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94. One might be tempted to write: "One DNA molecule = one gene." However, the quanta of factorial genetics, based on mutation, recombination, and enzymatic function, are all smaller than the DNA unit of molecular weight, $\sim 6 \times 10^6$ (*4*). There is increasing evidence that such a molecule is a natural unit rather than an artifact of fragmentation (*64*).
95. The experimental work from my laboratory summarized in this article has been generously supported by research grants from the National Institutes of Health, U.S. Public Health Service; the National Science Foundation; the Rockefeller Foundation; the Wisconsin Alumni Research Foundation, the University of Wisconsin, and, most recently, Stanford University. It is also a pleasure to record my thanks to the Jane Coffin Childs Fund for Medical Research for a research fellowship which supported my first association with E. L. Tatum.

Human and Amphibian Neoplasms Compared

Tumors in frogs and human beings are strikingly similar in cytological characteristics.

W. R. Duryee, M. E. Long, H. C. Taylor, Jr., W. P. McKelway, R. L. Ehrmann

The basic etiology of human tumors is not known and is not readily approachable experimentally. Some understanding of this important problem may be attained, however, by comparing neoplasms in human beings with those in experimental animals. Conferences between us have led to detailed comparison of cytological features from several widely divergent clinical neoplasms. The nuclear and nucleolar characteristics of these tumors are so strikingly similar as to be remarkable. Of possible etiological significance in the human being is the extremely close resemblance to the sequence of events observable in filtrate-induced renal cancers of the frog (*1*). In 1936 Lucké (*2*) noted strong similarities between neoplastic lesions in frog and human kidneys. For the frog he proposed a theory of tumor origin based on a transmissible organ-specific virus. This theory was confirmed and extended by Duryee (*3*) in 1956, using filtrates of homogenized tumors injected directly into host kidneys. A general sequence of nuclear events was observed in the treated kidney and was found to correspond in all details to those of transforming tubules in spontaneous tumor growth, as studied in histological section. Further experimental confirmation was made by exposing normal tubules to sources of virus in tissue cultures (*4*). The following observations on human tumors are of sufficient interest to be presented as isolated, although related, cases. Further research in the next few years will amply confirm or deny the implications of our observations; obviously much work needs to be done.

Amphibian Adenocarcinoma

As background for our comparisons, a brief summary of earlier experimental conclusions is presented. In the amphibian, a physiological sequence of nuclear events followed direct renal injection of tumor filtrate.

1) Simultaneous appearance of "new" deoxyribonucleic acid (Feulgen-positive) particles (presumably virus ag-

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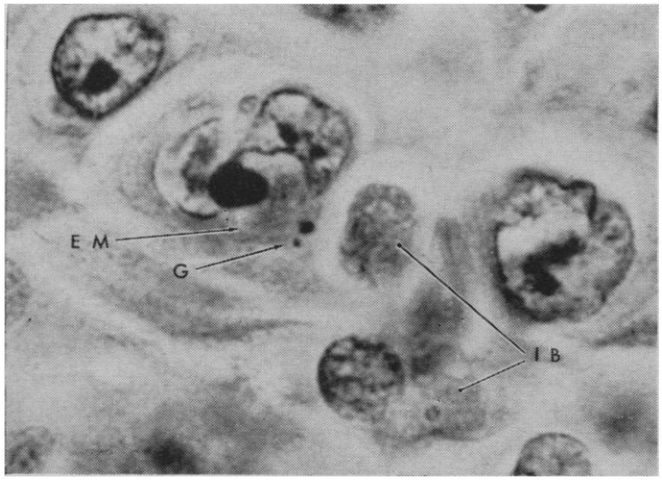
gregates) on the nucleolar surface near the chromosomal attachment point in a high proportion of proximal tubule cells.

2) Hyperactivity of the nucleolar machinery shown by increase in the ribonucleic acid mass of the nucleolus. Great variability between the cells was assumed to reflect different stages in a cyclical process. Eosinophilic intranuclear inclusions were *not* virus aggregates, as described by Lucké, but were simply greatly enlarged nucleolar cores that contained ribonucleic acid.

3) Extrusion of nucleolar ribonucleic acid and deoxyribonucleic acid into the nucleoplasm and thence into the cytoplasm, or directly through the nuclear membrane into the cytoplasm to form ribonucleic-acid-rich cytoplasmic inclusion bodies and occasional granules of aggregated deoxyribonucleic acid particles. The ribonucleic acid inclusion bodies slowly dissolved into the cytoplasm, acting as possible templates for new protein.

