Participants

Experts

Prof. Jay V. Beck
Professor of Microbiology
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Provo, Utah 84601
USA

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Antibiotics Process Section
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Research Associate
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Weismann Institute of Science
Rehovoth
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Mr. P.A. Stevens	Sanitary Engineer Wastes Disposal World Health Organization Avenue Appia 1211 Geneva 27 Switzerland
Mr. Claude Vezina	Associate Director of Research Head of Microbiology Department Ayerst Laboratories Montreal, P.Q. Box-6115 Canada
Dr. F. Wagner	UniversitÄtsdozent Institut für Biochemie und Biotechnologie Der Technischen Hochschule Stuttgart Azenbergstrasse 14 7000 Stuttgart Federal Republic of Germany

Observers

Prof. Dr. Phil. E. Bancher	Institut für Botanik, Technische Mikroskopie und Organische Rohstofflehre an der Technischen Hochschule in Wien Getreidemarkt 9 1060 Vienna, Austria
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Dr. R. Mukherjee	Radiation Biology Section International Atomic Energy Agency Kärntner Ring 11 A-1010 Vienna, Austria
Dr. M.R.S. Iyengar	Chief Chemist Alembic Chemical Works Baroda India
Prof. Dr. Wilhelm Obersill	Institute for Biochemical Technology and Microbiology Technische Hochschule Getreidemarkt 9 1060 Vienna, Austria

Mr. Piffl	Selv[illegible] Gie Vienna 1 Park Ring 12
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Dip.Ing. E. Urban	Technical Manager Vereinigte Mautner Markhof'sche Presshefe Fabriken Simmeringer Hauptstrasse 101 Vienna Austria
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Mr. Herbert Wutzel	Vogelbusch Gesellschaft M.B.H Mautner Markhof-gasse 40 1110 Vienna Austria

UNIDO Secretariat

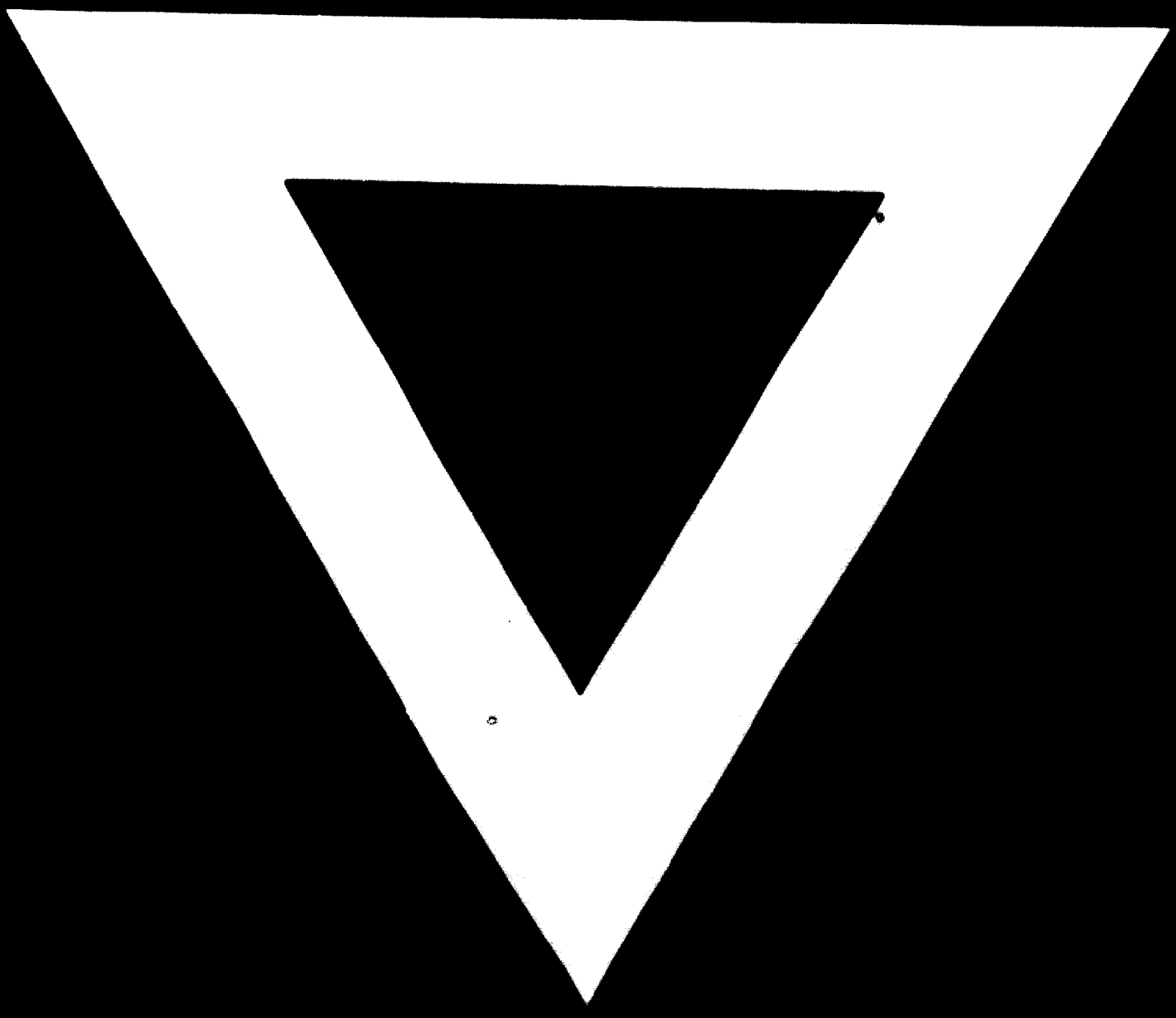
Mr. W.A. Caldwell	Chief, Basic Chemicals, Pharmaceuticals and Building Materials Industries Section Industrial Technology Division
Mr. C.S. Chiang	Industrial Development Officer Basic Chemicals, Pharmaceuticals and Building Materials Industries Section Industrial Technology Division

