CENTER PUBLICATIONS AND PRESENTATIONS

1974-1978

PREFACE

One of the functions of the Oregon Innovation Center is to conduct research into the Innovation Process. Reflecting the nature of the Innovation Process, the Center's research has covered a variety of topics and has been interdisciplinary. Accordingly, the output of that research has been published and presented to a diverse audience. The following report covers the Center's research activities during the past four (4) years. The findings and opinions expressed in these publications and presentations are those of the author and do not necessarily reflect the opinions of the Center or its funding agencies.

The Oregon Innovation Center
College of Business Administration
University of Oregon
Eugene, OR 97403

CENTER PUBLICATIONS
AND PRESENTATIONS

1974-1978

Funded by the National Science Foundation under contract ISP 73-20222 A02
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PUBLICATIONS AND PRESENTATIONS
INNOVATION CENTER
COLLEGE OF BUSINESS ADMINISTRATION
UNIVERSITY OF OREGON
EUGENE, OREGON 97403

BOOKS AND MONOGRAPHS

1. MARKETING MODERN ELECTRICS: AN ALTERNATIVE TO THE INTERNAL COMBUSTION ENGINE, (Action, MA: Publishing Sciences Group, Inc., 1974) (Gerald G. Udell, G.M. Naidu and George Tesar).

2. GUIDE TO INVENTION AND INNOVATION (Washington, D.C.: National Science Foundation, 1977)(Gerald G. Udell, Kenneth E. Baker, and Michael F. O'Neill).

3. WHAT'S NEW IN PRODUCT DEVELOPMENT LITERATURE - SELECTED ANNOTATED BIBLIOGRAPHY, (Washington, D.C.: National Science Foundation, 1978) (Gerald G. Udell and Michael F. O'Neill).

4. MANAGING THE SMALL SERVICE FIRM FOR GROWTH AND PROFIT (to be published by the Small Business Administration, 1979) (Gerald G. Udell).

5. APPROPRIATE TECHNOLOGY IN THE PACIFIC NORTHWEST (Washington, D.C.: National Science Foundation, 1979) (Gerald G. Udell).

6. SMALL BUSINESS BIBLIOGRAPHY ON SMALL BUSINESS (Washington D.C.: Small Business Administration, 1979) (Gerald G. Udell and Michael F. O'Neill).

7. THE OREGON NEW PRODUCT SCREENING SYSTEM: An Innovation Evaluation Model and System, 1979) (Gerald G. Udell and Kenneth G. Baker).

8. COMPUTATIONAL PROCEDURES FOR THE OREGON NEW PRODUCT SCREENING MODEL: A MANUAL FOR INVENTION AND INNOVATION EVALUATION (To be published by the National Science Foundation, 1979) (Kenneth G. Baker and Gerald G. Udell).

9. "A QUESTIONNAIRE TO IDENTIFY ENTREPRENEURIAL TYPES OF INDIVIDUALS" (National Science Foundation, To be published in 1979) (David Hull, John Bosely, and Gerald G. Udell)

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CENTER PUBLICATIONS

Exploration in Invention and Innovation - An Innovation Center Series

1. A Program of University and Community Assistance to Technological Inventors, Innovators and Entrepreneurs, Gerald G. Udell.

2. Bridging the Gap Between Invention and Innovation, Gerald G. Udell.

3. The Corporate and Outside Sources of New Products: An Analysis of Corporate Policies and Procedures for Evaluating Unsolicited New Product Ideas, Del Hawkins and Gerald G. Udell.

4. Exploring New Ideas, Gerald G. Udell and Kenneth G. Baker.

5. The Coupling Problem in Technological Innovation, Warren Brown.

6. A Guide to Invention and Innovation Evaluation, 2nd Ed., Gerald G. Udell, Kenneth G. Baker and Michael F. O'Neill.

7. A Guide to Venture Capital Funds, Paul Swadener.

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CONFERENCE PRESENTATIONS

1975 1. "Consumer Attitudes Toward the Automotive Retail Trade Industry," Wisonsin Automotive Trades Association Convention, Milwaukee, WI, May, 1975. (Gerald G. Udell)

2. "The Independent Inventor and His Impossible Dream," Inventor's Conference, Seattle, WA, 1975.

3. "The Role of the Independent Inventor in Technology Transfer," Conference on Technology Transfer via Entrepreneurship; The Engineering Foundation, New Hampshire, July, 1975. (Gerald G. Udell)

4. "The Role of Innovation Evaluation in Transferring Technology from the Independent Sector to the Corporate Sector," Conference on Technology Transfer via Entrepreneurship; The Engineering Foundation, New Hampshire, July, 1975. (Gerald G. Udell)

5. "Congress and the FTC," Pacific Northwest Business Law Association Conference, Lake Wilderness, Washington, April, 1975. (Gerald G. Udell with Phil Fischer)

1976 1. American Marketing Association Discussant, Memphis, TN, April, 1976. (Gerald G. Udell)

2. Western AIDS Discussant - San Diego, CA, Spring, 1976. (Gerald G. Udell)

3. "Going Beyond the Patent System to Stimulate Technological Innovation," Pacific Northwest Business Law Association Conference, Lake Wilderness, Washington, April, 1976. (Gerald G. Udell)

4. "The Innovation Centers - A Source of New Products," SMEI Northwest Council Conference, July, 1976. (Gerald G. Udell)

1977 1. "Evaluating New Product Ideas," Conference on Idea Evaluation, Golden State University, February, 1977. (Gerald G. Udell)

2. "An Analysis of a Model for Forecasting New Product Sales," Western AIDS Conference, Phoenix, AZ, March, 1977. (Gerald G. Udell)

3. "The Innovation Center Concept: An Interdisciplinary Approach to Educating Innovators and Entrepreneurs, Western AIDS, Phoenix, March, 1977. (Gerald G. Udell, Robert Colton and Kenneth G. Baker)

4. "Basic Methods of Evaluating New Product Ideas," Conference on Idea Evaluation, Golden State University, San Francisco, CA, Feb., 1977. (Gerald G. Udell)

5. "The Small Business Development Center Act," Small Business Institute Conference, Portland, OR, April, 1977. (Gerald G. Udell)

4. Basic ... Evaluation, Golden State University, San ... (Gerald G. Udell)

5. "The Small Business Development Center Act," Small Business Institute Conference, Portland, OR, April, 1977. (Gerald G. Udell)

6. Screening Systems for Evaluating New Products, Product Development and Management Association, Chicago, Nov., 1977. (Gerald G. Udell with Kenneth G. Baker)

7. "Small Business: Future Force in Industrial Innovation?," White House Conference on Small Business - To be Presented at Twelve Regional Forums and Forty-seven Open Meetings from August 1978 to January 1980. (Gerald G. Udell)

8. "Evaluating Appropriate Technology," Forum on Appropriate Technology in the Northwest, Eugene, Oregon, Sept. 1978.

9. "Management and Organization of Innovation Centers," Conference on Innovation, Entrepreneurship, and the University, Santa Cruz, Nov., 1978. (with Ed Clemens)

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CONFERENCE PROCEEDINGS

1974 1. "A Call for a Philosophy of Consumer Rights," Proceedings, American Marketing Association Educators Conference, Portland, Oregon, August, 1974. (Gerald G. Udell)

1975 1. "The Roots and Manifestations of Consumerism in the Automotive Trade Industry," Pub. Proceedings, Western AIDS Conference, Las Vegas, Nevada, March, 1975. (Gerald G. Udell and G.M. Naidu)

2. "Improving New Product Decision Making Through Systematic Innovation Evaluation," Proceedings, Western AIDS Conference, Las Vegas, Nevada, March, 1975. (Gerald G. Udell, G. Naidu and A. Kleimenhagen)

3. "Electric Cars: A Partial Solution to the Energy Crisis and for Geographic Areas with Temperature Inversions," Proceedings, Western AIDS Conference, Las Vegas, Nevada, March, 1975. (Gerald G. Udell, G. Naidu and A. Kleimenhagen)

1976 1. "Assistance for the Independent Inventor?" Proceedings, American Patent Law Association Conference, Washington, D.C., January, 1976.

1977 1. "The Innovation Process: Its Implications for a National Innovation Policy for Small Business," The Small Business Development Center Act: Hearings Before the Select Committee on Small Business of the United States Senate, 95th Congress, 1st Session, Washington, D.C., U.S. Government Printing Office: 1977. (Gerald G. Udell)

2. "A Preliminary Innovation Evaluation Instrument," The Small Business Development Center Act: Hearings Before the Select Committee on Small Business of the United States Senate, 95th Congress, 1st Session, Washington, D.C., U.S. Government Printing Office: 1977. (Gerald G. Udell and Kenneth G. Baker)

1978 1. "Will Academia Ever Reach Out to Small Business," SBI Conference, San Antonio, January, 1978. (Gerald G. Udell)

2. "Linking the SBI's with the Innovation Process," SBI Conference, San Antonio, January, 1978. (Gerald G. Udell)

3. "Educating Entrepreneurs: An Evaluation of the Innovation Center Concept," Western AIDS Conference, San Diego, 1978. (Gerald G. Udell with Robert Colton)

4. "Small Business Management and Technical Assistance Centers," Western AIDS Conference, San Diego, 1978. (Gerald G. Udell)

5. "The Innovation Center Concept," SBI Conference, San Antonio, January, 1978. (Gerald G. Udell)

6. "Providing Horizontal Incentives to Technological Innovation," Symposium on Innovation and Innovation Centers, Cambridge, Massachusetts, May, 1978. (Gerald G. Udell)

Western AIDS Conference, San Diego, 1978. (Gerald G. Udell)

5. "The Innovation Center Concept," SBI Conference, San Antonio, January, 1978. (Gerald G. Udell)

6. "Providing Horizontal Incentives to Technological Innovation," Symposium on Innovation and Innovation Centers, Cambridge, Massachusetts, May, 1978. (Gerald G. Udell)

7. "The Role of the Innovation Centers in Assisting Growth Oriented Entrepreneurs," Symposium on Innovation and Innovation Centers, Cambridge, MA, May, 1978. (Gerald G. Udell with James Anderson)

8. "An Overview of the Innovation Evaluation Concept," Symposium on Education . . . (Gerald G. Udell and Kenneth G. Baker)

9. "Invention Evaluation - The User's Perspective," Symposium on Innovation and Innovation Centers, Cambridge, MA, May, 1978. (Gerald G. Udell with Kenneth G. Baker)

10. "The Evolution of a Program Designed to Assist Independent and Small Business Inventors," Symposium on Innovation and Innovation Centers, Cambridge, MA, May, 1978. (Gerald G. Udell with Kenneth G. Baker)

11. "The Innovation Centers - An Innovation in Education," Conference on Innovation, Entrepreneurship, and the University, Santa Cruz, Nov., 1978.

