Detection, Diagnostic Evaluation, and Treatment of Dysplasia and Early Carcinoma of the Cervix

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Introduction

Dysplasia, in situ and early invasive carcinoma of the cervix are becoming an increasingly important part of the problem of cervical cancer. There is little doubt that the mounting frequency with which these diagnoses are made is directly related to the increased use of the Papanicolaou smear technique. We observed this in our own clinic over the past four years. Until 1966 only the women seen in Obstetrics and Gynecology had cervical smears done as a routine part of their examinations. In the fall of 1966, thanks to a Public Health Service grant, cervical cytologic screening was extended in an attempt to include all women admitted to the Kings County Hospital, a large municipal institution. The number of Stage 0 cases detected was increased two and one-half times from 30 cases in 1966 to 78 cases in 1967. (Table 1.) The number of Stage I cases was increased by 50 percent. There can be no doubt that these changes resulted from the increase in screening. At the same time, a significant decrease in the number of new patients with Stage II and Stage III was also noted. Whether this was related to cytologic screening is a more complicated problem and one that cannot be answered at this time. The number of cases of recurrent and/or persistent carcinoma of the cervix referred from other institutions has not declined during this period. Clearly then, today's physician must be aware not only of the importance of cytologic screening but also the details of how to carry it out. He must also understand the meaning of cytologic reports so that he knows which patients require further investigation. Finally, he should educate himself concerning the investigation that is indicated and see that it is done either by himself, if he is qualified, or by some one who is trained in this field. The purpose of this article is to outline the detection, diagnosis, and treatment of these early cervical lesions.

Detection

The majority of persons with dysplasia or carcinoma in situ of the cervix have no symptoms or abnormal findings of the cervix. Therefore, as dysplasia should be considered a part of the spectrum of abnormal epithelial changes that may ultimately culminate in malignant disease, it is imperative to dis-
cover these lesions early in order that these high risk patients may be followed closely.

The most important screening procedure is cytologic evaluation of the cervix. All adult women should have cervical smears taken every year up to age 35 and every 6 months thereafter. At the same time that the smear is taken, a careful speculum and pelvic examination should be made.

The results of the smear examination are reported by both a numerical classification and a description. The latter method is being used more and more and has its advantages. The numerical classification is as follows:

| Class | Description |
|-------|-------------|
| Class I: | Smear normal, no abnormal cells. |
| Class II: | Smear containing atypical cells but not suggestive of malignant disease. |
| Class III: | Smear containing abnormal cells suspicious of malignant disease but not pathognomonic. |

**TABLE 1—INTERNATIONAL CLASSIFICATION OF CERVICAL CARCINOMA**

| Stage  | Description |
|--------|-------------|
| Stage 0 | Carcinoma in situ, intraepithelial carcinoma. |
| Stage I | Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded). |
| Stage IA | Cases of early stromal invasion (preclinical carcinoma). |
| Stage IB | All other cases of Stage I. |
| Stage II | The carcinoma extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not the lower third. Subgrouping to Stage II cases into IIA (no parametrial involvement) and IIB (parametrial involvement) is recommended. |
| Stage III | The carcinoma has extended onto the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. |
| Stage IV | The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. A bullous edema as such does not permit allotment of a case to Stage IV. |
Class IV: Smear containing abnormal cells highly suggestive of malignancy.

Class V: Smear containing malignant cells.

Although Class I and Class II indicate benign conditions, many cases of dysplasia will be classified as Class II and, unless it is stated by the cytopathologist that dysplasia is present, these cases may be missed. This illustrates the need for some description of the lesion in addition to the numerical classification. When dysplasia is suspected, tissue examination is necessary.

The smear containing suspicious cells and classified as Class III indicates some abnormal epithelium. (Fig. 1.) However, inflammatory processes, particularly trichomoniasis, may produce abnormal cells. Therefore, in the presence of a normal appearing cervix, it is advisable to treat any infection which may be present and to repeat the smear in four weeks. If the second smear is reported as Class I or Class II, the procedure should be repeated, and if it is still normal, the patient should be seen at six-month intervals. If the first Class III smear is followed by a second Class III, then tissue examination is imperative. (Fig. 1.)

A report of Class IV or Class V demands an immediate tissue examination, because it is rare that there is no malignancy in the presence of a Class IV or Class V smear.