Appendix III

List of Documents

Symbol	Title
ID/WG.50/1 ID/WG.50/1 Summary	PROBLEMS OF CULTURE IMPROVEMENT IN INDUSTRIAL MICROBIOLOGY - Dr. C.T. Calam (Microbiologist, Pharmaceuticals Division, Imperial Chemical Industries Limited, Alderly Park, Macclesfield, Cheshire, England.)
ID/WG.50/2 ID/WG.50/2 Summary	METAL RECOVERY FROM LOW-GRADE ORES, SULFHUR RECOVERY FROM GYPSUM - Prof. Jay V. Beck (Professor of Microbiology, Department of Bacteriology, Brigham Young University, Provo, Utah 84601, U.S.A.)
ID/WG.50/3 ID/WG.50/3 Summary	NUTRITIONAL SUPPLEMENTS, VITAMINS, AMINO ACIDS, AND FLAVOURING AGENTS - Dr. H.T. Huang (Director, Biological Sciences, International Minerals and Chemical Corp., Libertyville, Illinois 60048, U.S.A.)
ID/WG.50/4 ID/WG.50/4 Summary	FERMENTATION PLANTS AND EQUIPMENT - Prof. Elmer L. Gaden, Jr. (Chairman/Professor, Department of Chemical Engineering, Columbia University in New York, New York, N.Y. 10027, USA)
ID/WG.50/5 ID/WG.50/5 Summary	USE OF WATER-INSOLUBLE ENZYME DERIVATIVES IN SYNTHESIS AND DEGRADATION - Mr. L. Goldstein (Research Associate, Department of Biophysics, Weizmann Institute of Science, Rehovoth, Israel)
ID/WG.50/6 ID/WG.50/6 Summary	MICROORGANISMS AND THEIR ROLE IN FERMENTATION - Dr. C.E. Hendeltine (Chief, Fermentation Laboratory, Northern Regional Research Laboratory, 1815 North University Street, Peoria, Illinois 61604, USA)

Symbol	Title
ID/WG.50/7	
ID/WG.50/7 Summary	MICROBIAL PRODUCTION OF THERAPEUTIC AGENTS - Mr. C. Vezina (Associate Director of Research, Head of Microbiology Department, Ayerst Laboratories, P.O. Box-6115, Montreal, Canada
ID/WG.50/8	
ID/WG.50/8 Summary	FERMENTATION PROCESSES EMPLOYED IN THE PHARMACEUTICAL INDUSTRIES AND THEIR ECONOMIC ASPECTS - Dr. I. Horvath (Director, Research Fermentation Division, Research Institute for Pharmaceutical Chemistry, Szabadsághercegok U.47-49, Budapest 4, Hungary)
ID/WG.50/9	FERMENTATION AND WASTE DISPOSAL
ID/WG.50/9 Summary	- P.A. Stevens (Sanitary Engineer, Waste Disposal, World Health Organization, Avenue Appia 1211, Geneva 27, Switzerland)
ID/WG.50/10	ENERGETIC AND ECOLOGICAL ASPECTS OF INDUSTRIAL
ID/WG.50/10 Summary	FERMENTATION - Prof. Dr. J. Meyrath (Vorstand, Hochschule für Bodenkultur, 1180 Vienna, Michaelerstrasse 25, Austria)
ID/WG.50/11	PROGRAMME OF WORK
ID/WG.50/12	PROVISIONAL LIST OF PARTICIPANTS
ID/WG.50/13	INDUSTRIAL CHEMICALS: ORGANIC SOLVENTS; ORGANIC ACIDS; MISCELLANEOUS PRODUCTS; MICROBIAL INSECTICIDES - Doz. Dr. Fritz Wagner (Gesellschaft für Molekularbiologische Forschung, Abt. Biotechnikum D 3301 Stöckheim, Mascheroder Weg 1, Federal Republic of Germany)
ID/WG.50/14	PROVISIONAL LIST OF DOCUMENTS



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