HORROR STORIES IN

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Prior to 1968, concerns were voiced that the results of DHEW funded research rarely reached the public. In light of this concern, the GAO conducted an investigation in 1968 of the pharmaceutical research in NIH. The report indicated that investigators found no NIH funded pharmaceuticals in commercial use despite the hundreds of millions of dollars annual investment. According to the report, the primary cause was identified to be DHEW's reluctance to involve the private sector in bringing the invention to the marketplace. Specifically, GAO indicated that industry would not underwrite the costly development process involved without sufficient patent protection for such high risk ventures. In general, development and marketing of a health invention is 10 times as expensive as the initial government investment in the research.

After issuance of the report, the Department devised a new patent policy which enabled universities and other recipients of DHEW research funds to retain invention rights through an Institutional Patent Agreement or a case-by-case petition procedure. This enabled universities in particular to license industrial concerns which, in turn, provided the necessary risk capital to complete development and commercialization.

Item "A" provides a partial list of inventions which have reached, or are about reach to, the market-place since 1968 when DHEW revised its patent policy. As can be seen, the list includes many revolutionary life-saving inventions which have attracted hundreds of millions of dollars of venture capital. Prior to 1968, not a single private dollar could be traced to an NIH invention.

seen, the list includes many revolutionary life-saving inventions which have attracted hundreds of millions of dollars of venture capital. Prior to 1968, not a single private dollar could be traced to an NIH invention.

Since August of 1977 the petition procedure, which involves a significant portion of Department inventions, has stopped functioning. The General Counsel's office now refuses to grant patent rights to the universities.

Item "B" lists the 27 petitions for inventions being held by the General Counsel's office at last count. All of the petitions have been reviewed by the sponsoring NIH institute and the Department Patent Branch, who recommended to the DHEW General Counsel that the petition be granted as an incentive toward industrial collaboration. As a result, all 27 inventions, for which patents have been applied, are lying fallow.

It is also noted that the three new petitions for IPA's being similarly delayed are listed on Item "B". Internal DHEW memoranda I have seen indicate that the Department is also contemplating abolishing the entire IPA system -- a move that would spell the end of NIH's transfer of research program.

Item "C" is a discussion in greater detail of some of the cases listed on Item "B". All of the inventions are deemed to be significant breakthroughs, as evidenced by the fact that a private company has agreed to invest sufficient venture capital for development, evaluation by FDA, and marketing. Because of DHEW's unwillingness to collaborate with the private sector, negotiations with an available and willing commercial developer are stymied. The decision to hold back these medical breakthroughs is so unconscionable that they are properly designated "Horror Stories". The period of time during which the General Counsel has refused to act is indicated for each invention as the "Delay". Prior to last August, delays were zero, since for the last ten years, the General Counsel did not choose to review these cases.

Also included, is a letter from the Director's Office of NIH, indicating that the delays in the General Counsel's office are not expected to end in the near future.

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ITEM A



## SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| | Inventor | University | Invention | Licensee | Approximate Investment |
|---|---|---|---|---|---|
| 1. | Walser | Johns Hopkins U. | Keto-Acid analogs of Amino Acids for treatment of uremia | Pfrimmer of Germany and Syntex of U.S.A | Millions - Clinical trials in process. Expected to be marketed in 6 mos. in Europe. |
| 2. | Wiktor | Wistar Institute | Rabies Vaccine | Wyeth Laboratories | On the market - millions |
| 3. | Kamen et al | Case Western Res. | Methotrexate Assay during Cancer Chemotherapy | Diamond Shamrock Corp. | Being test-marketed. Production scheduled for late 1977. Millions. |
| 4. | Lillehei/Kaster | U. of Minnesota | Pivoting Disc Heart Valve | Medical, Inc. | Being sold in world-wide market since 1971. Millions. |
| 5. | Blackshear et al | U. of Minnesota | Implantable Infusion Pump (Constant Infusion of Drugs for Treatment of Cancer, Diabetes, Pain, Morphine-addiction, etc.) | Metal Bellows Co. | Undergoing clinical trials. $750,000. |
| 6. | DeLuca | U. of Wisconsin | 25-Hydroxycholecalciferol for treatment of Osteo-dystrophy with liver dysfunction | Rousel-Uclaf (Hoechst) and | Have applied for equivalent of NDA in France. Approximately $5 million. |
| | | | | Upjohn | About to apply for an NDA and an NADA. Will spend about $10 million. |
| 7. | DeLuca | U. of Wisconsin | 1-Alpha Hydroxycholecalciferol for treatment of Osteo-dystrophy with Kidney Dysfunction | Leo Pharma-ceuticals | Applying for new drug applications in Denmark and Great Britain. May be marketed this year. Approx. $5,000,000. |

SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| | Inventor | University | Invention | Licensee | Approximate Investment | Approximate Investment |
|---|---|---|---|---|---|---|
| 8. | DeLuca et al | U. of Wisconsin | 1, 25-Dehydroxyergocalciferol for Treatment of Osteodystrophy with Kidney and Liver Dysfunction and Senile Osteodystrophy | Hoffman-LaRoche Inc. | About to apply for NDA. Will spend about $10 million. | About to apply for NDA. Will spend about $10 million. |
| 9. | Fox | Columbia U. | Silver Sulfadiazine used in Treatment of Burns | Marion Labs., Kansas City, Mo. | Now on market - Approx. $5,000,000 | Now on market - Approx. $5,000,000 |
| 10. | Heidelberger | U. of Wisconsin | Use of $F_3TDR$ for Herpes Infections of the Eye | Burroughs Wellcome Co., Research Triangle Park, N.C. | Approx. $5,000,000 NDA expected by end of 1977. | Approx. $5,000,000 NDA expected by end of 1977. |
| 11. | Fischell | Johns Hopkins U. | Rechargeable Cardiac Pacemaker | Pacesetter Systems Sylmar, California. | On market since Feb. 1975 - Approx. $720,000 | On market since Feb. 1975 - Approx. $720,000 |
| 12. | Holland | Tulane U. | Method of Reducing Intraocular Pressure in the Human Eyes (Glaucoma Treatment) | Cooper Labs., Bedford Hills, N.Y. | $2,000,000 - Development leading to NDA is in process and on schedule | $2,000,000 - Development leading to NDA is in process and on schedule |
| 13. | Pressman | U. of Miami | Application of X-537A in the Cardiovascular System (for stimulation in cardiogenic shock, congestive heart failure, etc.) | Hoffman-LaRoche, Nutley, N.J. | $500,000 to $1,000,000 Clinical evaluations still in progress | $500,000 to $1,000,000 Clinical evaluations still in progress |
| 14. | Higley | Natl. Institute of Scientific Research | Polycarbonate Dialysis Membranes (kidney dialysis) | C. R. Bard Inc., Murray Hill, N.J. | Over $1,000,000. Market introduction expected imminently. | Over $1,000,000. Market introduction expected imminently. |
| 15. | Talbot/Harrison | Johns Hopkins U. | Ballistocardiograph Apparatus | Royal Medical Corp. Huntsville, Ala. | Approx. $330,000. Now on market. | Approx. $330,000. Now on market. |

SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| | Inventor | University | Invention | Licensee | Approximate Investment |
|---|---|---|---|---|---|
| 16. | Plotkin | Wistar Institute | Rubella Vaccine | 1) Wellcome Foundation<br>2) L'Institut Merieux<br>3) Swiss Serum and Vaccine Institute and others (Merck, an Italian firm, etc.) | Approx. millions - Now on market. |
| 17. | Schaffner/Mechlinski | Rutgers U. | Derivatives of Polyene Macrolide Antibiotics | E.R. Squibb of U. S. A. and Dumex of Denmark | Millions - Clinical trials progressing favorably |
| 18. | Zweig | Syracuse U. | Apparatus for Measuring and Controlling Cell Population Density in a Liquid Medium | New Brunswick Scientific Co., Inc., of New Jersy | Millions - On the market since 1973 |
| 19. | Lovelock | Yale U. | Gas Analysis Method and Device for the Qualitative and Quantitative Analysis of Classes of Organic Vapors | Varian Associates, Palo Alto, Calif. | On the market |
| 20. | Fried | U. of Chicago | Prostoglandins for possible Treatment of Bronchial Asthma, Duodenal Ulcers, Inflammatory Conditions, etc. | Richardson-Merrell, New York, N.Y. | Several millions - In process of development and testing for marketin here and abroad |
| 21. | Leininger/Grotta et al | Battelle Memorial Institute | Preparation of Non-thrombogenic Surfaces and Materials | C. R. Bard, Inc., Billerica, Mass.; Sherwood Medical Industries, St. Louis Mo.; and American Hospital Supply Corp., Irvine, California. | $107,754 - Some products being marketed and others being tested. |

Approximate Investment

Approx. millions - Now on market.

e and others
an firm, etc.)

Millions - Clinical trials progressing favorably

Millions - On the market since 1973

On the market

Several millions - In process of development and testing for marketin here and abroad

$107,754 - Some products being marketed and others being tested.

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SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| Inventor | University | Invention | Licensee | Approximate Investment | Approximate Investment |
|---|---|---|---|---|---|
| 22. Merrifield | Rockefeller U. | Apparatus for the Automated Synthesis of Peptides | Beckman Instruments, Fullerton, California | Being marketed since 1973. | Being marketed since 1973. |
| 23. Smith/Kozoman | Duke U. | Apparatus and Method for Rapid Harvesting of Roller Culture Supernatant Fluid | Bellco Glass, Inc. Vineland, New Jersey | $25,000 - Being marketed since June 9, 1976 | $25,000 - Being marketed since June 9, 1976 |
| 24. Zweng | Stanford U. | Laser Photocoagulator | Coherent Radiation, Palo Alto, Cal. | Approximately $500,000 Standard tool of ophtholmologists | n, Approximately $500,000 Standard tool of ophtholmologists |
| 25. Sweet et al | Stanford U. | Cell Sorter | Becton-Dickinson, Rutherford, New Jersey | Approx. $200,000. Import research tool | Approx. $200,000. Import research tool |
| 26. Boyd/Macovski | Stanford U. | Computerized Axial Tomography | S.A.I. Cupertino, Cal. | Approx. $300,000. Will be marketed soon. | Approx. $300,000. Will be marketed soon. |
| 27. Saxena | Cornell U. | Method for Testing for Pregnancy | Carter-Wallace | Approx. 1/2 million On market | Approx. 1/2 million On market |
| 28. Calnek/Hitchner | Cornell U. | Cell-free virus Preparation | Merck | | |
| 29. Carlson | Iowa State | Respiratory Augmentor with Electronic Monitor and Control | Bourns, Inc. | On market since 1966; sales now in millions | On market since 1966; sales now in millions |
| 30. Leake/Rappoport | Harbor General Hospital | Bone Induction in an Alloplastic Tray | Am. Hospital Supply | Data not available | Data not available |

SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| | Inventor | University | Invention | Licensee | State of Development | ate of Development |
|---|---|---|---|---|---|---|
| 31. | Bradford/ Williams | U. of Georgia | Protein Assay Reagent and Method | Bio-Rad Labs, Inc; Quantimetrix Corp. | On the market since April 1977 | On the market since April 1977 |
| 32. | Tenckhoff | U. of Washington | Catheter Insertion Trocar | Sweden Freezer Mfg. Co; Cobe Labs; Physio-Control Corp; | On market | On market |
| 33. | Leonard et al | U. of Illinois | Fluorescent Derivatives of Cytosine-Containing Compounds | PL Biochemicals | On market | On market |
| 34. | Secrist et al | U. of Illinois | Fluorescent Derivatives of Adenine-Containing Compounds | PL Biochemicals | On market | On market |
| 35. | Asgar | U. of Michigan | Partial Denture Alloy | | On market | On market |
| 36. | Carlson/Ward | U. of Washington | Coherent Biological Cell Analyzer | 3M Company | Marketing development in progress. | larketing development n progress. |
| 37. | Charlson/ Alhquist | U. of Washington | Integrating Nephelometer and Photon-Counting Integrating Nephelometer | Battelle Development | On market | On market |
| 38. | Thomas | U. of Washington | Artery-Vein Shunt Applique | Battelle Development Corp. | Being marketed | Being marketed |

SAMPLING OF UNIVERSITY PATENT LICENSING PROGRAMS

| | Inventor | University | Invention | Licensee | State of Development | State of Development |
|---|---|---|---|---|---|---|
| 39. | Holcomb | Yale University | Method and Apparatus for Stimulation of Body Tissue | Avery Labs, Inc. | On the market since 1973 | On the market since 1973 |
| 40. | Dugan | Temple University | Novel Compositions for Radiotracer Localization of Deep Vein Thrombi | Rand Research & Development Corp. | Licensed in 1977. | Licensed in 1977. |
| 41. | Roelofs | Cornell University | Codling Moth Pheromone | Zoecon Corp. | On market since 1972. | On market since 1972. |
| 42. | Whitby | Univ. of Minnesota | Particle Counter | Name not available | On market since 1969 | On market since 1969 |
| 43. | Backaner | Univ. of Minnesota | Method for Suppressing Ventricular Fibrillation | Burroughs Wellcome | About to be marketed | About to be marketed |
| 44. | Whitby | Univ. of Minnesota | Aerosol Sampler | Not available | On market since 1969 | On market since 1969 |
| 45. | Bradley | Univ. of Minnesota | Apparatus to Stimulate the Bladder | Two licenses, names not available | On market since 1972 | On market since 1972 |
| 46. | BUTLER | Purdue Research Fdn. | Hydrophobic Noncovalent Binding of Proteins to Support Materials | Regis Chemical | On market since April 1977 | On market since April 1977 |



7

| | Inventor | University | Invention | Licensee | State of Development |
|---|---|---|---|---|---|
| . | Rosenberg | Michigan State Univ. | Platinum Compounds as Anti-Tumor Agents | Possibly Adria, Bristol or Miles Labs. | On market in late 1977 |
| 3. | Coller | Institute for Cancer Research | Process of Viral Diagnosis and Reagent (Radioimmuno-assay) | Abbot Labs. | Licensed in 1977 (Canada) On market in U.S.A. |
| 9. | Kosikowski | Cornell University | Antibiotic Test Kit | Bacto Strip | On market |
| 0. | Kosikowski | Cornell University | Process for Milk Sterilization | De Laval Alpha Laval | On market |
| 1. | McLafferty | Cornell University | Pregnancy Test | Carter-Wallace | On market |
| 2. | Kattwinkel et al | Case Western Reserve | Device for Administering Pressure via Nasal Route | Sherwood Medical | On market since 1975 |
| 3. | Neckers et al | (Univ. of New Mexico (Wayne State University | Polymer-based Photosensitizers | National Patent Development Corp. | Being sold for research purposes only at this time |
| 4. | Keith/Snipes | Penn. State Univ. | BHT Antiviral Agent | Key Pharmaceuticals | Development is at the IND stage |
| 5. | Najjar | Tufts University | Therapeutically Useful Polypeptides | Calbiochem | Being sold for research purposes only at this time |
| 6. | Story et al | Univ. of Georgia | Macrocyclic Compounds | (Chemical Samples Company (Albany International | Commercial marketing expected within the year |
| 7. | Mielke | Institutes of Medical Sciences | Template for Ivy Bleeding Time | Hemakit, Inc. | Being sold commercially |


