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PD-AAM-755

PROJECT SUMMARY

Project Title	:	The Contraceptive Properties of Biological Substances Controlling the Life Span of the Corpus Luteum
Proposed Contractor	:	Worcester Foundation for Experimental Biology, Inc., Shrewsbury, Massachusetts
Principal Investigator	:	John A. McCracken, Ph.D. Worcester Foundation for Experimental Biology, Inc.
Duration	:	Three years - July 1, 1968 to June 30, 1971 To achieve desired results, project may need to be extended for an additional three years.
Estimated Cost	:	a) Total - $165,085 b) FY 69 - 55,000 c) FY 70 - 53,500 d) FY 71 - 56,585
Action Officers:		R. T. Ravenholt, HOH/PS J. A. Cavanaugh, HOH/PS/RTD

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1. Background

Important for reduction of fertility rates in lesser-developed areas would be a contraceptive that is more convenient, non-toxic and which does not require great motivation to continue its use. Present contraceptives are better than previous ones, but still do not fulfill all the requisites necessary for rapid fertility reduction. It is, therefore, desirable that continuing research be performed on a convenient once-a-month contraceptive that can be taken orally and exhibits no toxic effects. This type of contraceptive would enhance motivation and virtually erase the present inconveniences surrounding present-day contraceptives. In addition, a convenient non-toxic contraceptive would preclude the necessity for expensive medical and public health infra-structures to administer it thus altering A.I.D.'s assistance program and reducing costs and staffing requirements.

2. Description of Proposed Project

This project proposes further research on a fundamental approach to producing a single contraceptive pill or dosage based on a luteolytic

substance produced by the uterus. It has been shown that in the reproductive cycle of sheep (and perhaps in man), the life span of the corpus luteum is terminated by a "luteolysin" produced in the uterus when there is no pregnancy. The investigator proposes to isolate this substance. The luteolytic effects of the substance will be tested on cell cultures and those fractions showing high activity will be further tested on ovarian transplants of sheep. The luteolysin substance will be chemically characterized using sophisticated analytical equipment already available at the Worcester Foundation.

Assuming that the above procedures can be carried out satisfactorily, a once-a-month contraceptive dose could be developed which can lead to a "natural regression" of the corpus luteum and prevent pregnancy from being established.

In summary this research has the following objectives:

a. The establishment of basal steroid secretion rates from the transplanted ovary of sheep throughout the course of the cycle and the response of the ovary to gonadotrophins.

b. The isolation of a luteolytic substance or substances from the uterus of the sheep which have the property of diminishing steroid secretion from the transplanted ovary with particular reference to progestins.

c. The chemical isolation, purification and identification of such substances by special analytical procedures with a view to establishing a simple single dose contraceptive.

d. To test these substances in other mammalian species including primates.

3. Significance of Project to A.I.D. Objectives

A.I.D. has, as one high priority and goal, the giving of assistance to nations so that there may be a better balance between population and natural resources. One important technique for achieving this goal is to encourage reduced fertility. However, modern contraceptives such as the pill and IUD still are not completely satisfactory as evidenced by some studies which show varying high rates of attrition. The greatest significance of this project for A.I.D. is that a very convenient non-toxic contraceptive may become available so that many more women of varying socio-economic conditions could avail themselves of it. It is also significant that if this contraceptive is found to be actually non-toxic, it could be administered outside as well as inside medical structures thus reducing greatly the cost of administration.

4. Relevance of Project to Existing Knowledge

The relevance of this proposed research to existing knowledge may be classified under the following three headings:

a. Steroid hormones present in ovarian vein blood.

Many investigators have measured steroid hormones in the ovarian vein blood including progesterone in a variety of animals such as ewes, hens, rabbits, dogs, rats, and cows since 1953. Most workers have been able to measure steroid concentration in blood draining the ovary collected under conditions of acute surgical stress but there has been considerable doubt as to the effect of surgery and especially cannulation on steroid secretion by the ovary. Additional research is needed on the rate of basal steroid secretion from the transplanted ovary of the sheep and response of the ovary to gonadotrophins.

b. Biological substances effecting steroid biosynthesis in vivo and in vitro.