12. "The Oregon Innovation Center - A No Wax Evaluation," Conference on Innovation, Entrepreneurship, and the University, Santa Cruz, Nov.,1978.

13. "Innovation Centers: Their Role in Assisting Independent and Small Business Inventors," Conference on Innovation, Entrepreneurship, and the University, Santa Cruz, Nov., 1978. (with Ken Baker and Gary Grimm)

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ARTICLES

1974 1. "Potential Pitfalls in Franchising," Australian Franchise Review, May, 1974. (Gerald G. Udell)

2. "Independence and Franchising: A Conceptual Framework for Determining the Degree of Appropriate Control in Franchising," Colorado Business Review, 1974. (Gerald G. Udell)

3. "An Alternative for Inventors," Oregon Business Review, Fall, 1974. (Gerald G. Udell with Dr. Leslie D. Shaffer)

4. "Marketing Technologically New Products," Journal of the Academy of Marketing Sciences, Fall, 1974. (Gerald G. Udell, G. M. Naidu, and George Tesar)

1975 1. "Some Myths and Other Facts About Electric Cars," Oregon Business Review, Spring/Summer, 1975. (Gerald G. Udell)

2. "The Calf Path in Franchising," Victoria Law Institute Journal, 1975. (Gerald G. Udell)

3. "The Essential Nature of the Idea Brokerage Function," Journal of the Patent Office Society, October, 1975. (Gerald G. Udell)

4. "Toward An Improved Model for Forecasting New Product Sales," Oregon Business Review, Fall, 1975. (Gerald G. Udell)

5. "Yes, A Change Agent Can Evaluate," Journal of Extension, Sept./Oct., 1975. (Gerald G. Udell)

6. "NSF Funded Experimental Centers Train Innovators, Research and Innovation Process and Help Inventors," Marketing News, November, 1975. (Gerald G. Udell)

7. "Can Academia Really Reach Out?" Journal of Extension, Nov/Dec., 1975. (Gerald G. Udell)

1976 1. "The National Science Foundation's Innovation Centers -- An Experiment in Training Potential Entrepreneurs and Innovators," Journal of Small Business Management, April, 1976. (Gerald G. Udell with Robert Colton)

2. "For the Independent Inventor, Assistance of Abuse?" American Patent Law Association Journal, Spring, 1976. (Gerald G. Udell with Eglington, Vigil, Sears & Blasetti)

3. "Franchising: The Carrot or the Stick?" Australian Franchise Review, 1976. (Gerald G. Udell with Ken Ramsing)

4. "Corporate Caution and Unsolicited New Product Ideas," Journal of the Patent Office Society, June, 1976. (Gerald G. Udell with Del Hawkins)

5. "Creativity, Necessary But Not Sufficient," Journal of Creative Behavior, June, 1976. (Gerald G. Udell, Kenneth G. Baker & Gerald Albaum)

3. "Franchising: The Carrot or the Stick?" Australian Franchise Review, 1976. (Gerald G. Udell with Ken Ramsing)

4. "Corporate Caution and Unsolicited New Product Ideas," Journal of the Patent Office Society, June, 1976. (Gerald G. Udell with Del Hawkins)

5. "Creativity, Necessary But Not Sufficient," Journal of Creative Behavior, June, 1976. (Gerald G. Udell, Kenneth G. Baker & Gerald Albaum)

6. "An Experiment In Stimulating Innovation," Les Nouvelles (Journal of the Licensing Executives Society), June, 1976. (Gerald G. Udell and Robert Colton)

7. "The FTC in the Matter of IRD: An Analysis of Recent FTC Action Against Invention Promoters", Journal of the Patent Office Society, July, 1976. (Gerald G. Udell and Michael F. O'Neill)

8. "Outside New Product Submittals: A New Evaluation Program," Research Management, July, 1976. (Gerald G. Udell)

9. "A Survey of Corporate Procedures for Evaluating Unsolicited New Product Ideas," Les Nouvelles, September, 1976. (Gerald G. Udell with Del Hawkins)

10. "The Sampling Problem in Validation of Multiple Discriminant Analysis," Journal of Market Research Society, July 1976 (Gerald Albaum and Kenneth Baker)

11. "Selecting Specialized Creators: The Independent Inventor", Psychological Reports, August, 1976 (Gerald Albaum)

12. "The Managerial Motivation of Successful Entrepreneurs", Oregon Business Review, Winter 1976. (Norman R. Smith)

1977 1. "Technological Innovation - A Crisis?" Quarterly Business Journal, March, 1977. (Gerald G. Udell with Kenneth G. Baker)

2. "The Other Half of the Magnuson-Moss Warranty Act: An Examination of the FTC Improvement Act," Journal of Marketing, April, 1977. (Gerald G. Udell and Michael F. O'Neill)

3. "The Importance of and Methodology for Stimulating Non-Corporate Technological Innovation," Business Horizons, August, 1977. (Gerald G. Udell and Michael F. O'Neill)

4. "A Small Business Extension Service?" Journal of Small Business Management, July, 1977. (Gerald G. Udell)

5. "Franchising Most Important Contractual Elements," Quarterly Business Journal, Fall, 1977. (Gerald G. Udell and Kenneth G. Baker)

6. "Outside Evaluation: A Solution to the Unsolicited New Product Idea Problem," UNIT, No. 10, Vol. 77. (Gerald G. Udell and Kenneth G. Baker)

7. "Birth Order and Creativity: Some Further Evidence," Psychological Reports, April, 1977. (Gerald Albaum)

1978 1. "Unsolicited Product Ideas: A Survey of Corporate Policies and Procedures," Research Management, Nov., 1978. (Gerald G. Udell)

2. "Public Law and Technological Innovation," Journal of Law and Technology, June, 1978. (Gerald G. Udell)

3. "The Role of the Business School in the Transfer of University Technology," Journal of the Licensing Executive Society, Fall, 1978. (Gerald G. Udell with Rick Johnson)

7. "Birth Order and Creativity: Some Further Evidence," Psychological Reports, April, 1977. (Gerald Albaum)

1978 1. "Unsolicited Product Ideas: A Survey of Corporate Policies and Procedures," Research Management, Nov., 1978. (Gerald G. Udell)

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3. "The Role of the Business School in the Transfer of University Technology," Journal of the Licensing Executive Society, Fall, 1978. (Gerald G. Udell with Rick Johnson)

55

1979 1. "The SBI Innovations Program: Involving Students in the Innovation Process," Journal of Small Business Management, January, 1979. (Gerald G. Udell)

2. " Stimulating Non-Corporate Industrial Innovation: Experiences of An Experimental Innovation Center." Journal of the Patent Office Society, January 1979. (Gerald G. Udell)

3. "Some Considerations for Successful Innovation in a Technical Environment," I.E.E.E. Transactions on Professional Communications, First Quarter 1979. (Gary Grimm and Gerald G. Udell)

4. "In Pursuit of the Heffalump: Identifying Entrepreneurial Types of Individuals by Personality Characteristics", Journal of Small Business Management. (David Hull, John Bosely, and Gerald G. Udell

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JAPANESE PROFESSORS' INVENTIONS

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JED'S GOALS

JED's main goal is to sponsor the exchange of technology. It seeks to make a major contribution to the global community by encouraging university research in needed practical areas. It catalogues these developments with the hope that important new inventions will be put at the service of people everywhere to better their lives Its patenting service provides the protection and incentive for professors everywhere to advance their valuable work.

In addition to encouraging promising research JED promotes its professor clients achievements in the industrial world. By holding regular briefings with company representatives from many areas it seeks to channel developments into actual production and thus realize the inventor's dream of utilizing research for the benefit of all.

JED likewise seeks to involve the creative possibilities of university and research facilities all over the world in a common effort. It fosters work from abroad in Japanese industrial circles, and it promotes the developments of Japanese professors in foreign areas. It serves the international area, and it strives to promote the bettering of life for all.

JED challenges the university community to produce the solutions for the needs of our age. It provides the research activity with the needed contact for development. Its Board of Directors, shareholders, and officials are of the academic area, and they are at the same time well versed in the functioning of the industrial circles. JED then is the promotor, the protector, the organizer and instrument of invention research in the world of production. It is an active catalyst in the exchange of technology.

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ELECTROTECHNOLOGY

A PROCESS FOR WELDING AND CUTTING TEXTILES OF THERMALLY FUSIBLE FIBERS (E-279)

Patent Application No. : 1630/1976
Date of Application : January 9, 1976
Yamagata University

The present invention relates to a process for welding and cutting textiles of thermally fusible fibers, in particular to a process for welding and cutting textiles of thermally fusible fibers such as glass, acetate, polyester, etc. by the use of more rational and pertinent double lazer beam which can prevent any disturbance on the textile structure with loose texture, such prevention being practically impossible by conventional process by the use of single focussed beam.

According to the present invention, thermally fusible fiber textiles are irradiated with focussed double infra-red laser beam splitted into cutting beam and fusing beam at a wave length of 10.6 μm with the highest absorption efficiency and are fused and cut by controlling such beams independently in accordance with the widths of warf and woof texture.

In short, the process of the present invention is carried out as follows: A texture is stretched between two pairs of rollers and passed beneath the exiting opening of beam at a constant speed. The fusing beam is aligned with the cutting beam to the moving direction of the textile. It is important for setting the diameter of double laser beam that the spot diameter of the cutting beam be set so that depending on the width of texture, there remains a portion of texture which has been prefused in a thin width by the action of the fusing beam. If the energy density of the two beams

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that the single beam is splitted spatially and the splitted beams are focussed independently. The irradiation position and the diameter of beams can be controllable minutely by tilting or moving vertically the ring concave mirrors independently. Because (1) the present multiple beam generator comprises a number of mirrors which are not subjected to the heat damage as done in conventional beam splitter and (2) multiple beam can be splitted spatially and continuously from a single beam by arranging spatially such ring mirrors, it is characterized by the easy and controllable focussing at a very small point. As a result, each beam is imparted a respective function and a number of steps for finely working materials to be processed can be carried out continuously and concurrently within the range from several ten to several μm.

Such characteristics of the present invention cannot be achieved by conventional single beam process and thus novel. The present generator is a convenient apparatus of a small size which can provide multiple beam in place of conventional lens systems.

TRAVELLING WAVE PARAMETRIC SYSTEM EMPLOYING JOSEPHSON'S ELEMENTS (E-273)

Kyushu University

The Josephson's element known as a superconductive microwave element is of a concentrated type and has disadvantages in the characteristics such as the output and the like. Based on similar principle, the present invention is designed so that the element is allowed to act as an element of constant distribution type.

