

October 8, 1952

Memorandum on Conference with Roy Hertz in Washington
on October 7, 1952

1. Progesterone

One-half gram per day ~~mf~~ for 12 days shows no acute toxicity, neither does 250 mg. per day for 130 days. In all these experiments, progesterone was given by injection.

Of 12 patients who received 250 mg. per day, 9 ovulated, though menstruation was not stopped. The lack of ovulation was seen at the time when surgery was performed, and the ovary was inspected.

Greenblatt at the Medical School of the University of Georgia, Augusta, Ga., believes that progesterone is highly effective^{-ive} when given orally.

It is not clear that Roy Hertz accepts this assertion.

19-nor-progesterone is 5 to 8 times as active as progesterone (both injected).

Anhydrohydroxic progesterone (ethanyl testosterone) is effective orally, but its effectiveness is 1/5 that of injected progesterone.

However, ethanyl-nor-progesterone is 3 to 4 times as active, so that this compound given orally is ~~very~~ not very much less effective than injected progesterone.

2. Stilbestrol

No one knows very much about the effect on ovulation of administering stilbestrol, but Hertz thinks that 10 mg. per day given orally might suppress ovulation.

The dangers involved in this therapy are the following:

fibroid tumors, breast enlargement, lumpy breast, about 10% might be nauseated, but this might perhaps be avoided by giving Vitamin B Complex or, more precisely, riboflavin B₁ folic acid.

Uterine enlargement is a possible and disagreeable side effect.

Hertz gave 15 mg. per day stilbestrol per os for three years to about 100 women suffering from breast cancer. These were older women. Ten per cent showed vaginal bleeding; two of them showed severe bleeding. Ten to fifteen per cent showed nausea or vomiting, which Hertz thinks is not due to administration per os but rather that it is a systemic effect. Five per cent of the women showed bladder symptoms.

The relative effectiveness of various estrogens was examined by Willard Allen, Medical School, Washington University, St. Louis.

Material on the prolonged action of estrogen administration for older women can be obtained through Dr. Paul Wermer, Secretary of the Committee on Therapeutic Trials, A.M.A., Chicago.

Hertz thinks the pituitary will not escape as long as medication is continued. 0.05 mg. of estradiol or 1 mg. of progesterone are equivalent to each other from a point of view of suppressing pituitary in rats. Ten mg. of progesterone per kilogram body-weight is needed for the female rat to suppress the pituitary. The male takes 2 to 3 times more.

3. Antagonists

R. K. Meyer of the University of Wisconsin is screening compounds which are antagonists of estrogens ~~tested in the genital tract of the chick~~. The following compounds have weak progestational effect and strong anti-estrogenic effect (tested in the genital tract of the chick): (a) allopregnens; (b) desoxycorticosterone. Such anti-estrogens could suppress fertility by a direct effect on the uterus but the anti-estrogenic effect would cause the kind of disturbances which are experienced in the menopause.

4. Antihormones

(Work done jointly by Hertz and R. K. Meyer)

Hertz says that pig pituitary extract, crude, injected into sheep, will lead to circulating antihormones in the sheep and will also suppress the gonadotropic action of the sheep's pituitary. This would look like active immunization against some pituitary principle which interferes with the sheep's pituitary (remark by Szilard).

Similarly, crude extract from pig pituitary injected for 100 days daily into the rabbit will, after initial stimulation of the gonads, apparently lead to the suppression of the gonadotropic hormones of the rat (rabbit?). When the injections stop, the gonads recover.

Dr. Emil Witchi, University of Iowa, Iowa City, and Dr. Rowlands, England, work in this field.

Oct. 10, 1952

Memorandum on Conversation with Pincus and White, October 9, 1952

Joe Jailer and Earl Engle work with progesterone; study bucal versus injected administration (dose about 25 mg. per day?)

Henry Guterman, Michael Reece Hospital, University of Chicago, studies progesterone in pregnant women.

Dr. Charles Fried, University of California, published in AMA, 5 or 10 years ago, a paper on the effect of testosterone on relieving pre-menstrual distress.

Ethanyl estradiol given by mouth is a very effective estrogen.

White can make available 10 compounds of the allopregnen series, and 5 normal pregnanes, which could be produced in large quantities at a reasonable cost. Pincus says it would take about 4 months and \$1500 to test one such compound on rats and rabbits and to determine ~~and to~~ the dose at which it inhibits ovulation.

Pincus says testolo lactone counteracts the local effects of testosterone (could it be used as a anti-libido agent?).

Does testosterone actually produce hypertrophy of the prostate--ask Charles Huggins.