The procedure to be followed where tissue examination is necessary depends upon the circumstances. If a suspicious lesion exists on the cervix, a biopsy of the lesion should be done. (Fig. 1.) A report of invasive malignant disease on the biopsied material indicates a need for therapy without any further tissue examination. However, if the report is either dysplasia or carcinoma in situ, then more tissue examination is necessary to rule out invasive disease. Conization of the cervix is probably the best biopsy procedure.

Frequently, carcinoma in situ has multicentric sites of origin. Therefore, before conization, the vagina and cervix should be painted with Lugol Solution or Gram's iodine. This is the Schiller test and it is invaluable to detect all sites of abnormal epithelium. Normal epithelium will stain a deep mahogany while abnormal areas will not stain. This test is not specific for malignant disease, because ulcerations, inflammatory processes, and keratotic lesions may not stain. However, it does indicate abnormal epithelium which should be included in a biopsy procedure.

Conization should be done with a cold knife and not an electrocautery, for the latter may destroy tissue at the cut edge and, since the only cancer tissue may be at this point, the diagnosis may be missed.

The material obtained by conization must be examined completely. This requires many sections taken at frequent and regular intervals throughout the entire specimen.

Carcinoma in situ separates easily from the underlying stroma in many cases, and, therefore, the definitive tissue may be lost at the time of a dilatation. In suspected cases, therefore, it is best to do the conization before any dilatation. If a patient has abnormal uterine bleeding, the dilatation of the internal os and the curettage of the endometrium should be performed after the conization.

The main complication of conization is bleeding. However, if the procedure is done properly, unusual bleeding should occur infrequently. The increased vascularity of the uterus during pregnancy increases the risk of hemorrhage. Also, conization during
pregnancy may precipitate uterine contractions leading to abortion. It is advisable during pregnancy to make the conization a more shallow procedure than in nonpregnant patients. The phrase "more shallow" in this instance means that it should not extend as far up the canal as in the nonpregnant patient.

Although cytologic screening is the most important procedure to discover unsuspected malignancy of the cervix, our experience is that a punch biopsy of the cervix at the time of emptying the uterus for an incomplete abortion has led to the finding of many cases of malignancies. If a lesion of the cervix is present, it should be biopsied, but if no lesion is present, the specimen should be obtained from the areas between eleven and one o'clock or between five and seven o'clock. These two areas are the most frequent sites of carcinoma in situ.

Subsequent conization should be done to rule out invasive disease if the report of the biopsy specimen is dysplasia or carcinoma in situ.

Pretreatment Evaluation

The basic principle in pretreatment evaluation of any malignancy is simply stated: know the extent of disease as accurately as possible before treatment is considered. This axiom applies in all cases of pelvic malignancy but is critical in cervical carcinoma.

The foregoing discussion has been directed entirely at accurately determining the extent of the local lesion. This constitutes step one and until this is completed do not proceed with treatment. Only after step one will the clinician know whether he is dealing with dysplasia, carcinoma in situ, or invasive carcinoma of the cervix. Now, knowing the nature of the local lesion, he is prepared to proceed with the other indicated pretreatment studies.

Dysplasia

When the diagnosis has been properly established, it can be said with confidence that fear of unexpected findings of carcinoma has been eliminated. Therefore, it is not necessary to carry out diagnostic studies for evidence of metastatic disease. One must decide upon the therapy and evaluate the general health of the patient to make certain that whatever therapy is selected it is within the capacity of that patient to withstand.

Carcinoma in situ

The existence of this lesion, also referred to as Stage 0 carcinoma of the cervix, is established by conization. It is the preinvasive stage and requires no additional search for metastatic disease. When the diagnosis is established, the pretreatment evaluation is concerned almost entirely with the decision whether to advise definitive surgery or not. If definitive surgery is advised, then the clinician's responsibility is the same as for any other patient about to undergo major surgery, namely, evaluation of her general state of health, to be certain she can withstand major surgery.