The Josephson's element comprises two sheets of super-conductive metal electrodes (Pb, Sn, Nb or the like) and an insulating layer sandwitched therebetween and having a thickness from 10 to 20 Å. When a D.C. voltage is applied therebetween, a high frequency wave is generated at a frequency proportional to the applied voltage. A great number of studies has been published recently concerning the oscillation of microwave bands, frequency conversion, parametric amplification, detection and the like by utilizing this phenomenon. The element is employed in these circuits as an element of concentrated constant type but is disadvantageous in that the operation level is low and the frequency range is narrow. In the present invention, the elongated electrodes are applied with a D.C. magnetic field in parallel direction to the surface thereof and perpendicularly to the longitudinal direction

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circuit is changed, according to the amount to be measured, change in said amount to be measured can be measured at a high sensitivity by measuring the change in oscillation energy at the time.

While, according to the present invention, oscillation frequencies can be selected freely over a wide range without changing the basic circuit, thus, the optimum frequency for the amount to be measured can be selected for measurement.

For example, with the conventional inductance variable type thickness meter, quality, dimension, etc. of a test material determine the variable inductance converter, however, the measuring circuit is changed accordingly.

The method according to the present invention, replacement of said variable inductance converter enables extensive measurements without changing said measuring circuit.

The scope of application of the present invention includes, but not limited to, the measurement of moisture content and thickness of paper, lumber, etc. mixing ratio of different granular materials, moisture content of grain and other particlar powder-like material, and composition and concentration of solutions, non-destructive test of metals, detection of metals, non-contact switches, measurement of various thickness and positions, etc.

A PROCESS FOR MANUFACTURING METALLIC FILM RESISTORS

(E-266)

Nagano Technical School

The present invention is associated with a pending Japanese application: "A process for manufacturing metallic film resistors" (Japanese Application No. 87672/1971). These two inventions include many common characteristics. There will be listed again herein such common characteristics and those particular to the present invention.

1. Common characteristics of the present invention and the that disclosed in the pending application.

   (1) Since the processes according to the inventions are not an electrytic plating process, no vacuum generator on a large scale is quite required as so in conventional vacuum plating processes.

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Conventionally, thyristors, inverters, etc. are used for high speed drive of induction motors, and induction furnaces for power, etc. These power supply units comprise power rectifiers and power inverters.

The frequency multiplier invented this time doubles or triples the frequency of commercial AC directly without the intervention of DC, having a feature that the waveform of multiplied output voltage can be made almost square, etc.

The single phase input frequency multiplier with a triode AC switch used as the switching element of parallel inverter and with AC applied as the power supply, which was already published in the Academic Society, is greatly restricted according to applications, since the output multiplied waveform contains many higher harmonics.

The frequency multiplier developed this time has completely eliminated the above mentioned disadvantage, and the above mentioned single phase frequency multiplying circuit is applied to three phase AC for frequency tripling and to two phase AC for frequency doubling respectively.

This multiplier can be operated stably irrespective of the load power factor, by performing peculiar gate control according to the number of multiplication. This is because the triode AC switch can be provided with the feedback diode function by the application of gate signal.

Therefore, the multiplier can make highly efficient operation, and the circuit configuration is simples as a converter of this kind. It is considered to be suitable for relatively large power frequency conversion.

Applications

1) Power supply for high speed drive of induction motors
2) Power supply for induction
3) Power supply for lighting

The application range is considered to be very wide for power.

METHOD OF CONTROLLING THE SPEED OF A DC MOTOR (E-255)

Patent Application No. : 75-60185
Date of Application : May 22, 1975
Kyushu Institute of Technology

For measuring the number of revolutions of a DC motor, the rotary shaft is used in any form, as with a tachometer, etc. However, if the

METHOD OF CONTROLLING THE SPEED OF A DC MOTOR (E-255)

Patent Application No. : 75-60185
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According to the method of this invention, many conversational patterns are tape-recorded in appropriate arrangement using a cassette tape recorder or a special tape recorder. This invention relates to a device which selectively reproduces most suitable pattern of conversation as necessary in the shortest possible time.

The answer to any question is selectively reproduced immediately, and such process is repeated to make daily conversation possible through this device.

In the selection of the conversational pattern, the numerical value corresponding to the number of pattern is set in the counter, the balance between the above value and the numerical value and the numerical value corresponding to the present position of the reproducing head is sought, and then the head or the recording medium moved to the position corresponding to the balance and stopped. Subsequent push of the start button will reproduce selected conversational pattern.

With cassette tape recorders, for example, the selection of pattern is accomplished through the detection of the punched hole in the tape optically, while with special tape recorders using a wide tape capable of accommodating many patterns in parallel, the selection of pattern is accomplished by moving the head in the direction normal to the direction of tape movement by means of the pulse motor.

By selecting proper arrangement of patterns of answers to questions, the answer can be selected and reproduced in a much shorter time.

DIELECTRIC PLATE ANTENNA (E-157)

Patent Application No. : 53424/72
Date of Application : May 31, 1972
Saitama University

The invented dielectric plate antenna consists of a half-wavelength dipole antenna directly coupled with the strip line and a lagging wave element which consists of a dielectric plate with a high dielectric constant and which is arranged in front of the dipole antenna. Technically, the antenna circuit can be formed in a plain on the same base plate by means of an integrated circuit construction technique. Therefore, an integrated circuit can be used in the antenna circuit of the invented micro-wave antenna. The features of this invention are:

dipole antenna directly coupled with the strip line and a lagging wave element which consists of a dielectric plate with a high dielectric constant and which is arranged in front of the dipole antenna. Technically, the antenna circuit can be formed in a plain on the same base plate by means of an integrated circuit construction technique. Therefore, an integrated circuit can be used in the antenna circuit of the invented micro-wave antenna. The features of this invention are:

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CONDUCTING ELECTRODE (E-137)

Patent Application No. : 021080/72
Date of Application : March 2, 1972
Shinshu University

The usual electrodes for dry cells and batteries consist of a rod or plate of such materials as carbon and lead having comparatively large masses. Their surface area is relatively small in spite of the heavy weight.

This idea concerns electrodes formed from carbon filament either along or coated with a metal (such as zinc and lead).

The carbon filaments used are very thin, with diameters of less than 300 microns. They may be used in the form of a single filament, or in the form of a bundle, a net, a string or woven fabric. In this manner, it is possible to increase the surface area of the electrode without increasing the weight thereof. In particular, with metal coating it is possible to obtain electrodes light in weight and having superior electric conductivity.

COMMUTATING BRUSH (E-136)

Pattent Application No. : 009444/72
Date of Application : January 27, 1972
Shinshu University

A carbon filament finer than 300 microns is a good conductor and has high mechanical strength, so that it may be used as commutating brush for micromotors in the form of a single filament or as a group of several filaments gathered together.

The gist of this idea resides in a brush formed by bundling a plurality of monofilaments insulated from one another, with its end face rendered into contact with the rectifying face.

When the contact faces undergoes frictional movement relative to each other, the brush resistance itself changes to effect resistance commutation. Thus, this brush has excellent characteristics.

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resistors of various steady resistance values and with temperature coefficients of below 30 ppm per degree Centigrade. By suitably adjusting the concentration and temperature of the plating solution and the immersion period it is possible to manufacture a wide variety of resistors.

This plating method is broadly applicable to metallic and non-metallic surfaces. Particularly, it provides an extreme advantage over the conventional methods of forming film resistors such as by deposition and spattering, and it is suited to the manufacture of CR composite circuit elements with TiO_2 used as substrate.

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2. Cellulose triacetate is dissolved into an organic solvent, the solution is suspended in an aqueous medium in the spherical form, the suspension is heated to evaporate the organic solvent and then spherical particles of cellulose triacetate are formed. After saponifying the particle, spherical cellulose particles of from low density to high density are obtained. The particle size can be regulated at mill from several um to several hundreds um depending on the preparation conditions.

The present invention establishes the process for preparing spherical cellulose particles. It is expected that the technical application field is developed where such particles are used as a basic material for GPC fillers, spherical cellulose ion exhangers, supporting agents for fixing enzymes etc.

Field of Application:

1. Supporting agents for fixing enzymes.
2. Basic material for cellulose ion exchangers.
3. GPC fillers.

A PROCESS FOR SELECTIVELY REMOVING AN ARSENIC COMPOUND BY THE CHROMATOGRAPHY (C-182)

Patent Application No. : 49,893/1976
Date of Application : May 4, 1976
Kyushu University

The present invention relates to a process for selectively absorbing and concentrating an arsenic compound (arsenic acid, arseneous acid, arsonic acid, etc.) which is existed in an aqueous solution, and is effectively used for selectively removing the arsenic compound existent dissolved in a low concentration.

The principle of the present process in that the arsenic compound is absorbed and removed by means of the column chromatography where inert particles are used, on which a metal ion of transition element having a large ability to the arsenic compound, for example iron ion, is carried. Methods for carrying the metal ion are as follows:

1) a metal hydroxide is deposited on silica gel,
2) a metal ion is deposited on a cationic ion exchange resin,

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2) a metal ion is deposited on a cationic ion exchange resin,

Application No.: 50-141959
Application Date: Nov. 25, 1975
Kyushu Industrial College

Dimerization reaction of alcohol is called Guerbet reaction. When alcoholic solution of sodium alcoholate is heated under pressure, the following reaction takes place;

$$R\cdot CH_2CH_2OH \xrightarrow[\text{heat}]{R\cdot CH_2CH_2ONa} R\cdot CH_2CH_2\underset{\displaystyle +\ R}{CH}CH_2OH + R\cdot CH_2COOH$$
(I) (II)

This reaction is of interest as a method of preparing alcohol as in (I), however, due to a byproduct of carbonic acid as in (II) it is disadvantageous industrially. For example, a 5-hour heating of octanole at 295°C under catalysts of Na (7.6g) and powered Cu (0.6g) produces desired 2-hexyldecanol 34.8% is produced, but only with a byproduct of capric acid (II) 23.6%.

A method has been developed wherein a combination of basic substance and dehydrated catalyst is employed in place of Na. For example, butanol is heated for 8 hours at 245°C in the presence of K_2CO_3, MgO and $CuCr_2O_4$. Though this method almost eliminates the production of byproduct such as carbonic acid, substance of high boiling point, etc., the yield of desired 2-ethylhexanol is as low as 18%.

The method according to the present invention employs alkali salt of easily recoverable phenol (soda and potash salt of phenol and naphthol) and the yield of desired alcohol (I) is very high with little or no carbonic acid in the product. For example, a 12-hour heating of pentanol at 260°C in the presence of phenol potassium yield 2-propyl heptanol at the rate of 40% (73% when recovered alcohol is subtracted) with valeric acid (II), a byproduct, being as small as 0.8%.