| State of Development |
|---|
| On market in late 1977 |
| Licensed in 1977 (Canada) On market in U.S.A. |
| On market |
| On market |
| On market |
| On market since 1975 |
| Being sold for research purposes only at this time |
| Development is at the IND stage |
| Being sold for research purposes only at this time |
| Commercial marketing expected within the year |
| Being sold commercially |

| | Inventor | University | Invention | Licensee | State of Development |
|---|---|---|---|---|---|
| 58. | Murray/Somerset | State Univ. of N.Y. | Knee Joint Prosthesis | Howmedica, Inc. | On commercial market since 1976 |
| 59. | Volz/Brownlee/Tyers | Penn. State Univ. | Rechargeable Cardiac Pacemaker | Intermedics, Inc. | Near market |
| 60. | Volz et al | Penn. State Univ. | Rechargeable Cardiac Pacemaker | Intermedics, Inc. | Being sold commercially |
| 61. | Travis/Pannell | Univ. of Georgia | Albumin Recovery Method | Calbiochem | Research quantities of albumin isolated by this method being sold to investigators. |
| 62. | Schaffner et al | Rutgers | Derivatives of Polyene Macrolide Antibiotics | E. R. Squibb | Nearing commercial market |
| 63. | Kupchan et al | Univ. of Virginia | Ansa Macrolide Tumor Inhibitor | Bristol-Myers | In clinical development |

| State of Development |
|---|
| commercial market since 76 |
| Near market |
| ng sold commercially |
| earch quantities of bumin isolated by this thod being sold to vestigators. |
| ıring commercial market |
| clinical development |

ITEM B

PETITIONS FOR INVENTION RIGHTS

| Sponsoring Institute | Date Sent to General Counsel | Inventor and University | Invention |
|---|---|---|---|
| | 1977 | | |
| Employee - Bureau of Standards | 9/28 | CETAS - Employee | Birefringement Crystal Thermometer for measuring heat of cancerous tissue during ultrasonic treatment |
| National Institute of Allergy and Infectious Diseases (NIAID) | 10/6 | REMERS/KUMAR - University of Arizona | New Mitomycin anticancer agents |
| National Institute of General Medical Sciences (NIGMS) National Heart, Lung and Blood Institute (NHLBI) | 10/14 | POWERS - Georgia Institute of Technology | Compounds to treat emphysema and arthritis |
| NIGMS | 10/14 | FOX - Columbia University | Aqueous Hypertonic Solution for treatment of burns |
| NIGMS | 11/1 | EVERETT - University of Houston | Apparatus and synthesis of film transfer characteristics |
| National Cancer Institute (NCI) | 11/4 | SELA/ARNON - Weizmann Institute | Test for diagnosing cancer |
| NHLBI | 12/8 | NORMANN - Baylor University | Remote monitoring of blood pumps |
| NCI | 12/20 | GOLDSTEIN - University of Texas | Thymosin is a hormone for treatment of immune system malfunction diseases, e.g. cancer, arthritis, lupus and Thymosin $\alpha 1$ - muscular dystrophy. |
| NCI | 12/29 | SALMON/HAMBURGER - University of Arizona | Bioassay for the treatment of cancer |
| | 1978 | | |
| NCI | 1/26 | TOWNSEND/EARL - University of Utah | Synthesis of anti-cancer compounds |

ITEM B

IONS FOR INVENTION RIGHTS

vention

nt Crystal Thermometer
g heat of cancerous tissue
sonic treatment

n anticancer agents

treat emphysema and

rtonic Solution for
burns

d synthesis of film trans-
ristics

gnosing cancer

oring of blood pumps
a hormone for treatment
stem malfunction diseases,
arthritis, lupus and
-muscular dystrophy.

the treatment of

anti-cancer compounds

| Sponsoring Institute | Date sent to General Counsel 1978 | Inventor and University | Invention | Invention |
|---|---|---|---|---|
| National Cancer Institute | 1/27 | POGELL/McCANN - Saint Louis University | Pamamycin - a new broad spectrum antibiotic | new broad spectrum |
| National Institute of Dental Research (NIDR) Division of Research Resources (DRR) | 1/31 | LATHAM/GEORGIADE - University of North Carolina | Appliance to be placed in the mouth of infants to correct bilateral cleft of the lip and palate | e placed in the mouth of rect bilateral cleft palate |
| NIAID NHLBI | 1/31 | GOETZEL/AUSTIN - Harvard Univ. | Synthetic therapeutic agents for anaphylaxis, asthma, etc. | apeutic agents for sthma, etc. |
| NHLBI | 2/10 | MAHONEY - University of Colorado | Device to examine hemoglobins to detect abnormalities | ine hemoglobins to detect |
| National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) | 2/13 | WALSER - Johns Hopkins Univ. | Salts of Keto Acids for purpose of alleviating hyperammonemia due to liver damage caused by such disorders as cirrhosis, hepatitis or genetic liver damage | Acids for purpose hyperammonemia due to aused by such disorders nepatitis or genetic |
| Employee | 2/28 | VUREK - NIH Employee | Measurement of Carbon dioxide in blood plasma for diagnostic purposes | Carbon dioxide in blood gnostic purposes |
| Employee | 4/5 | WALKER - Employee NIH | Needle Valve Detent Attachment for controlling cuff deflation during the taking of blood pressure | etent Attachment g cuff deflation during the od pressure |
| NCI | 4/7 | APPLE/FORMICA - University of California | Anticancer drug - AZETOMICINS | g - AZETOMICINS |
| NCI | 4/11 | SPIEGELMAN - Columbia Univ. | Method for detecting cancer | ecting cancer |
| NIGMS | 4/20 | MARSHALL/RABINOWITZ - University of Miami | Synthetic Carbohydrate-Protein Conjugates for extending conditions under which enzyme can be used in biochemical processes | hydrate-Protein Conjugates conditions under which enzyme biochemical processes |
| NCI | 4/20 | FARNSWORTH - University of Illinois | Anticancer drug - JACARANONE | g - JACARANONE |
| NCI | 5/1 | TURCOTTE - University of Rhode Island | Anticancer drug | g |