Stages I and IIa

Table 1 gives the international classification of carcinoma of the cervix.1 Stage I is now subdivided into Stage Ia and Ib. Stage Ia represents the preclinical lesions of the cervix or those patients in whom the invasive carcinoma is detectable only by microscopic examination of the tissue. Stage Ib includes all other cases of Stage I carcinoma of the cervix. Stage IIa carcinoma of the cervix includes only the very earliest of Stage II cases; more specifically, those cases with minimal spread of the disease from the cervix on to the vaginal mucosa. Stage IIa is included under this discussion of early
FLOW CHART

POSITIVE

CLASS IV OR V

LESION PRESENT

LESION PRESENT

NO LESION

DYSPLASIA

CA IN SITU

CONIZATION

BIOSPY OF LESION

INVASIVE CARCINOMA

TUMOR STUDY FOR METASTASES

PHYSICAL EXAM FOR STAGING LESION

SURGERY OR RADIATION FOR DEFINITIVE TREATMENT

FOLLOW UP SMEARS AND EXAMS FOR LIFE

IN SITU CARCINOMA

CONIZATION

IN SITU CARCINOMA

DEFINITIVE SURGERY

FOLLOW UP SMEARS AND EXAMS FOR LIFE

REPEAT AT 3 MONTH INTERVALS

DEFINITIVE SURGERY

FOLLOW UP SMEARS AND EXAMS FOR LIFE

IF PREGNANCY DESIRED
carcinoma of the cervix because it is invasive and including Stage IIa carcinoma of the cervix there is an option available to the clinician in so far as treatment is concerned. Beyond Stage IIa it is the general consensus that radiation therapy is the only form of treatment that should be seriously considered. The hazards of radical surgery in Stage IIb cases are such that it has been discontinued in most clinics around the world.

The pretreatment evaluation of patients with invasive carcinoma of the cervix should be the same regardless of the stage of the disease. This requires a thorough investigation for evidence of metastatic spread. These studies should be directed first at the structures immediately surrounding the cervix because this disease spreads mainly by direct extension. Therefore, cystoscopic examination is most important to rule out direct extension to the base of the bladder and also to rule out any unassociated but significant bladder pathology. For the same reason, sigmoidoscopic examination should be carried out on all patients with invasive carcinoma of the cervix. The ureters which lie in close lateral proximity to the cervix must be examined before treatment by intravenous pyelography. Barium enema has not been done in our clinic in recent years except in patients over the age of 50 or in patients with symptoms suggestive of colon disease. Finally, chest X-rays and skeletal X-rays are done to rule out possible distant metastases to those sites. Blood chemistries are done with two purposes in mind. The first purpose is to add to the overall evaluation of the patient's general health, and for this purpose the blood urea nitrogen and fasting blood sugar are obtained. Second, liver chemistries are obtained to detect any latent liver disease and also to serve as a baseline during and after therapy. Aside from the usual battery of liver chemistries, we feel that it is important to carry out the BSP test, which is the most sensitive of all the liver function tests available.

The final, and perhaps the most important, step in pretreatment evaluation is that of the pelvic examination to describe in detail any deviation from normal. The speculum examination is important to visualize the cervix and the extent of any lesion that may be present. The rectovaginal examination is the critical part of the pelvic examination since it permits the palpation of the lateral extension of the disease into the paracervical ligaments.

By breaking the pelvic examination down into those three basic components, namely, speculum examination, bimanual, and rectovaginal examinations, one can see and palpate the extent of the local lesion. When this procedure is combined with the previously described diagnostic studies, the individual case can be placed in the proper class of the International Classification. Then, but not before, treatment may be considered.

**TREATMENT**

**Dysplasia**

The basic understanding of the current concept of dysplasia is necessary before dealing with the question of treatment for patients with dysplasia. A number of reports strongly suggest that dysplasia of the cervix is a transitional state in carcinogenesis of the cervix. All these reports have demonstrated that patients with dysplasia may have one of three courses. The lesion may revert to normal, although Stern has demonstrated that it tends to return. A second possible course is persistence of the dysplastic state. Finally, a significant number progress to carcinoma in situ and invasive carcinoma. The report by Hall and Walton from our own institution is a study of 206 cases which were followed from
TABLE 2—BIOLOGIC SIGNIFICANCE ACCORDING TO SEVERITY OF DYSPLASIA

| Degree of dysplasia | Regressed (%) | Persisted (%) | Progressed (%) |
|---------------------|---------------|---------------|----------------|
| Slight              | 62.2          | 24.4          | 13.4           |
| Moderate            | 32.9          | 48.7          | 18.4           |
| Marked              | 19.1          | 47.6          | 33.3           |