White says he can make a progesterone analogue with ~~its member drink~~ in place of ~~five-member drink~~.

a 6 membered ring
the four membered ring

November 6, 1952

Memorandum Concerning the Financing of Medical Education

by Leo Szilard

Medical schools find it difficult to obtain the funds necessary for expansion and it is even more difficult to find funds for starting new medical schools. The basic cause of these difficulties lies in the fact that medical education is sold below cost. The situation would be quite different if medical education were sold at "cost" or perhaps even at a modest profit to the school.

Since his training as a doctor greatly enhances the earning power of a student, and since many more capable students would wish to go to medical school than can be accommodated at present, there seems to be no valid economic reason for selling medical education below cost. It would be much sounder to sell such education at cost and to "invest" in students who are admitted to a recognized medical school enough to pay for their medical education including their living expenses while going through medical school. The student should be able to repay out of earnings this initial investment, with interest, or some other form of "profit ~~sharing~~".

The funds needed might be provided by private investors if a suitable form can be found or they might be provided by the Federal Government. It would be preferable not to look to the Federal Government for funds but merely for tax relief in the sense that a doctor who pays out of his earnings for the cost of his medical education be permitted to deduct from his income these payments, as professional expenses, for income tax purposes. The Government could be helpful in another way: If medical education is financed on the basis of bonds or other certifi-

cates issued by medical schools, the Federal Government could guarantee these bonds or certificates in the same way in which it guarantees today bank deposits of less than \$5,000.00.

In the following are enumerated different possible ways to cope with the problem:

1. Investment by a private corporation in medical students.

A private corporation could issue stock and use the capital thus obtained for financing the medical education of students whom it approves on the basis of their school records and their medical aptitude test. The students so financed may enter into an agreement under which they pay to the corporation a certain fraction of their income. The fraction to be paid would be proportioned to the total sum invested in the student and could be graduated, so as to increase with increasing income of the doctor. The corporation would pay out a certain fraction of its income as dividend on its stock and the rest of it could be reinvested in other students. Thus those who hold stock could look forward to receiving dividends and also, as time goes on, to an increase in the value of the stock.

Assuming that this stock is made sufficiently attractive to the investor ~~so that~~ ^{may} large funds seek investment of this type, and in particular ^{by} if insurance companies are permitted and desirous ^{to invest} in such stock.

2. Administration of investments by medical schools.

The medical school could make available to its students the cost of their medical education out of:

a) funds provided by private investors;

In this case the general scheme discussed under 1.) could be followed with the modification that medical schools would guarantee to the investor a minimum dividend and that perhaps the Federal Government would guarantee the medical schools' guaranty.

If a medical school should get careless in the selection of students and if as a result its graduates would mostly be in the lower earning brackets, it might have to use its own funds to be able to pay the minimum dividend.

New medical schools which might be created for the purpose of drawing profit out of medical education, if they failed to select carefully their student material would - even if they ~~would~~ provide a good education - ultimately be forced out of business, while the investor might still be protected by a Federal guaranty. This might appear perhaps undesirable, but if we wish private enterprise to enter the field of medical education, we must accept the method of natural selection which operates in the field of private enterprise and which consists in the elimination of the unfit through bankruptcy.

b) funds provided by the State Government;

The State Government could make available funds to medical schools (both state and private ^{ly} operated schools), which the State Government could in turn raise by issuing tax exempt bonds for the purpose.

The medical schools would pay the State Government interest on the funds which they accept and would finance the medical education of their students on the basis of repayment by the students of the capital with interest. The interest rate charged to students should

be higher than the rate paid by the medical school to the State Government, but on the other hand no individual doctor should be obliged to pay more to the school in any one year than a certain fraction of his income.

c) funds provided by the Federal Government to medical schools;

The medical schools would pay a certain interest rate on funds provided by the Federal Government for investment in the education of its students. Otherwise this scheme would operate the same way as the preceding one.

3. Federal administration of funds provided by the Federal Government.

Under this scheme the Federal Government would set up a government corporation which would "invest" in medical students who qualify on the basis of their school certificates and their medical aptitude tests, and who are admitted to medical school which is recognized^a by the Federal Government. The students would repay the Federal Government the investment with interest, but no doctor would be required to pay in any one year more than a certain fraction of his income.

In order to determine what fraction of his income would have to be charged to a doctor to cover the investment in his medical education, or alternatively to set the proper interest rate that he should be charged, and to determine at what rate the investment should be

amortized, it would be necessary to set up a special study. Because Mr. Milton Friedman in the Department of Economics of the University of Chicago is keenly interested in this problem, it appears likely that a study could be set up under the auspices of this Department if a special fund of about \$6,000.00 were provided for the purpose. There might be other suitable localities were such a study might be organized. In any case it would seem, however, that an actuarial study of the problem will have to be made before an intelligent decision can be made among the number of possible alternative solutions of the problem.