2

| Sponsoring Institute | Date Sent to General Counsel 1978 | Inventor and University | Invention | Invention |
|---|---|---|---|---|
| National Institute of Neurological and Communicative Disorders and Stroke | 5/8 | JOBSIS - Duke University | Method for non-invasive monitoring of oxygen sufficiency in human tissues and organs by infra-red radiation | non-invasive monitoring afficiency in human tissues by infra-red radiation |
| NIGMS | 5/24 | MONTALVO - Gulf South Research Institute | An invention to selectively measure substances in the blood to diagnose blood disorders | n to selectively measure in the blood to diagnose ders |
| NCI | 5/26 | PETTIT/ODE - Arizona State University | Anticancer drug | drug |
| Employee | 6/21 | LEIGHTON - Employee | Intracranial pressure gauge | l pressure gauge |
| NCI | 6/29 | KUEHNE - University of Vermont | A method for synthetically preparing a useful naturally-occuring substance. The natural substance is used in making a drug for treatment of high blood pressure | or synthetically preparing aturally-occuring substance. l substance is used in rug for treatment of high sure |



3.

REQUESTS FOR INSTITUTIONAL PATENT AGREEMENTS

IONAL PATENT

| Sent Down | |
|---|---|
| 1977 | |
| 12/22 | University of Arizona |
| 1978 | |
| 1/12 | University of Chicago |
| 6/30 | Cedars-Sinai Medical Center, California |

1. Salmon/Hamburger - University of Arizona (DELAY IN GENERAL COUNSEL'S
"Bioassay for Cancer Treatment" OFFICE: 7 MONTHS)

On June 26, 1978 Time magazine described the invention as follows:

"Doctors play a guessing game about which drugs to use in combatting cancer. One problem is human individuality - what helps one person may fail to help another. In the search for the proper medicine, doctors most often subject a patient to a sequence of powerful drugs, many of which turn out to be ineffective against malignant cells. Now a simple technique promises a means of testing the effectiveness of drugs in a specific case of cancer - without having to administer them to the patient." (Emphasis added)

"The main value of the laboratory test, says Salmon, is that it can help the physician plan individual courses of treatment. For example, only 20 percent of people with cancer of the colon or rectum respond to the drug fluorouracil; the other 80 percent suffer needlessly from the drug's toxic effects. The new technique may have another benefit. It could be used to evaluate new anticancer drugs without endangering cancer patients."

In order to advance the invention to the point of practical application, it will be necessary to perform large-scale clinical trials to determine if the response of the patients' calls to drugs would be predictive of the patients' clinical response and to develop marketing

cation, it will be necessary to perform large-scale clinical trials to determine if the response of the patients' calls to drugs would be predictive of the patients' clinical response and to develop marketing

procedures. It is estimated that this will take from three to five years at a cost of $2,500,000 to $5,000,000 to obtain clearance from the Food and Drug Administration.

Technicon Instruments has indicated a strong interest in proceeding with the necessary developmemt if the petition is granted. Preliminary discussions have led to a proposed license agreement wherein Technicon will support further research and development work at the university for a right of first refusal to market the invention. After completion of the Technicon funded research at the university, Technicon will undertake all the additional development necessary to obtain Food and Drug Administration clearance.

2. Walser - Johns Hopkins University (DELAY: 5 MONTHS) CM

"Ornithine and Arginine Salts of Branched-Chain Ketoacids in the Treatment of Hyperammonemia" due to liver damage caused by such disorders as cirrhosis, hepatitis or genetic liver damage.

Hyperammonemia is a buildup of ammonia which causes nausea, drowsiness, ataxia, coma and ultimately either death or mental retardation in infants. In adults hyperammonemia is marked by mental confusion, tremor, lethargy and ultimately coma and death.

Hyperammonemia occurs in the millions of people affected by liver damage caused by such disorders as cirrhosis (occasioned by alcoholism), hepatitis, or genetic liver damage.

The invention is closely related to Walser's keto-acid analogs of amino acids now marketed by Pfrimmer of Germany and Syntex of the United States for the treatment of uremia. Licensing of Pfrimmer and Syntex

testing ?

amino acids now marketed by Pfrimmer of Germany and Syntex of the United States for the treatment of uremia. Licensing of Pfrimmer and Syntex

testing ?

was made possible by a petition of the type being sought in this case. Johns Hopkins believes that these same manufacturers have indicated enough interest that they would complete development and obtain FDA clearance if the petition were granted. FDA clearance averages approximately 14 million dollars in cases of this type. Johns Hopkins has met with Senator Mathis staffers to discuss the invention and the policy resulting in delay of their petition.