The use of 2-naphthol potassium as catalyst further facilitates synthesis and the yield of (I) for 5 hours at 28°C is from 40% to 56% (70 - 80% when recovered alcohol is subtracted). In all cases, the production of carbonic acid was less than 2%.

Advantages:

1. Synthesizable in one process (one step)
2. Very small amount of byproduct (easily separable)

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from worn-out track tyres show physical and mechanical properties as good as those of commercially available vulcanized products of fresh rubber and show mechanical strength far better than those of vulcanized products from the softened and reclaimed rubber employing phenyl hydrazine and ferrous chloride. Moreover, vulcanized products from the softened and reclaimed rubber obtainable by the process of the present invention show far better heat aging property than that of vulcanized products from commercially available reclaimed rubber.

In putting the process of the present invention into practical use, particulated vulcanized rubber is added with a copper salt or organic amine, preferably in combination in a catalytic amount or amounts concurrently and the mixture is allowed to stand at room temperature for several hours in the atmosphere, followed by the mastication. Thus the process is very simple without any special equipment.

Advantages of Process According to Present Invention:

The present invention provides the most convenient process for softening and reclaiming particulated vulcanized products of any type of rubber without need for any special apparatus in any place by anyone on a large scale or a small scale. Rubber to be reclaimed is required nothing but admixing with the catalyst in a small amount and standing for several hours, so that the process requires no heating, thus is economical.

METHOD OF MANUFACTURING CYCLOPROPANE DERIVATIVE

(C-170, 176)

Application No.: 50-137728 50-138193
Application Date: Nov. 18, 1975 Nov. 19, 1975
Kyoto Kogei Seni University

The present invention relates to a new method of manufacturing cyclopropane derivative.

Generally, olefin and polyhalomethane derivative and powered metal copper are caused to react to obtain cyclopropane derivative. The method according to the present invention is a superior and more unique method than any known method in that compared to conventional method the reaction process is very smooth, operation is extremely simple, dangerous explosion and ignition are entirely

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Application No.: 50-129915
Application Date: Oct. 30, 1975
Hokkaido University

It was found that the mechanical destruction of marco-molecules would result in broken main chains and that the free radical (called mechano-radical) thus produced would stably exist at the temperature below the glass transition point. Subsequent introduction of a monomeric compound to the surface of a solid organic macro-molecular material promotes polymerization of said monomeric compound by the action of said mechano-radical as a starter as the monomeric compound is heated beyond the melting point thereof. Said polymerization is controllable through the temperature and time adjustment. The word "destruction" here implies breakage of macro-molecular solid material as well as partial breakage such as "scratching", "grinding", etc. In other words, when the surface of a macro-molecular solid material is mechanically cut, living polymer is produced along the cut. When various monomeric compounds are caused to contact with said living polymer, polymerization of said monomer is started, the surface is covered with said monomer and the end of said polymer is copolymerized with the solidified polymer. Since said mechano-radical is formed only on the surface resulted from the mechanical destruction, said mechano-radical start copolymerization takes place only on the surface. Accordingly, a proper selection of said copolymerization polymer enables improvement of only surface quality of macro-molecular solid material leaving other portion intact. For example, the surface of Teflon can be changed to hydrophilic by copolymerizing a hydrophilic polymer PVAC on the Teflon surface by the above method leaving mechanical strength and other properties of Teflon intact. Generally, a solid surface can be designed to have desired physical properties while maintaining overall properties of said macro-molecular solid material.

Advantages and Applications

The present invention is featured by the fact that the surface properties of macro-molecular solid material is controlled while maintaining overall properties intact. Applications include, but not limited to,

1) Only the surface of hydrophobic macro-molecular material can be converted to hydrophilic.

2) Adhesive property of a surface can be controlled.

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1) Only the surface of hydrophobic macro-molecular material can be converted to hydrophilic.

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A METHOD FOR THERMAL DIFFUSION SEPARATION OF MIXED GAS AND ITS DEVICE (C-152)

Patent Application No.: 63353/74
Hiroshima University

As practical device for separation consentration of a specific component from a mixed gas above two components, there is a convection stack type invented by Clusius-Dickel. The device has not been however tried to improve since they invented it. Operative feature of heat ray type separation column used from long ago has a lot theoretically indefinite points, for example, about appended mechanisms such as a spacer which is used for the purpose of disturbing oscillation of heat ray, there are reports that it improves efficiency of thermal separation and a reverse opinion that it decreases only said efficiency.

A plan to improve the efficiency is not considered at all. The present invention is based on theoretical elucidation, a suitable device is appended inside a separation column used heretofore, thereby flow of gas in the column is changed, thus the present invention has an effect that achieves more than 3 times as much separation as a conventional type.

According to the present invention, the separation column having one third as long as a conventional type is enough to establish as high separation efficiency as the conventional type, and time to attain to a stationary separation is outstandingly shortened.

In conventional process, a separation column from 10m to 30m is used, adjustment of flow rate between steps is very difficult if cascade system is employed. These preceding problems are outstandingly improved.

Shortening the length of the column increases efficiency per space volume in the mill, is of advantage to an operative stability and decreases combination numbers between steps even in case of employing the cascade system.

Reduction of time to attain to the stationary separation means a cutback of a requisite electric power.

Up to now thermal difusion method is admitted to have no practical use except for use limited from respect of electric power cost, but according to the present invention enlargement of applicable scope can be expected.

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- 23 -

A plating waste liquid and a waste liquid containing other component than metal except metallic salts are great expensive to use by withdrawing, therefore said liquid is heretofor thrown away after dilution or buried in the ground after changing into sludge.

Recently, such treatments as mentioned above induce problems on environmental pollutions, and accelerate resource shortages from wasting resources and costing a lot.

In these days when environmental problems are critisized, researches in regard to withdrawal and reutilization of available matters, especially metals, in waste liquid have been awfully done.

The present invention is conceived on background of such days.

A method according to the present invention can withdraw metallic ions in waste liquid by means of simple operation, and can take out cheaply sulfate at that.

The feature

(1) By utilizing that metallic ions react with formamide to produce metal-formamide complex, metallic ions selectively react with formamide and metal-formamide complex is precipitated to withdraw out therefrom.

(2) By adding sulfuric acid to the withdrawn metal-formamide complex, a new reaction is occurred to synthesize sulfates of metals.

(3) By the process of the preceding (1) and (2), metallic ions in the waste liquid are passed into sulfates.

The resultant sulfates can be used as a plating bath if only dissolved in solvent.

If metals which forms formamide complex are employed, sulfates of the metals can be produced with simple operation of (1) and (2) and cheaply in addition.

These sulfates can be utilized not only as reagents for industry and agriculture, but as electrolytes for plating bath as they are crude.

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- 25 -

carbon with saturated aqueous solution of ammonium sulfate, and published it on the relevant proceedings (Bulletin of the Technology for Industrial Circumpherence, No. 61 & 62 (combined), p42-50, 1968: Bulletin of Industrial Chemistry, 73, No. 9, 1893-1898, 1970).

We have studied for the application of the above principle to the liquid purifying process, whereby the combustion gas is continuously washed and impregnated with aqueous solution of ammonium sulfate of more than 5% concentration at it continuously passes over the activated carbon in the fixed bed as in liquid purifying process. The present process significantly improves the adsorption rate of sulfur dioxide as compared with the process in which washing and impregration are effected only by water thereby enabling to desulfur large amount of combustion gas in relatively small scale and providing much more advantages in the construction of the apparatus. The activated carbon can be used continuously while it is left in the fixed bed without the degradation of its performance.

PROCESS FOR PRODUCING BENZENE AND XYLENES FROM TOLUENE (C-138)

Patent Application No. : 79343/73
Yamaguchi University

This invention relates to a novel process for producing xylenes and benzene. Since toluence has been supplied somewhat exessively so far, the process has been developed for disproportionating the same into benzene and xylenes which are more needed.

In these prior processes, solid acidic catalysts are employed, the reaction is effected at elevated temperature above 300°C and the xylenes produced are mixture of isomers thereof, and it requires the step for separating these isomers.

The process for the separation of xylene isomers is not so easy.

In this process, complex compounds are used instead of so called solid acidic catalysts and the complex catalysts have higher activity and excellent selectivity even in lower temperatures.

In this process, complex compounds are used instead of so called solid acidic catalysts and the complex catalysts have higher activity and excellent selectivity even in lower temperatures.

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minutes, and (I) plus derivative A (0.05 percent) had a life of 13,800 minutes.

At 150°C (I) alone had a life of 19 minutes, (I) plus BHT (0.1 percent) had a life of 1,000 minutes, and (I) plus derivative B (0.1 percent) had a life of 5,400 minutes.

The derivative compounds according to the invention may be readily synthesized from simple organic chemical reactions, and their mixture also exhibit excellent suppressing effects.

METHOD OF MANUFACTURING UNSATURATED KETONE (C-132)

Patent Application No. : 45092/73
Date of Application : April 23, 1973
Kumamoto University

Heretofore, it has been though to be very difficult to directly dehydrate saturated fatty ketone into corresponding unsaturated ketone. According to the invention, fatty saturated ketone with each molecule having 4 to 6 carbon atoms is directly dehydrated under normal pressure or reduced pressure and in the presence of a binary oxide catalyst not containing any harmful component to thereby obtain corresponding unsaturated ketone with high selectivity.

For example, by using the catalyst according to the invention at a temperature of 450 to 530°C methylethyl ketone may be converted into methylvinyl ketone with high selectivity of 80 to 100 percent.

METHOD OF DESULFURIZING DISCHARGE SMOKE (C-131)

Patent Application No. : 31902/73
Date of Application : March 22, 1973
Saitama University

A method of desulfurizing discharge by adding a calcium compound or magnecium compound to the discharge gas passing through the flue, wherein the desulfurizing effect is enhanced by adding a metal salt such as zinc chloride in addition to a small quantity of metal.

Saitama University

A method of desulfurizing discharge by adding a calcium compound or magnecium compound to the discharge gas passing through the flue, wherein the desulfurizing effect is enhanced by adding a metal salt such as zinc chloride in addition to a small quantity of metal.

methods in which a membrane is used. In such separating methods the use of a hollow thread-like membrane offers many advantages. For example, such a hollow thread-like membrane has a large surface area per unit volume and has a structure which can stand pressure, so that a separator can be simplified by eliminating pressure supporting members.

A hollow thread-like membrane has been manufactured mostly by forming a plasticizer under heating. However, this method differs from the reverse osmosis method and even when cellulose acetate which is a material commonly employed in the reverse osmosis method is used, the resulting membrane does not always provide satisfactory performances.