TABLE 3—INCIDENCE OF CARCINOMA IN SITU

| Degree of dysplasia | Cases of carcinoma in situ |
|---------------------|-----------------------------|
|                     | No. | %   |
| Slight              | 6   | 6.2 |
| Moderate            | 11  | 12.9|
| Marked              | 7   | 29.1|

The results are shown in Tables 2 and 3. The cases were differentiated morphologically into slight, moderate, and marked degrees of dysplasia depending on the proportion of the thickness of the epithelium that was involved by the dysplasia. (Figs. 2, 3 and 4.) The subsequent course was directly related to the degree of dysplasia. Those cases with a slight degree of dysplasia regressed 62.2 percent of the time, while 13.4 percent progressed. On the other hand, those with a marked dysplasia regressed only 19.1 percent of the time while 33.3 percent progressed. Progression in these cases may indicate progression to carcinoma in situ. Table 3 demonstrates the number of cases that progressed all the way to carcinoma in situ. Most important is the fact that 7 cases of our 24 originally found to have marked dysplasia ultimately developed carcinoma in situ. In other words, 29.1 percent, or roughly 3 out of every 10 patients with marked dysplasia, when followed, ultimately developed carcinoma in situ. Also important in this discussion is the fact that these patients are on the average significantly younger than patients with carcinoma in situ or invasive carcinoma. This group of 206 patients had a median age of 25.6. This is in keeping with the concept of dysplasia as a forerunner of carcinoma of the cervix and suggests that the carcinogenic factors require a longer period of time to produce the change to carcinoma. Further support for this concept comes from Stern's finding that the majority of new cases of cancer originates in a population of women with dysplasia. Furthermore, the patients with dysplasia have the same predisposing factors as those so clearly demonstrated for cancer of the cervix, namely, women of the lowest socioeconomic status and women who were quite young at first intercourse. Finally, in support of the concept of dysplasia as a forerunner of cervical carcinoma is the finding by Shingleton and associates that no real
difference can be detected between dysplasia and preinvasive cancer morphologically by electron microscopy.\(^1\)

The overwhelming evidence in support of dysplasia as a precursor of carcinoma of the cervix has led to a more rational basis for treatment. Since dysplasia is a precursor of cervical carcinoma there is no urgency for carrying out definitive treatment. If the patient is young and desires preservation of her childbearing function, no treatment should be recommended. The problem should be explained in detail to the patient. She should be instructed as to the necessity for regular follow-up examinations with cervical smears. In cases where marked dysplasia is found on the conization specimen, definitive treatment should be considered. Whether definitive treatment is recommended should depend on whether or not the patient desires to have additional children. If she is desirous of further childbearing, then she can be followed safely so long as regular examinations are carried out and cervical smears taken. This should be done at 3-month intervals. If the patient with severe dysplasia has no desire for further childbearing, it seems best to advise the patient to undergo definitive treatment in the form of a total abdominal hysterectomy. If the patient has demonstrated an infertility problem, the cause for this should be investigated and if it is found to be on the basis of chronic salpingo-oophoritis with obstruction of the fallopian tubes, definitive surgery should be recommended. Whatever course of treatment is recommended, patients with dysplasia, regardless of the degree, should be followed in the same manner as the pa-

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Fig. 2. Slight dysplasia. The cellular changes involve up to 1/3 of the thickness of the epithelium.
Fig. 3. Moderate dysplasia. From $\frac{1}{3}$ to $\frac{2}{3}$ of the thickness of the epithelium show the changes of dysplasia.

Fig. 4. Severe dysplasia. Over $\frac{2}{3}$ of the thickness of the epithelium is involved by the cellular changes of dysplasia.
tient who has developed carcinoma in situ or invasive carcinoma.

Reports have begun to appear describing the use of cryosurgery and cautery as a means of treatment for dysplasia. Such reports may prove to be very important in the future, but, at the present time, they are preliminary reports on clinical investigation and should be so regarded.