3. Spiegelman - Columbia University

"Method for Detecting Cancer" (DELAY: 3 MONTHS)

The invention relates to a method for detecting the presence and status of cancer in humans by assaying for certain tumor specific viral related proteins in plasma ~~samples and novel reagents useful therein~~. Such a method would be useful in diagnosis as in initial screening programs for early detection of the disease, in therapy as in evaluating the status of the disease after surgical, radiation and/or chemotherapeutic treatment and in prognosis such as in detecting the possibility of recurrence of metastases.

In order to advance the invention to the point of practical application, it will be necessary to confirm the results of Dr. Spiegelman's research, prepare adequate amounts of the reagent, develop the final product, conduct clinical trials, compile data for pre-marketing clearance by the FDA, educate personnel, develop suitable packaging, produce the reagent commercially, and perform all other steps necessary to bring the product to the market. It is estimated that this will take from three to six years at a cost of from $1,500,000 to $3,750.000.

produce the reagent commercially, and perform all other steps necessary to bring the product to the market. It is estimated that this will take from three to six years at a cost of from $1,500,000 to $3,750.000.

Columbia University indicates that preliminary discussions with Hoffman-LaRoche has led to a proposed license agreement wherein the company will support further research and development leading to FDA approval in return for a right of first refusal to market the invention.

4. POGELL/McCANN - St. Louis University

Pamamycin (Antibiotic) (DELAY: 6 MONTHS)

The invention comprises a new broad spectrum antiobiotic which may possibly have activity against tuberculin type organisms and cancer tumor cells. In collaborative experiments with Eli Lilly, it has been determined that this new antibiotic is "sufficiently unique to qualify as a new "family type" in (their) file of over 1,200 antibiotics." In order to advance the invention to the point of practical application, it will be necessary to purify the antibiotic, establish quality controls, elucidate any changes in structure or biological activity, determine the efficacy of the product and any possible side effects, perform all testing necessary to meet FDA requirements, and to finally market the invention as a standardized, useful product. This will require the collaboration of a commercial concern because the grantee lacks facilities and capability to develop this invention to the point of practical application by itself.

The St. Louis University indicates that preliminary discussions with Eli Lilly indicate a possibility of support of further research and development leading to FDA clearance in return for a right of first

with Eli Lilly indicate a possibility of support of further research and development leading to FDA clearance in return for a right of first

refusal to market the invention. As noted, such development averages approximately 14 million dollars.

5. SELA/ARNON - Weizmann Institute of Science

"Undecapeptide and Tumour Assay" (DELAY: 9 MONTHS)

It should be noted that Dr. Michael Sela, the identified inventor, is the President of Weizmann Institute and predictably interested in pursuing development of this invention with industrial aid. Yeda Research and Development Co., Ltd., the patent manager for Weizmann, has indicated that one potential licensee has withdrawn because of in the eight months delay following NIH approval in processing the Weizmann petition but are conducting conversations with another potential licensee.

The invention is a rational extension of world-wide research on carcino-embryonic antigen (CEA) as a diagnostic marker for human cancer. It may not be suitable for mass screening or as the only main criterion for cancer diagnosis but could be of value in a follow-up for post-operative diagnosis and prognosis. If, on the basis of further testing, the invention continues to be promising, it would be expected to be widely utilized and has the potential to replace the currently available CEA assay.

In order to advance the invention to the point of practical application, it will be necessary to obtain patient blood samples and tumor material, isolate the antigen from tumor material, determine the chemical sequence of the antigen, synthesize the specific antigen fragment, compare

material, isolate the antigen from tumor material, determine the chemical sequence of the antigen, synthesize the specific antigen fragment, compare

the synthetic material with that of the inventors and with existing commercial CEA material in CEA assay tests, obtain approval from the FDA, and perform all of the other steps necessary to bring the invention to the marketplace. It is estimated that this will take two to three years, and will cost from one to five million dollars.

6. CETAS - University of Arizona (DELAY: 10 MONTHS) DNC

"Birefringent Crystal Thermometer"

The invention comprises a probe birefringent crystal optical thermometer which uses the temperature dependence of the birefringence of certain single crystals as the temperature sensitive parameter. It is designed to be used in the presence of strong radio frequency electromagnetic fields. The invention monitors tissue temperature during ultrasonic treatment administered in an effort to treat cancer by altering the temperature of tumerous tissue. Ultrasonic treatment of cancer requires extremely accurate measurement of temperature. The invention, therefore, is essential to determining the efficacy of this potentially revolutionary treatment of cancer.

Technicon Instruments has indicated a strong interest in proceeding with the necessary development if the petition is granted. Preliminary discussions have led to a proposed license agreement wherein Technicon will support further research and development work at the university for a right of first refusal to market the invention. After completion of the Technicon funded research at the university, Technicon will undertake all the additional development necessary to obtain Food and Drug Administration clearance.

of the Technicon funded research at the university, Technicon will undertake all the additional development necessary to obtain Food and Drug Administration clearance.