The method of this invention, which employs the conventional reverse osmosis process and conditions for manufacturing a hollow thread-like membrane, overcomes the low coagulability and spinability of the membrance-forming liquor and enables to manufacture membranes having widely varying inner and outer diameters.

A METHOD FOR MANUFACTURING TERT-BUTYL BENZENE

(C-123)

Patent Application No. : 096201/72
Date of Application : Sept. 27, 1972
Yamaguchi University

This invention relates to a novel method for manufacturing tert-butyl benzene, wherein toluene and propylene are brought into contact with a complex compound of anthracen natrium.

Conventionally tert-butyl benzene has been manufactured through a multiple-step synthesizing process based on a stoichiometric reaction. According to the invention a complex compound of anthracen natrium is used as a catalyst. This allows a single-step synthesizing process of tert-butyl benzene, omitting many of the conventional synthesizing steps. More specifically, anthracen and natrium are made to react with each other to prepare a complex compound of anthracen natrium. In the same manner as in a common catalytic reaction, the complex compound of anthracen natrium is put into a reactor and then toluene and propylene are introduced into the reactor so that they are allowed to react with each other to form tert-butyl benzene. Sec-butyl benzene is also obtained as a by-product.

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PROCESS FOR PRODUCING COPOLYMER OF EPOXIDE AND CARBON DIOXIDE (C-14)

Patent No. : 676052
Tokyo University

A process for producing high molecular weight copolymers of an epoxide, such as propylene oxide, ethylene oxide, styrene oxide, isobutylene oxide or epichlorohydrin, and carbon dioxide, wherein the copolymerization reaction occurs under the pressure of carbon dioxide gas and in the presence of an organometallic compound as a catalyst.

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reduce disordering of the scanning electron beam, with careful consideration given to minimize the energy loss of the electron beam. Light alloy film was used as the transmission window.

The drawing of reflected electronic images in this instrument resulted in obtaining the resolution close to the case of placing samples in vacuum, with metal with high reflection factor (gold, silver, etc.). Moreover, an experiment with animate samples resulted in obtaining images distinct by several thousand times. The scintillator used was a cadmium sulfide thin film scintillator, with the acceleration voltage of 25KV.

This instrument is considered to be interesting for animate samples.

METHOD OF MEASURING THE QUANTITY OF COATING OF HIGH VISCOSITY LIQUID (MA-169)

Patent Application No. : 37589/73
Date of Application : April 2, 1973
Chiba University

The present invention relates to a novel and simple method of measuring the thickness of particularly ink layer on the surface of the printing roller, and which is applicable to the presently available means. In the printing machines, ink is rolled into a uniform thin layer by an ink roller. When ink is transferred from the ink roller to the printing roller, however, the ink film is broken, so that the ink film on the roller surface has a rough surface for a short time. The invention is based on the fact that this roughness differs with the quantity of ink constituting the ink film, and that intensity of light reflected from the rough surface that is brought about by directing a light beam to the surface at a certain angle thereto varies with the roughness of the surface.

By determining the light intensity the quantity of ink constituting the ink film may be determined. This principle may be used to operate an ink control means by an automatic control means.

VIBRATION ABSORPTION DEVICE UTILIZING MAGNETIC REPULSION (MA-141)

an ink control means by an automatic control means.

VIBRATION ABSORPTION DEVICE UTILIZING MAGNETIC REPULSION (MA-141)

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Date of Application : December 27, 1971
Vocational Training School

In the gas welding, the gas flame is enclosed within an outer shielding cup of an inert gas. By so doing, the gas flame can be rendered narrower to reduce swallowing of ambient air. In this manner, the oxidation of the weldment, and hence deterioration thereof, may be eliminated so that an excellent weld joint may be steadily obtained.

The strength of the weldment may be increased by about 60 percent, in the average, compared to those obtained with the usual gas welding. Also, its fluctuation can be extremely reduced. The invention is very promising since the gas welding method is very convenient and hence is extensively employed and involves great marketability.

POSITION CONTROL SYSTEM FOR THE FEEDBACK CONTROL OF RELATIVE POSITIONS OF TOOL AND WORKPIECE TO EACH OTHER (MA-134)

Patent Application No. :
Date of Application : January 15, 1971
Chiba University

In the cutting work with machine tools, the relative positions of the tool and workpiece are subject to variation due to such factors as the force of cutting, heat produced thereby and wear of the tool, resulting in inaccurate cutting plane.

An object of the invention is to provide a position control system with which a tool support is displaced by a control command cam designed according to previously measured errors, a dimension control cam and a hydraulic servo mechanism so as to control the relative positions of the tool and workpiece so that the workpiece may be cut as exactly to a given shape as possible. The excellence of this system is recognized from sufficient empirical data.

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(4) There are other advantages including elimination of necessity for quenching characterizing the boronization method by conventional hot bath, suitable to mutikind and small quantity production.

A PROCESS FOR PREPARING ALUMINIZED STEEL HAVING A CONTROLLABLE THICKNESS OF ALLOYED LAYER BY THE ADDITION OF LEAD (ME-36)

Patent Application No. : 50-7028
Date of Application : Jan. 17, 1975
The University of Kanazawa

The term "aluminizing" means a process for coating Al on the surface of iron and steel by dipping the latters in a molten Al-bath to enhance the oxidation and corrosion resistances at elevated temperatures. This process is employed widely for the construction of air conditioners, dryers, combustion furnaces and the like.

Notwithstanding of the fact that Fe and Al have been known to produce various intermteallic compounds as Fe and Zn or Fe and Sn, the history of aluminizing process is relatively novel. This is resulted from the fact that no suitable flux has been found. Once the aluminizing process has been developed, a thick alloyed layer of Fe/Al is formed in several seconds, the thickness depending on the dipping temperature. The increased thickness of alloyed layer serves to an improvement heat resistance, but affects adversely on the workability and formability. Hence there has occured a requirement for inhibiting the growth of alloyed layer.

Such disadvantages have conventionally been overcome by adding Be, Cu, Si or the like in the molten Al-bath. However, such an addition process has disadvantages of contaminating the Al-bath and deteriorating the corrosion resistance of the resulting layer. The present inventor have found that the thickness of alloyed layer can be controlled by adding Pb in the Al-bath without contaminating the Al-bath.

As apparent from the binary phase diagram of Al and Pb, Pb has substantially no solubility in the solid phase. The binary system is of monotectic reaction type in which Al is dissolved in Pb in a concentration of about 0.02% by weight at the vicinity of the melting point of Pb and Pb is dissolved, in turn, in Al in a concentration of about 0.2% by weight in Al at the vicinity of the melting point of Al. In the compositions beyond the solubility curve at the Pb side, no alloyed layer is formed by immersing steel

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HIGH CURRENT-DENSITY ELECTROLYSIS (ME-31)

Patent Application No. : 52961/72
Date of Application : May 30, 1972
Kyoto University

The invented electrolysis of copper is such that 30% H_2O_2 water is added to a conventional electrolyte at the rate of 3 to 5 ml per liter of electrolyte to obtain a high current-density of 5000 to 1000 A/m^2. The copper electrolysis using this high current-density results in a high current efficiency of 90% or more.

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313-271-1500

August 10, 1978

PLEASE FORWARD YOUR THOUGHTS TO
LEN MACKEY PROMPTLY

Mr. Leonard B. Mackey
I.T.T.
320 Park Avenue
New York, New York 10022

PATENT BRANCH, OGC
DHEW

AUG 28 1978

Re: Political Action

Dear Len:

But for completing formalities, APLA has now employed Mr. Michael Blommer (resume enclosed) to be a student of and political action consultant to the intellectual property community and to be a representative of APLA and all other segments of the intellectual property community who wish to participate in the undertaking, hopefully including LES.

In round figures APLA is now, temporarily, committed to about $15 per member per year to the endeavor, wants to cut that back to $10 if we can.

If the endeavor is to grow to its full potential the intellectual property community must find ways (1) to learn from Mr. Blommer; (2) to teach to Mr. Blommer; (3) to employ Blommer and (4) to provide significant financial support to his function.

All of these are of course optional with each intellectual property association, but every nonperformance by any association of any of those functions subtracts from the potential value which he and an adequate staff could generate for all of them.

As the first step in all three of these functions, I suggest that LES invite Mr. Blommer to the New Orleans annual meeting. He might be invited to sit in on all Board and other meetings, where he could be consulted as to current legislative matters and as to the political action function. Equally important he needs to listen and learn .

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PRESIDENT
Leonard B. Mackey
ITT
320 Park Avenue
New York, NY 10022
PRESIDENT-ELECT
Niels J. Reimers
Encina 6-930
Stanford University
Stanford, CA 94305
PAST PRESIDENT
William Poms
Poms, Smith, Lande & Glenny
1888 Century Park East
Los Angeles, CA 90067
V.P.—EASTERN REGION
David J. Mugford
Bristol-Myers Company
345 Park Avenue
New York, NY 10022
V.P.—CENTRAL REGION
Robert H. Johnson
Eltra Corporation
P.O. Box 931
Toledo, OH 43694
V.P.—WESTERN REGION
Harry C. Donkers
Avery International
415 Huntington Drive
San Marino, CA 91108
V.P.—CANADA
William S. Campbell
Consumers Glass Company Limited
701 Evans Avenue, Suite 510
Etobicoke, Ontario, Canada M9C 1A3
V.P.—INTERNATIONAL
Gerard J. Weiser
Weiser, Stapler & Spivak
1420 Three Penn Center
Philadelphia, PA 19102
SECRETARY
Tom Arnold
Arnold, White & Durkee
2100 Transco Tower
Houston, TX 77056
TREASURER
William Marshall Lee
Lee & Smith
10 South Riverside Plaza
Chicago, IL 60606
TRUSTEES
Robert E. Bayes
Shell Development Company
One Shell Plaza-P.O. Box 2463
Houston, TX 77001
Peter F. Casella
Hooker Chemicals & Plastics Corp.
P.O. Box 189
Niagara Falls, NY 14302
Roger G. Ditzel
Iowa State University
Research Foundation, Inc.
213 Beardshear Hall
Ames, IA 50011
David E. Dougherty
Carborundum Company
P.O. Box 337
Niagara Falls, NY 14302
Corwin R. Horton
Crown Zellerbach Corp.
One Bush St.
San Francisco, CA 94119
Cyrus S. Nownejad
Tosco Corporation
10100 Santa Monica Blvd.
Los Angeles, CA 90067
William F. Pinsak
American Motors Corporation
27777 Franklin Road
Southfield, MI 48034
Philip Sperber
Cavitron Corporation
1350 Avenue of the Americas
New York, NY 10019
EDITOR OF LES NOUVELLES
Jack Stuart Ott
1225 Elbur Avenue
Cleveland, OH 44107
GENERAL COUNSEL
Richard G. Moser
Patterson, Belknap, Webb & Tyler
30 Rockefeller Plaza
New York, NY 10020
MEMBERSHIP CHAIRMAN
Edwin A. Shalloway
Sherman & Shalloway
413 North Washington Street
Alexandria, VA 22314
(703) 549-2282

Western Regional Meeting
February 3, 1978
Stanford Court
San Francisco, California

Eastern Regional Meeting
April 7, 1978
Key Bridge Marriott Hotel
Washington, D.C.