Many of the steroid biosynthetic pathways have been demonstrated by use of in vitro preparation of ovarian tissue. Most investigators have found that gonadotrophic stimulation of the ovary in vivo was effective in increasing the biosynthetic capacity of the preparation. A major research objective is to observe and more accurately measure the response of the animal ovary to gonadotrophins especially in vivo.

c Uterine luteolysin controlling the life span of the corpus luteum.

Existing knowledge demonstrates that the life span of the corpus luteum is closely associated with changes taking place in the uterus. For example, removal of the endometrium produces secretion of progesterone for a much longer period than normal. The amount of endometrium required to maintain the normal cycle rhythm varies in different animals but in primates at least partial ovarian function continues in the absence of the endometrium. More knowledge is necessary about how to control the life span of the corpus luteum and to better understand and analyze the as yet unidentified substance called luteolysin secreted by the uterus which causes regression of the corpus luteum.

5. Description and Evaluation of Methodology

The evidence indicates that a substance termed luteolysin secreted by the uterus in sheep has a local effect in producing regression of the corpus luteum. It is further believed that this substance given as a single dose contraceptive could bring about the "natural" regression of the corpus luteum in higher primates including man thus preventing pregnancy.

The research methodology proposes to isolate large and small molecular substances by a unique extraction and fractionation technique. The luteolytic effects of these substances will be tested on vitro incubations of luteal slices or cell cultures. Fractions showing high luteolytic activity will be tested on the isolated ovarian transplant in the sheep. Using the latest and most advanced techniques, the luteolysin substance will be chemically characterized. Another important part of the research methodology will be to find the most suitable means for collecting material from the sheep uterus at various times in the cycle. The proposal describes various methodological ways this might be done under in vivo conditions.

6. Evaluation of Research Competence of Investigators

The principal investigator will be Dr. John A. McCracken who has a Ph.D. from the University of Glasgow, Scotland. His major research interest is reproductive endocrinology and he has published a number of articles on the subject of progesterone and steroid secretion in animals. Dr. McCracken and his team have developed a new technique for the study of the isolated ovary in the unanesthetized unstressed sheep.

The Worcester Foundation for Experimental Biology is world famous in the field of reproductive biology and has been responsible for pioneering work on contraceptives. The co-investigator is Burton V. Caldwell who has a Ph.D. from the University of New Hampshire. His major research interest is also endocrinology and he has published principally in the area of uterine transplantation and luteolysis in the hamster.

7. Appraisal of Research Resources and Budget

It is considered that the research resources at the Worcester Foundation are well suited to the current research project, especially in respect to animal surgical facilities and animal quarters. Several expensive analytical instruments will be available for use in the project including a Liquid Scintillation Spectrometer. Other senior scientists who have related research specialities have agreed to participate and will be available as supervisory consultants.

Although no detailed inspection has been made, it appears that the budget is very modest especially in respect to the salaries of the investigators. Additional equipment requested also appears modest. It is assumed that the percentage figures for indirect costs have been established on the basis of other U.S. Government contracts.

8. Technical and Scientific Review of the Project

A review of this project has been requested from three research specialists. They are Dr. Sheldon Segal, Population Council, Anna L. Southam, M.D., Ford Foundation, and Philip Corfman, M.D., NICHD/NIH. To date their evaluations have not been received. The TARC (AID Technical Assistance and Research Council) has reviewed this proposal and has recommended it be forwarded to the RAC.

9. Summary Evaluation

We believe that this research project could have a high pay-off value in the future. We do not believe that it is absolutely certain that a greatly improved contraceptive will be forthcoming from the results of this research alone. However, it is felt that the approach the investigators are taking merits our support especially in view of the rather modest budget amount.

Attachment

WOR/PS:J.A.Cavanaugh:5/20/68

Attachment

Funding Requirements

	FY 1969	FY 1970	FY 1971	Total
1. Salaries and Benefits	$28,825	$31,350	$33,625	$ 93,800
2. Travel	1,000	1,000	1,000	3,000
3. Equipment	4,950	--	--	4,950
4. Supplies	9,700	9,700	9,700	29,100
5. Indirect Costs	10,525	11,450	12,260	34,235
Total	$55,000	$53,500	$56,585	$165,035