7. Goldstein/Lou - University of Texas

Treatment for Several Autoimmune diseases (Arthritis and Others) Call

(DELAY: 8 months)

Thymosin is a hormone which is expected to prove effective in treating patients with malfunctioning immune systems, i.e. for several kinds of cancer, rheumatoid arthritis, systemic lupus erythematosis and perhaps muscular dystrophy. It may also be useful in treating paranoid schizophrenia which is thought to involve a malfunctioning immune system. It may also be useful in treating patients with immunodeficiencies. These people suffer from raging infections because the body's natural immune mechanism is not functioning. This is more common in children than in adults.

Hoffman La Roche has made a commitment to underwrite the development which may reach $12 million, and they have filed patent applications worldwide.

Call ?

8. GREEN - Stanford Research Institute

Ultrasonic Scanning Device

(This was the case identified in the cover memorandum which was forwarded by the General Counsel with the recommendation to deny the petition but was reversed by the Assistant Secretary for Health.)

These instruments in their present form provide instantaneous and continuous real time enlarged TV images of the cross-sections of peripheral arteries such as the carotid arteries in the neck, which are so vital to blood circulation to the brain. Impairment of flow in these arteries due to atherosclerosis or "hardening of the arteries" is one of the principal causes of stroke and may lead to senility or other forms of disease or injury to the brain.

A new capability is provided for medical care with significant cost reduction, elimination of risks and increased diagnostic accuracy. The usual diagnostic approach to date for patients with symptoms of blood vessel disease is to insert a catheter into the artery and inject a contrast agent to improve the contrast in the X-ray picture that is taken, known as an angiogram. There is a risk of 1-2 percent mortality from the diagnostic technique alone from the catheter insertion when the X-ray method is used. Moreover, there is an ionizing radiation hazard.

With ultrasound, on the other hand, the vessels and their lesions or abnormalities can be seen without any known hazard, because the method is noninvasive and uses no catheter or X-rays. Since it is a non-radiation method, it can also be used to screen patients without

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symptoms as a means of detecting diseased arteries at an early stage. This could soon become a major public health technique on a wide scale for the prevention of arterial disease and stroke (within a few years).

Because very small abnormalities or lesions can now be visualized when they are quite small and can be followed by periodic ultrasonic examinations as often as desired, physicians no longer have to resort to surgery as often or as early as they formerly did, thereby reducing both risks and costs.

In the case of an angiogram described above, the catheter insertion in the artery necessitates a hospitalization usually overnight with a cost often exceeding $1,000. The comparable ultrasound examination of both carotid arteries can be done in less than one hour on outpatients who pay on the order of $200. Until the ultrasound technique is more fully validated, it will continue to be a complementary diagnostic tool with X-ray methods. However, preliminary clinical examinations by ultrasound on several hundred patients at Mayo Clinic and elsewhere indicate that the ultrasound images are comparable with the best X-ray images, and in some cases show more detail because the ultrasound displays both longitudinal and transverse cross-sections of the arteries.

Since ultrasonic techniques have no known risk, the ultrasound examination will in many cases be the first method used before the X-ray method or eventually, in some cases, without the necessity for angiography.

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This petition was pending in the General Counsel's office for approximately 10 months before a recommendation for denial was forwarded to the Assistant Secretary and in the Department for a total of two years. The basis for the denial was stated as the belief that no further risk capital was necessary to bring the invention into public use. In fact, the Stanford Research Institute had already convinced a potential licensee, Picker Instrument Co., into collaborating with SRI in developing the invention. During the two year period that the petition was pending in the Department, Picker committed nearly a million dollars to the development of the scanner, and it was clear even at the time that the petition was forwarded to the Assistant Secretary that many hundreds of thousands of dollars were still necessary in order to complete the development of the unit. Because the equities in the prospective licensee and SRI were so strong due to their prior commitment and prospective future commitment, the Assistant Secretary was compelled to overturn the recommendation of the General Counsel. However, it appears clear that the expenditure of energy undertaken by the petitioner and lower level Department personnel to overturn the General Counsel opinion could not be duplicated in the future without encouragement from equivalent outside forces. It must, therefore, be presumed that in the future that even cases of as obvious importance as this may never reach fruition if attitudes of the General Counsel's office are left to prevail.

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY

TO : Mr. Latker

DATE: 26 June 1978

File

FROM : Mr. Ferris

Done
Call Reagan
Sidelock

SUBJECT: Review of Morris et al, "Monellin, The Sweet Principle of Dioscoreophllum Cumminsii", Case No. G-96-72. (HEW and VA supported)

Monellin is the sweet principle ~~from~~ of the fruit of a tropical plant, Dioscoreophyllum cumminsii. The sweet principle of this fruit is a protein which is free of carbohydrate. It is believed to be the first protein sweetener ever discovered. It has enormous potential ~~x~~as a sugar substitute, particularly since cyclamates were banned and saccharine has been identified as potentially carcinogenic. From the health standpoint this invention is of great importance to diabetics ~~xx~~ and others who must limite their carbohydrate intake, including dieters. The National Institute of Dental Research has been funding research to investigate ~~xxxxx~~ sugar substitutes as a way of reducing dental caries.