Central Regional Meeting
May 26, 1978
Drake-Oakbrook Hotel
Oakbrook, Illinois

FOURTEENTH ANNUAL MEETING
Jointly with
LES (International) Conference
November 4-10, 1978
Fairmont Hotel
New Orleans Louisiana

LES interests, and the personalities and attitudes of LES people so that he can develop judgments as to them, their policies and what political advocacy can properly do for them.

I suggest that this trip be at LES expense.

Depending upon how APLA and others develop and use the concept in the upcoming months, it may be that in the case of future meetings of LES and other associations, an appropriate fee (perhaps $50/hour) could be paid for his time with each association guaranteeing a minimum of so many dollars per member annual contribution towards support of him and his staff. But for November 1978 APLA asks nothing more than that his expenses be paid.

In extending the invitation, LES should make it clear whether his wife's expenses will also be paid. I suggest coach class airfare be designated.

Of course a decision must be made as to which meetings of the Board, the international Board, etc., he is invited to attend -- I would suggest all.

A decision must also be made as to whether to give him audience -- time on the agenda of the Board, or an introduction and five or ten minute comment time before the entire membership, or both. Again, my suggestion is some of both, and very early on the program, so he can be identified by all who may want to talk to him over coffee, at receptions, etc.

Regards,

Tom Arnold

TA: ef
encl.

cc: APLA Board
LES Board (w/encl)

cc: APLA Board
LES Board (w/encl)

RESUME

Michael W. Blommer
4100 Blackthorn Street
Chevy Chase, Maryland 20015

Home 301-656-2908
Office 202-225-4111

PROFESSIONAL EXPERIENCE

Office of Representative Charles E. Wiggins - Administrative Assistant (October, 1975 to present).

Provides to corporate constituents and to corporations and other private sector organizations affected by legislation pending before a Committee on which Congressman Wiggins serves, assistance in evaluating pending legislation and in gaining access to those Members of Congress and Committee staff responsible for considering such legislation; and provides assistance to corporate constituents in their dealings with the Executive Branch, primarily ascertaining the meaning and effect of regulations, rulings, or administrative decisions and determining the status of pending applications for licenses, orders, grants, or rulings.

Provides assistance to officials of public constituents such as municipalities and school, housing, water and employment authorities, the County of Orange, and the State of California in understanding and evaluating pending legislation which affects them, and in gaining access to those Members of Congress, and Committee staff responsible for considering such legislation; and provides to these officials information, advice, and support in seeking funds through the categorical grant programs administered by the Executive Branch, and in evaluating the effect of Federal laws and regulations on the State or local government agency they represent.

Provides legal advice to Congressman Wiggins on bills and Resolutions introduced by him, including amendments to the Federal Criminal Law, and private relief and immigration bills, and on matters before the Committee on the Judiciary, including amendments to the Bankruptcy Act, the Hart-Scott-Rodino Antitrust Improvements Act of 1976, and a bill to regulate and control lobbying; as well as on matters before the House Administration Committee including the Federal Election Campaign Act Amendments

Federal Criminal Law, [illegible]
and on matters before the Committee on the Judiciary, including amendments to the Bankruptcy Act, the Hart-Scott-Rodino Antitrust Improvements Act of 1976, and a bill to regulate and control lobbying; as well as on matters before the House Administration Committee including the Federal Election Campaign Act Amendments

of 1976 and of 1978; and the Federal Trade Commission Amendments of 1977, the Debt Collection Act of 1977, the Financial Disclosure Act of 1978, and the Anti-Trust Improvements Act of 1978.

Supervises and manages Congressman Wiggins' Washington and California offices and staff. The staff provides a wide range of services to the constituency of the 39th Congressional District including responding to all incoming mail on legislation or government operations, assisting constituents with casework problems, preparing and publishing informational newsletters and reports, and issuing press releases to local media outlets.

U.S. House of Representatives, Committee on the Judiciary - Associate Counsel (minority counsel) to the Subcommittee on Civil and Constitutional Rights (February, 1973 to April, 1974) and the Subcommittee on Criminal Justice (April, 1974 to September, 1975).

Committee counsel is responsible for analyzing bills and resolutions as assigned and the Federal law each affects, preparing descriptive memoranda of law and fact on bills which become the subject of hearings, assisting Committee Members in marking up bills both in Subcommittee and full Committee, drafting Committee Reports for legislation approved by the Committee, preparing for and assisting in Rules Committee and House Floor consideration of reported legislation, and preparing for and assisting in Conference Committee resolution of House passed legislation.

Provided legal counsel for the consideration of the following matters: Security and Privacy of Criminal Arrest Records Act of 1973 and 1974; Amendments to and the Revision of Title XI of the United States Code (The Bankruptcy Act); Oversight investigation of the operation of the Civil Rights Acts regarding Equal Employment Opportunities; the Office of Special Prosecutor Acts of 1973 and 1974; the Nomination of Gerald R. Ford to be Vice President of the United States, the Impeachment Inquiry of President Richard M. Nixon; the Federal Rules of Evidence Act of 1974; the Nomination of Nelson A. Rockefeller to be Vice President of the United States; the Pardon of Richard M. Nixon and Related Matters; and the Amendments to the Criminal Rules of Procedure Act of 1975.

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the Criminal Rules of Procedure Act of 1975.

U.S. House of Representatives, Select Committee on Crime - Counsel (minority counsel) (March, 1971 to February, 1973).

Legal duties including drafting legislation and interpreting federal laws, federal regulations, state laws, Rules of the House of Representatives, and Rules of the Select Committee on Crime.

Staff duties including research, speech writing and report writing; supervision of staff investigations and research; participation in the public and private hearings of the Committee; preparation for the appearance of the Committee Chairman before other Committees of the House and Senate.

The Select Committee on Crime investigated the federal regulation of controlled substances, heroin and amphetamine abuse, prison riots, fraudulent practices in the banking and securities industries, and organized crime's influence in the parimutuel sports industry.

Criminal Division, Department of Justice - Trial Attorney (October, 1966 to February 28, 1971).

Participated in all phases of federal criminal practice; including proceedings before U.S. Magistrates, presentments to grand juries, motion practice, trial practice, and appellate practice.

Supervised investigations of organized crime conducted by agents of the Departments of Justice, Treasury, Labor, Transportation and Post Office Department, Securities and Exchange Commission, State and local police departments.

Legal and Legislative Office, Administrative Division, Department of Justice - Attorney (February, 1964 to September, 1966).

Conducted surveys of the administrative and legal procedures and audited the financial records of Court and Justice Department offices in the Northern District of Ohio, Middle District of Pennsylvania, Middle District of Tennessee, Eastern District of South Carolina, Western District of Virginia, Eastern District of Missouri, and the District of Columbia.

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EDUCATION

University of Wisconsin Law School, Madison, Wisconsin (1960 - 1963) Juris Doctor Degree

University of Wisconsin, Madison, Wisconsin (1956 - 1960) Bachelor of Science Degree

Marquette University High School, Milwaukee, Wisconsin (1952 - 1956)

MEMBERSHIPS AND AFFILIATIONS

Wisconsin Bar (1963); District of Columbia Bar (1970); and the American Bar Association.

The Columbia Country Club.

PERSONAL PROFILE

Birthdate:	March 9, 1939
Marital Status:	Married to Margaret King Blommer. Two children; Michael Bradley and Elizabeth Selden.

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that brings an idea to the fruition of an active chemical compound, and then takes the compound through years of study to produce a new drug, is as complex as a natural ecosystem. You might as well ask a forest to explain how it replenishes its floor or a stream how it purifies itself as to ask the drug-development system how it works.

I'm not talking about the science of it; that's all well understood. I'm talking about the motivation behind the complex history of ups and downs that every research program goes through. Nothing is more impenetrable than the motivation of our actions; yet we must try to penetrate what motivates the search for new drugs, or we will lose our way and perhaps never find it again.

Every research program must have enthusiasts. That fact is well known. And, almost as inevitably, it must have detractors — scientists and managers in the same firm who are not as enthusiastic, who'd like to replace it with their program, their compound. The competition is for funds, for computer time and for a dozen other scarce resources.

Also, in the modern large firm, the decision to "take research overseas," as we used to say it, is different now. Research is now overseas as much as it is here. The United States is now the "overseas" to much of the research on new drugs.

Another consideration is that pharmaceutical companies are the world's greatest counters and measurers of things present and to come. By every method known to man, they research the potential market for new drug therapy. They try, in other words, to measure future economic incentive to decide present financial support.

And they try to measure *disincentives*. For the past 15 years the FDA new-drug-approval process has made up a large part of that effort. And if this bill is enacted, new worrisome questions will be asked at quarterly and annual reviews of research and development programs and of compounds in the laboratories of some 20 or 30 pharmaceutical companies. These questions will force a new compound to declare itself much too early, not just to the FDA, but to the managers of the money to be invested in it. It's as though the entire FDA approval process were moved up several years and previewed in each company by a whole new generation of nail-biting industry people guessing how many conferences, hearings, 60-day waits, formal rejections and unexplained delays lie ahead of a new compound. Everybody plays "What will FDA say?" and discouragement dominoes down through the organization.

It doesn't matter that industry may be misreading the FDA, or that it may be foolish to try to play "What will FDA say?" Experience tells the companies that the FDA will more frequently than now say, "no," or "not now," or "do more work."

So I predict that, with 20 or 30 companies trying constantly to measure research incentives and disincentives in quarterly budget reviews, fewer and fewer of the hundreds of risky, positive commitments needed will be made as companies opt for the surer and safer. The result will be a sort of cloning of the whole process as research programs, preclinical work, and clinical protocols hew close to the official, approved standard. And the change will be insidious — scarcely noticeable when it occurs.

I could be wrong. Things may work out. But that is not the modern way to decide on big changes. Ordinarily, in this age when the complexity of socioeconomic processes is well recognized, the burden is on those who would change a process to prove that they will do no harm. In this case, the process is complex and it does work, and those who are nearest to it, those who do make it work, are warning that it needs to be nurtured and cherished and can be hurt by the proposed changes. Those who do not make it work say it would not be hurt.

The question seems to be: Is the pharmaceutical industry standing up too close to its research process to understand it, or is the FDA standing back too far?