**Carcinoma in Situ**

Carcinoma in situ is now accepted throughout the world as a precursor of invasive carcinoma. This is based on two general types of evidence: first, the finding of carcinoma in situ and invasive carcinoma simultaneously in the cervix; and second, the development of invasive carcinoma of patients followed without treatment after a diagnosis of carcinoma in situ has been made. The most compelling studies were those reported by Peterson and Funck-Brentano. Peterson reported on 127 patients with carcinoma in situ who were followed without definitive treatment in the Radium Center at Copenhagen. They found that invasive carcinoma developed in 11 percent of the patients at the end of 3 years, in 22 percent at the end of 5 years, and in 39 percent at the end of 9 years of follow-up. Beyond nine years, the numbers of patients in follow-up were too small to be significant. Such studies are no longer reported because of the fact that it is no longer acceptable to follow patients without treatment unless childbearing is an important consideration.

The findings in 402 cases of carcinoma in situ detected in our own institution reflect those reported by many other clinics. Patients with carcinoma in situ are for the most part from the lowest socioeconomic group, and in this country that group is largely comprised of Negro and Puerto Rican women. The median age is younger than previously reported and in our series was 31.8 years. The patient with carcinoma in situ is characteristically one who began sexual activity at an early age. This is reflected in our series by the fact that 89.7 percent of the patients were married, separated, divorced, or widowed. Their marital status is concrete evidence of sexual activity and, when tied to the fact that only 4.9 percent of the series had not been pregnant it allows one to calculate in the individual case the latest that sexual activity may have occurred. These foregoing statistics are of real importance in a discussion of treatment, for they allow the clinician to pinpoint the high risk patient. The patient over 35 years of age should be advised to have definitive surgery when a diagnosis of carcinoma in situ is made. The patient under 35 years of age who desires further childbearing should have a full explanation of the problem and should be allowed to proceed to have more children, provided she is willing to undergo regular follow-up examinations including cervical smears. This should be done at three-month intervals. If the patient's past obstetrical history indicates a long standing problem of infertility, then it is advisable for her to undergo definitive surgery. If the patient under 35 years of age is one known to follow instructions poorly, then serious consideration should be given to advising definitive surgery.

What is definitive surgery for carcinoma in situ? There is still some debate in the literature on this question although such debate has largely subsided in the past few years. A few people still advocate conization as definitive treatment for carcinoma in situ. Statistics overwhelmingly indicate that conization condemns approximately one out of three patients to recurrence or persistence of carcinoma in situ and
potential progression to invasive carcinoma.\textsuperscript{11-19} In view of this statistic, which has appeared repeatedly in the literature, what logical reason, except the preservation of the childbearing function, can there be for not treating carcinoma in situ by removal of the organ? In general, definitive surgery for carcinoma in situ means a total abdominal hysterectomy, generally with no vaginal cuff. Way has reported a 21 percent incidence of involvement of the vaginal cuff by carcinoma in situ when the upper third of the vagina is removed with the uterus and when that vaginal cuff is subjected to serial sections.\textsuperscript{10} Others have shown involvement of the vaginal mucosa. \textsuperscript{11-13} Way states that the recurrence rate is at least three times greater after simple total hysterectomy than after modified radical hysterectomy. In our own institution, the modified radical hysterectomy with removal of the upper third of the vagina has been the procedure of choice for some 15 years. By January 1, 1969, 237 patients with carcinoma in situ had undergone the modified radical hysterectomy. There were no deaths in that group of patients and only one ureterovaginal fistula (0.4 percent). The one ureterovaginal fistula healed spontaneously and has been followed for over two years. The patient has consistently had a normal intravenous pyelogram. One hundred and seventy-five of these patients were reported by Hall, Boyce, and Nelson, and had received their treatment at least two years before the report, and none had had recurrence of their disease.\textsuperscript{14} It should be pointed out that only 50 percent of the cases reported by Hall, Boyce, and Nelson had been followed for more than five years. This is a most important consideration in a discussion of methods of treatment for carcinoma in situ because of the lag period or incubation period, which some feel is, on the average, ten years between the onset of carcinoma in situ and the transformation to invasive carcinoma. Equally important is the fact that there are no statistics available showing that a significantly large number of patients have been followed for over ten years after total abdominal hysterectomy with no vaginal cuff. In 1968, two patients with widespread metastatic epidermoid carcinoma died on our service. They had had total abdominal hysterectomy for carcinoma in situ nine years previously. It is not possible to support a point of view with two cases, however, and so until large numbers of cases have been followed for 10 years, 15 years, and 20 years after total abdominal hysterectomy, final judgment must be reserved on the adequacy of this form of treatment. Total abdominal hysterectomy is, without question, the most commonly used form of definitive treatment.