The invention was made at the Monell Chemical Senses Center. The Center was set up by a foundation to be administered by the University of Pennsylvania. It is funded primarily be grants from industry and the Veterans Administration.

The invention was made by three coinventors, Drs. Kare, Cagan and Morris. At the time they made the invention Dr. Kare was Director of the Monell Chemical Senses Center and Professor of Physiology at the University of Pa. School of Veterinary Medicine and Chief of Sensory Physiology, Veterans Administration. His salary was paid solely by the University of Penn. Dr. ~~JxxxxxA~~ Cagan was a Research Chemist with the VA Hospital and an Assistant Professor of Biochemistry at the University of Penn. His salary was paid by the VA. Dr. Morris was a research associate of the Monell Center and a post-docioral trainee. A portion of his salary was paid from a grant

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from NINDS. The Monellin project was supported by two PHS grants, NS 08775 and NS 05668.

The University of Pennsylvania was interested in getting the invention developed and marketed and had negotiated a limited exclusive license with Dynapol Corp. Under the terms of this license Dynapol was obligated to invest $10,000,000 of its private risk capital for the development of Monellin. The University requested that it be permitted to administer the invention under the terms of its IPA with HEW so that it could complete negotiations with Dynapol. Since two of the inventors were VA employees HEW requested VA to assign its interest in the invention to HEW so that the University could administer the invention under the IPA. The VA queried the Department of Justice as to its authority to assign its interest to HEW. Based upon the opinion received from Justice the VA concluded that an assignment to HEW in this case would not be appropriate. The VA obtained assignments from its employees, Drs. Cagan and Kare.

The VA knew from past experience that in order to attract private development capital some incentives are necessary and that its inability to assign its rights to HEW would jeopardize the further development of the invention. Accordingly, VA explored the possibility of releasing its interest in the invention to the University as surplus property. However, nothing ever came of this and all rights remain in the Government. We have had no interest in nonexclusive licensing of this invention and Dynapol did not proceed when the University was unable to grant it limited exclusive rights. In 1977, five years after reporting the invention to HEW, the University reported that it had been unsuccessful in obtaining a licensee.

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From the foregoing it appears clear that an invention potentially important for reasons of public health and which has great commercial potential has not been developed and marketed because of the inability to grant the incentives ~~necessary~~ required to attract the private risk capital necessary for the development and marketing of the invention. So long as the Veterans Administration lacks the authority to grant greater rights ~~and~~ than nonexclusive license this invention will never reach the public.

9. Townsend/Earl - University of Utah

Novel Nucleoside Compounds

Forgot

(DELAY: 6 months)

These are compounds which have shown significant anticancer activity in preliminary investigations. FDA approval of the compounds will be required, at an estimated expenditure in excess of $1,000,000.

G. D. Searle, Inc. has shown special interest in the invention, and appears to be willing to enter into some form of licensing arrangement if a waiver can be obtained.

10. Goetzel/Austen - Harvard University

Synthetic therapeutic agents

Cell

(DELAY: 6 months)

The invention composes a family of synthetic therapeutic agents which have potential value in the treatment of parasitic diseases, anaphylaxis and bronchial asthma. Initial studies have been completed, and activity of the compounds has been established in animals and in humans. FDA clearance must now be obtained before human clinical trials can begin, and the complete development cost has been estimated at $5 million. Hoffmann-La Roche, Inc. is interested in developing the invention for the market, and has even assumed the expenses incident to preparation and prosecution of patent applications, with the anticipation that Harvard will receive a waiver of rights.

Money ?
Population effected

an allergic manifestation

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Population effected

an allergic manifestation

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1.. Montalvo - Gulf South Research Institute

Sensitized Phosphate Ion Selective Electrode System

(DELAY: 2 months)

The invention will be used in the phosphate analyses in diagnostic measurement of biofluids such as blood, to test environmental water and monitor it for phosphate, in food chemistry and in some industrial process control operations. The invention is designed to replace some very expensive computerized systems, and is relatively inexpensive in comparison. Fourteen commercial companies have contacted Gulf South concerning the invention, in anticipation of a waiver of rights.

12. Remers - University of Arizona

New Mitomycin antitumor agents

The invention has shown significant anticancer activity, and is considered to be a significant scientific advancement from the standpoint of synthetic organic chemistry. Bristol Laboratories, a prospective licensee if a waiver can be obtained, has already financed half of the development of this invention, has contributed the starting materials, financed larger scale preparations of the compounds for testing, screened all the compounds for antitumor activities in mice and in vitro systems, and will undertake the additional development at a cost of several millions, if rights are left to Arizona.

13. Apple/Formica - University of California (DELAY: 3 months)

Azetomicins, a New Anticancer Drug

This is a potentially important anticancer drug, which will require the usual FDA clearance at a cost of $20,000,000 and about ten years of trials and testing. The University says there is commercial interest in the compounds, but in the absence of a waiver from HEW, they would not be in a position to offer the inventions for development. PCR, Inc., a chemical manufacturer, has expressed interest in the compounds for domestic and Japanese distribution, as well as Calbiochem, another chemical manufacturer. All commercial cooperation depends upon the waiver to the University.

FDA clearance ...

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