SmithKline Corporation
Philadelphia, PA 19101

ROBERT L. DEAN

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

Edited by
JONATHAN E. FIELDING, M.D., M.P.H., AND PEARL K. RUSSO

THE ECONOMIC COSTS OF STROKE IN MASSACHUSETTS

ELIZABETH MILLS, M.A., AND MARK THOMPSON, PH.D.

The morbid and mortal harm of strokes may be reduced by public-health programs addressed to the underlying risk factors — particularly the early diagnosis and control of hypertension — as well as by medical management of the condition. The benefits of such programs are alleviation of both the human and the economic costs of stroke. Although a consideration of both cost categories is critical to effective public-health policy, only the economic consequences can be measured. Of economic costs, the more evident and readily measured are the direct costs: hospital expenses, fees for physician visits, nursing-home charges

Further information may be obtained from Dr. Thompson at the Center for the Analysis of Health Practices, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115 ([617] 732-1060).

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that brings an idea to the fruition of an active chemical compound, and then takes the compound through years of study to produce a new drug, is as complex as a natural ecosystem. You might as well ask a forest to explain how it replenishes its floor or a stream how it purifies itself as to ask the drug-development system how it works.

I'm not talking about the science of it; that's all well understood. I'm talking about the motivation behind the complex history of ups and downs that every research program goes through. Nothing is more impenetrable than the motivation of our actions; yet we must try to penetrate what motivates the search for new drugs, or we will lose our way and perhaps never find it again.

Every research program must have enthusiasts. That fact is well known. And, almost as inevitably, it must have detractors — scientists and managers in the same firm who are not as enthusiastic, who'd like to replace it with their program, their compound. The competition is for funds, for computer time and for a dozen other scarce resources.

Also, in the modern large firm, the decision to "take research overseas," as we used to say it, is different now. Research is now overseas as much as it is here. The United States is now the "overseas" to much of the research on new drugs.

Another consideration is that pharmaceutical companies are the world's greatest counters and measurers of things present and to come. By every method known to man, they research the potential market for new drug therapy. They try, in other words, to measure future economic incentive to decide present financial support.

And they try to measure *disincentives*. For the past 15 years the FDA new-drug-approval process has made up a large part of that effort. And if this bill is enacted, new worrisome questions will be asked at quarterly and annual reviews of research and development programs and of compounds in the laboratories of some 20 or 30 pharmaceutical companies. These questions will force a new compound to declare itself much too early, not just to the FDA, but to the managers of the money to be invested in it. It's as though the entire FDA approval process were moved up several years and previewed in each company by a whole new generation of nail-biting industry people guessing how many conferences, hearings, 60-day waits, formal rejections and unexplained delays lie ahead of a new compound. Everybody plays "What will FDA say?" and discouragement dominoes down through the organization.

It doesn't matter that industry may be misreading the FDA, or that it may be foolish to try to play "What will FDA say?" Experience tells the companies that the FDA will more frequently than now say, "no," or "not now," or "do more work."

So I predict that, with 20 or 30 companies trying constantly to measure research incentives and disincentives in quarterly budget reviews, fewer and fewer of the hundreds of risky, positive commitments needed will be made as companies opt for the surer and safer. The result will be a sort of cloning of the whole process as research programs, preclinical work, and clinical protocols hew close to the official, approved standard. And the change will be insidious — scarcely noticeable when it occurs.

I could be wrong. Things may work out. But that is not the modern way to decide on big changes. Ordinarily, in this age when the complexity of socioeconomic processes is well recognized, the burden is on those who would change a process to prove that they will do no harm. In this case, the process is complex and it does work, and those who are nearest to it, those who do make it work, are warning that it needs to be nurtured and cherished and can be hurt by the proposed changes. Those who do not make it work say it would not be hurt.

The question seems to be: Is the pharmaceutical industry standing up too close to its research process to understand it, or is the FDA standing back too far?

SmithKline Corporation
Philadelphia, PA 19101

ROBERT L. DEAN

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

Edited by
JONATHAN E. FIELDING, M.D., M.P.H., AND PEARL K. RUSSO

THE ECONOMIC COSTS OF STROKE IN MASSACHUSETTS

ELIZABETH MILLS, M.A., AND MARK THOMPSON, PH.D.

The morbid and mortal harm of strokes may be reduced by public-health programs addressed to the underlying risk factors — particularly the early diagnosis and control of hypertension — as well as by medical management of the condition. The benefits of such programs are alleviation of both the human and the economic costs of stroke. Although a consideration of both cost categories is critical to effective public-health policy, only the economic consequences can be measured. Of economic costs, the more evident and readily measured are the direct costs: hospital expenses, fees for physician visits, nursing-home charges

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More and more, juvenile-onset diabetes appears to be a result of a spectrum of autoimmunity, ranging from pure autoimmunity in the kindreds with multiple autoimmune endocrine deficiencies to that with little autoimmunity and related to possible direct viral destruction of beta cells. Most cases probably lie in between, with viral damage as a possible initiator of the autoimmune event. In maturity-onset diabetes, progress has been even slower. As discussed by Volk and Wellmann, a decrease in islet mass is present in almost all diabetic patients, as well as an increased incidence of degenerative findings in and about the beta cells, especially in older patients and those with long standing diabetes. Westermark and Wilander[4] have recently corroborated this observation. With the finding, originally by Goldstein,[5] of Hamilton, Ontario, and subsequently by G. M. Martin et al., of the University of California, and Rowe et al., in Seattle, that fibroblasts and other cells from diabetic patients do less well in tissue culture, a ubiquitous cellular lesion is suspect: perhaps the degeneration of the beta cell is characteristic of the total animal. With all the other evidence for premature aging in diabetic kindreds, such as atherosclerosis, osteoporosis, senile cataract and perhaps even the increased vascular basement-membrane thickening noted by Siperstein and his colleagues[6] in offspring of two parents with maturity-onset diabetes, the cellular defect in the diabetic pancreas might simply be an early aging and death of the beta cells as well. Perhaps all persons at age 150 or over might have diabetes, as well as having gray hair, or, for that matter, no hair!

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The pharmaceutical industry thinks the disincentives are important. These disincentives have their origin in four provisions of the bill. The first is revealing all the safety and efficacy data created by a drug's sponsor and submitted to the FDA. This provision means revealing scores of research protocols and case report forms, which are the very framework of discovery of safety and efficacy of a new drug, the result of months or years of painstaking, creative work on the part of many people. They will, obviously, be protocols approved by the FDA, so they represent an official roadmap to success for a competitive compound — a roadmap obtainable for the price of Xeroxing. I think this policy will give innovative companies an incentive to do as much work as possible overseas to get a good head start.

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The fourth provision changes the present Investigational New Drug (IND) system radically. It proposes a two-step process whereby an applicant wishing to investigate a compound in man could do so initially in a Drug Innovation Investigation; in this phase the FDA would confine its interest to patient safety, would not attempt to rule on the scientific validity of research protocols. This, says the FDA, would be a great boon to the sponsor, permitting him to explore efficacy in a larger number of compounds reasonably quickly and without undue burden. It is this provision that the FDA cites when asked how this bill encourages the development of new drugs. Such encouragement, by the way, is one of the important avowed purposes of the bill, featured in its second paragraph and in every pronouncement that HEW made about the bill at its introduction.

But the innovative phase does not seem to be much different from the present system, in which the FDA's interest is also almost entirely the safety of subjects, not the scientific validity of the proposed studies. It does provide an opportunity to generate some efficacy data, as opposed to the present policy, which unofficially discourages such data, but I do not think this is an important incentive.

So if the proposed innovative phase is not much better than the present IND system what is it better than? It is clearly better than the provisions for Drug Development Investigations, the second phase provided for by the bill.

A group of us at the blackboard a month or so ago tried to trace the course of a new drug through this second phase. It took us an hour, and it proved a discouraging course, starting with a 60-day wait for the Secretary to decide whether the investigations may begin. That 60 days is to be spent by the FDA in evaluating potential risks to patients, of course, and whether these risks are outweighed by benefits, a difficult evaluation when benefits have not yet begun to declare themselves. Also, in those 60 days the Secretary must decide whether the overall study plan is adequate to meet objectives and whether the parts of the study plan — the proposed investigations — are adequate.

I can understand these latter provisions; the FDA has in the past seen study plans so flawed that they simply could not be expected to meet objectives. So they respond in the way that professional regulators must; they reach for a regulation to assure the adequacy of study plans, and then they require that any deviation in protocol be approved. These provisions are more rigid, more formal and more time-consuming than the present system, in which the FDA frequently provides helpful advice on study plans; they will interfere with the way in which this business of discovery really works. New insights come unexpectedly, and they require quick turns.

In the present system, if the FDA reviewer delays an IND application because he is concerned, let us say, about the electrocardiogram of dog No. 3, the sponsor can bring his dog expert, the FDA brings its experts, and, given a satisfactory outcome, the FDA can, as likely as not, conclude on the spot that the study can begin. That will not happen under the new law; a letter of approval will be needed, and experience tells us to expect many weeks of delay.

The FDA knows that the present system can work informally, but not in every FDA division, so the new law tries to create a standardized system. The trouble is that the proposed system standardizes things in the wrong direction, and it mandates by law what now sometimes works pretty well without it. And it deprives the agency of simple solutions. Often, now, technical points of difference about protocols, and just plain misunderstandings, can be settled by a telephone call.

Industry wonders, too, why a bill that so tightens the investigative phase in every respect, with prior approval of all protocols and even of changes in the protocols, must then insist on a 390-day period to consider the application. If nothing were being changed about regulating the investigational phase, I could understand doubling the approval phase, to reflect better the pace at which approval takes place now. Or the other way around, if the 180-day approval phase in the present law remained the same in the new law, I could see why we should have provisions for stretching out the investigative phase. But why make both changes?

The bill has other examples of overkill, provisions written for the past, when indeed there was no public participation, no postmarketing surveillance and no real give-and-take on study plans and protocols. Now all these procedures are developing well as a result of the hundreds of policy decisions, regulations and improvements to working relations that have filled the years from 1962 to 1978, especially the past few years.

* * *

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THERE is much about the Drug Regulation Reform Act of 1978 that can be improved, but I will confine my comments to the *disincentives* that it would create for the research and development of new drugs in this country. I don't think anybody questions that there are such disincentives in the provisions of the bill. But are they important? Do they outweigh the advantages the bill provides the public?

The pharmaceutical industry thinks the disincentives are important. These disincentives have their origin in four provisions of the bill. The first is revealing all the safety and efficacy data created by a drug's sponsor and submitted to the FDA. This provision means revealing scores of research protocols and case report forms, which are the very framework of discovery of safety and efficacy of a new drug, the result of months or years of painstaking, creative work on the part of many people. They will, obviously, be protocols approved by the FDA, so they represent an official roadmap to success for a competitive compound — a roadmap obtainable for the price of Xeroxing. I think this policy will give innovative companies an incentive to do as much work as possible overseas to get a good head start.