**Stage Ia Carcinoma of the Cervix**

Stage Ia carcinoma of the cervix is not a rare lesion. Its reported incidence varies from 3.2 percent of 243 cases of carcinoma in situ in Freidell and associates' report to 50.3 percent in LaTour's series of 274 cases.\textsuperscript{14-16} The prognosis of Stage Ia carcinoma of the cervix is excellent. The main problems are: first, how to rule out cases of frankly invasive carcinoma, and second, how to treat the individual case.

The definition of Stage Ia carcinoma of the cervix, as indicated earlier, is a point of real dispute, but the desirability of subdividing Stage I into the very early microscopically detectable lesions versus the later clinically obvious Stage I cases is universally agreed upon. To be dogmatic beyond that point, however, at this time, is unwise, because the lesion is being studied intensively by many clinics around the world both in terms of how
it can best be defined and treated. Not enough information has accumulated in the literature to make any hard and fast statements concerning its treatment. There are some who indicate that it can safely be treated exactly like carcinoma in situ. Others, although they feel it can be treated less radically than Stage Ib carcinoma of the cervix, are reluctant to move it all the way back to the category of Stage O carcinoma of the cervix as far as its biological potential is concerned. Thus, the reported methods of treatment range all the way from total abdominal hysterectomy with no vaginal cuff to radical hysterectomy and pelvic node dissection. The trend currently holding sway was most clearly articulated by Mussey and associates. They state that a Stage Ia lesion can be treated in the same way as carcinoma in situ unless tumor cells are seen in vascular spaces of the cervical stroma. In this event it should be treated by the same radical procedures employed for Stage Ib, be it radiotherapy or radical hysterectomy and pelvic node dissection. Mussey and associates, as well as others, feel that lesions penetrating no more than three mm. into the stroma can be treated as carcinoma in situ. The obvious danger inherent in this approach is related to the thoroughness with which the conization specimen is examined. If representative sections are taken, it is possible to miss frankly invasive areas which would be detected on serial sectioning of the specimen. These considerations undoubtedly explain the unusually mild statements and the singular lack of dogmatism in the literature on this problem. In summary, it remains an area of clinical investigation with a number of questions unanswered. The physician in practice will do well to refer such patients to a center where the patient can receive adequate treatment and become part of a larger series which will lead to an earlier answer to this problem.

In our own clinic over the past five years, the modified radical hysterectomy has been the treatment of choice for Stage Ia carcinoma of the cervix. (For a detailed description of modified radical hysterectomy see Nelson, ref. 30.) This is the same operation described under carcinoma in situ. The ovaries are not removed in young women. We have had no recurrences using this form of treatment; however, our period of follow-up is much too short for any conclusions to be drawn.

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MEDICAL OMBUDSMAN

With no claims to superior virtue, let the health professional, the scientist, the intelligent layman support by his voice, by his writings, and, hopefully, by his personal behavior this pursuit of the new morality. Let it become an increasingly audible reply to those who, so enfraptured in the present, would doom us to its unimproved continuance. . . .

It can be debated that no man today has the free and moral right to condemn his grandchildren to the same perils of disease to which he is exposed by virtue of the present lack of effective scientific information, and his failure to participate in a search for it.

It would help greatly to educate the population about this principle if the defects in our present medical armamentarium were made evident. This should be done by a program of public education and periodic jury-of-peers reviews of the results of present-day medical care.

The health professional in whose training society has invested so heavily, owes it to that society to provide the required leadership. He must accept the responsibility for 1) indicating the present weakness of our medical knowledge and the futility of limiting our approach to its mass production; 2) informing the citizen of the importance of research, the prevention of disease, population control, and protection of the environment—all of these as aspects of society's needs for the future; 3) demonstrate by personal example the great relevance of fighting for the improvements of medical care that can come only from future discoveries; and 4) play the role, as part of the new morality, of ombudsman for the improved protection of the health of unborn generations.

—George James, "Clinical Research in Achieving the Right to Health." Annals of the New York Academy of Sciences. 169: 306-307, 1970.