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Thirdly, the bill provides that if a second comer wishes to market a drug, he may rely on the data of the original applicant to do so, provided he waits five years. In its early drafts, the bill contained no waiting period; the five-year provision was added in recognition of a source of disincentive. So the five years is an arbitrary measure of disincentive, too short by industry standards, but long enough by the government's.

The fourth provision changes the present Investigational New Drug (IND) system radically. It proposes a two-step process whereby an applicant wishing to investigate a compound in man could do so initially in a Drug Innovation Investigation; in this phase the FDA would confine its interest to patient safety, would not attempt to rule on the scientific validity of research protocols. This, says the FDA, would be a great boon to the sponsor, permitting him to explore efficacy in a larger number of compounds reasonably quickly and without undue burden. It is this provision that the FDA cites when asked how this bill encourages the development of new drugs. Such encouragement, by the way, is one of the important avowed purposes of the bill, featured in its second paragraph and in every pronouncement that HEW made about the bill at its introduction.

But the innovative phase does not seem to be much different from the present system, in which the FDA's interest is also almost entirely the safety of subjects, not the scientific validity of the proposed studies. It does provide an opportunity to generate some efficacy data, as opposed to the present policy, which unofficially discourages such data, but I do not think this is an important incentive.

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that brings an idea to the fruition of an active chemical compound, and then takes the compound through years of study to produce a new drug, is as complex as a natural ecosystem. You might as well ask a forest to explain how it replenishes its floor or a stream how it purifies itself as to ask the drug-development system how it works.

I'm not talking about the science of it; that's all well understood. I'm talking about the motivation behind the complex history of ups and downs that every research program goes through. Nothing is more impenetrable than the motivation of our actions; yet we must try to penetrate what motivates the search for new drugs, or we will lose our way and perhaps never find it again.

Every research program must have enthusiasts. That fact is well known. And, almost as inevitably, it must have detractors — scientists and managers in the same firm who are not as enthusiastic, who'd like to replace it with their program, their compound. The competition is for funds, for computer time and for a dozen other scarce resources.

Also, in the modern large firm, the decision to "take research overseas," as we used to say it, is different now. Research is now overseas as much as it is here. The United States is now the "overseas" to much of the research on new drugs.

Another consideration is that pharmaceutical companies are the world's greatest counters and measurers of things present and to come. By every method known to man, they research the potential market for new drug therapy. They try, in other words, to measure future economic incentive to decide present financial support.

And they try to measure *disincentives*. For the past 15 years the FDA new-drug-approval process has made up a large part of that effort. And if this bill is enacted, new worrisome questions will be asked at quarterly and annual reviews of research and development programs and of compounds in the laboratories of some 20 or 30 pharmaceutical companies. These questions will force a new compound to declare itself much too early, not just to the FDA, but to the managers of the money to be invested in it. It's as though the entire FDA approval process were moved up several years and previewed in each company by a whole new generation of nail-biting industry people guessing how many conferences, hearings, 60-day waits, formal rejections and unexplained delays lie ahead of a new compound. Everybody plays "What will FDA say?" and discouragement dominoes down through the organization.

It doesn't matter that industry may be misreading the FDA, or that it may be foolish to try to play "What will FDA say?" Experience tells the companies that the FDA will more frequently than now say, "no," or "not now," or "do more work."

So I predict that, with 20 or 30 companies trying constantly to measure research incentives and disincentives in quarterly budget reviews, fewer and fewer of the hundreds of risky, positive commitments needed will be made as companies opt for the surer and safer. The result will be a sort of cloning of the whole process as research programs, preclinical work, and clinical protocols hew close to the official, approved standard. And the change will be insidious — scarcely noticeable when it occurs.

I could be wrong. Things may work out. But that is not the modern way to decide on big changes. Ordinarily, in this age when the complexity of socioeconomic processes is well recognized, the burden is on those who would change a process to prove that they will do no harm. In this case, the process is complex and it does work, and those who are nearest to it, those who do make it work, are warning that it needs to be nurtured and cherished and can be hurt by the proposed changes. Those who do not make it work say it would not be hurt.

The question seems to be: Is the pharmaceutical industry standing up too close to its research process to understand it, or is the FDA standing back too far?

SmithKline Corporation
Philadelphia, PA 19101

ROBERT L. DEAN

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

Edited by
JONATHAN E. FIELDING, M.D., M.P.H., AND PEARL K. RUSSO

THE ECONOMIC COSTS OF STROKE IN MASSACHUSETTS

ELIZABETH MILLS, M.A., AND MARK THOMPSON, PH.D.

The morbid and mortal harm of strokes may be reduced by public-health programs addressed to the underlying risk factors — particularly the early diagnosis and control of hypertension — as well as by medical management of the condition. The benefits of such programs are alleviation of both the human and the economic costs of stroke. Although a consideration of both cost categories is critical to effective public-health policy, only the economic consequences can be measured. Of economic costs, the more evident and readily measured are the direct costs: hospital expenses, fees for physician visits, nursing-home charges

Further information may be obtained from Dr. Thompson at the Center for the Analysis of Health Practices, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115 ([617] 732-1060).

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contemporary fashion the morphologic and biochemical data collected over the last few years. The chapters trace the comparative development of insulin-like proteins in invertebrates, the first beta cells in lower vertebrates and the complicated gastroenteropancreatic interplay in the higher vertebrates, especially in mammals. Somatostatin and pancreatic polypeptide, which both appear in the islets of Langerhans in the D cells and perhaps in other special cells not yet labeled, are discussed. The confusing and at times disappointing pathologic findings in the human diabetic pancreas, probably mainly of adult maturity onset, are reviewed and correlated with the newer immunologic and viral data that have recently been collected and bear directly on the pathogenesis of the juvenile-onset type of diabetes.

It is interesting to compare the previous volume by Lazarus and Volk in 1962 to the present volume, especially the components dealing with physiology. The beta cell has emerged from being a difficult-to-examine isolated site of the insulin deficiency in diabetes to probably the best characterized of any cell in the body (the red cell and white cell are probable exceptions, but how easy they are to obtain for study!), but still the precise cause of both common forms of diabetes remains to be clarified.

More and more, juvenile-onset diabetes appears to be a result of a spectrum of autoimmunity, ranging from pure autoimmunity in the kindreds with multiple autoimmune endocrine deficiencies to that with little autoimmunity and related to possible direct viral destruction of beta cells. Most cases probably lie in between, with viral damage as a possible initiator of the autoimmune event. In maturity-onset diabetes, progress has been even slower. As discussed by Volk and Wellmann, a decrease in islet mass is present in almost all diabetic patients, as well as an increased incidence of degenerative findings in and about the beta cells, especially in older patients and those with long standing diabetes. Westermark and Wilander[4] have recently corroborated this observation. With the finding, originally by Goldstein,[5] of Hamilton, Ontario, and subsequently by G. M. Martin et al., of the University of California, and Rowe et al., in Seattle, that fibroblasts and other cells from diabetic patients do less well in tissue culture, a ubiquitous cellular lesion is suspect: perhaps the degeneration of the beta cell is characteristic of the total animal. With all the other evidence for premature aging in diabetic kindreds, such as atherosclerosis, osteoporosis, senile cataract and perhaps even the increased vascular basement-membrane thickening noted by Siperstein and his colleagues[6] in offspring of two parents with maturity-onset diabetes, the cellular defect in the diabetic pancreas might simply be an early aging and death of the beta cells as well. Perhaps all persons at age 150 or over might have diabetes, as well as having gray hair, or, for that matter, no hair!

The *Diabetic Pancreas* is a unique volume, selectively and succinctly reviewing the literature of the past and adding and integrating former and present morphologic knowledge with much of the large body of physiologic and biochemical data that have only recently been collected. It will stand for a long time as the source book on the beta cell.

Joslin Diabetes Foundation
Boston, MA 02215 GEORGE F. CAHILL, JR., M.D.

REFERENCES

1. Rotter JI, Rimoin DL: Heterogeneity in diabetes mellitus — update, 1978: evidence for further genetic heterogeneity within juvenile-onset insulin-dependent diabetes mellitus. Diabetes 27:599-605, 1978
2. Coleman DL: Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 14:141-148, 1978
3. The Diabetic Pancreas. Edited by BW Volk, KF Wellmann. New York, Plenum Press, 1977
4. Westermark P, Wilander E: The islet volume in maturity onset diabetes mellitus. Acta Endocrinol [Suppl](Kbh) 209:60, 1977
5. Goldstein S, Moerman EJ, Soeldner JS, et al: Chronologic and physiologic age affect replicative life-span of fibroblasts from diabetic, prediabetic, and normal donors. Science 199:781-782, 1978
6. Siperstein MD, Unger RH, Madison LL: Studies of muscle capillary basement membranes in normal subjects, diabetic, and prediabetic patients. J Clin Invest 47:1973-1999, 1968

SOUNDING BOARD

HOW THE PROPOSED DRUG REGULATION REFORM ACT WILL DISCOURAGE THE SEARCH FOR NEW DRUGS

THERE is much about the Drug Regulation Reform Act of 1978 that can be improved, but I will confine my comments to the *disincentives* that it would create for the research and development of new drugs in this country. I don't think anybody questions that there are such disincentives in the provisions of the bill. But are they important? Do they outweigh the advantages the bill provides the public?

The pharmaceutical industry thinks the disincentives are important. These disincentives have their origin in four provisions of the bill. The first is revealing all the safety and efficacy data created by a drug's sponsor and submitted to the FDA. This provision means revealing scores of research protocols and case report forms, which are the very framework of discovery of safety and efficacy of a new drug, the result of months or years of painstaking, creative work on the part of many people. They will, obviously, be protocols approved by the FDA, so they represent an official roadmap to success for a competitive compound — a roadmap obtainable for the price of Xeroxing. I think this policy will give innovative companies an incentive to do as much work as possible overseas to get a good head start.

Secondly, the bill provides for a longer, more formal, complex process of approval than the present law does, 360 days instead of 180, in addition to a 30-day period up front in which the Secretary decides whether or not he will even accept an application. The industry worries about this lengthening and formaliz-

ing, and when an industry worries, there is less incentive to invest in a more doubtful future.

Thirdly, the bill provides that if a second comer wishes to market a drug, he may rely on the data of the original applicant to do so, provided he waits five years. In its early drafts, the bill contained no waiting period; the five-year provision was added in recognition of a source of disincentive. So the five years is an arbitrary measure of disincentive, too short by industry standards, but long enough by the government's.

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