Parallel Phenomena in the Human Being

In ovarian carcinoma Taylor and Long (*5*) have noted increases in nucleolar size in highly malignant grade III tumors over that in benign tumors and in tumors of a lower histological grade of malignancy. Nuclei of grade III tumors showed extreme nucleolar hyperactivity and stages in extrusion of nucleolar ribonucleic acid into the cytoplasm. Similar nucleolar ribonucleic



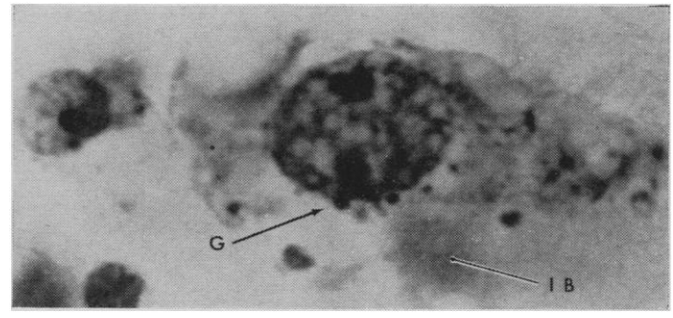
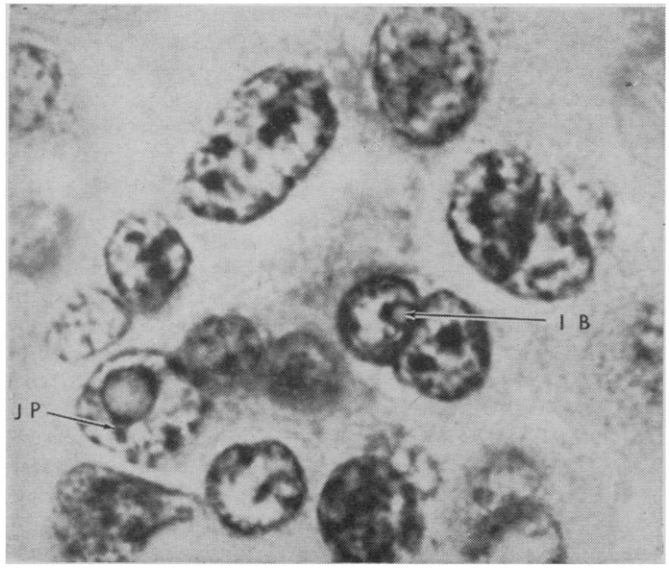


Fig. 1 (left). Human epidermoid cervical carcinoma (10384, M.H.), showing nuclei of highly malignant tumor cells with large eosinophilic inclusion bodies (*IB*) in the cytoplasm. Note the escape of eosinophilic material (*EM*) from the nucleus together with basophilic granules (*G*). Nucleolar hyperactivity is evident in the adjoining cells. (Oil immersion; hematoxylin-eosin.) (About × 1730) [College of Physicians and Surgeons, Columbia University] Fig. 2 (right). Human endometrial carcinoma, grade 3 (59-673, R.S.) in an ascites fluid smear preparation. The large arrow indicates extrusion of deoxyribonucleic acid material (*G*) from the nucleus. A pyronin-positive ribonucleic-acid-rich inclusion body (*IB*) is visible in the adjacent cytoplasm. (Oil immersion; methyl green pyronin Y.) (About × 1730) [College of Physicians and Surgeons, Columbia University]



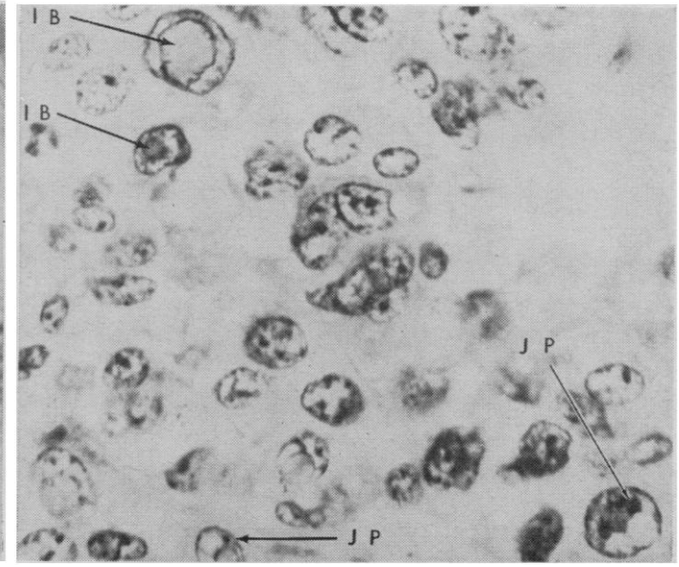


Fig. 3 (left). Human renal adenocarcinoma, grade 1 (S-59-571, M.M). Note the stages in the development of intranuclear eosinophilic inclusion bodies (*IB*) which are developed within the nucleolus and the enlarged nucleolar-chromosomal junction point (*JP*). Nucleolar hyperactivity is evident in several nuclei. (Oil immersion; hematoxylin-eosin.) (About × 1870) Fig. 4 (right). Lower magnification of human renal adenocarcinoma (from the same slide as Fig. 3). Note the large eosinophilic inclusion bodies developing inside the nucleoli (*IB*). The nucleolar chromosomal attachment point is visible in several nuclei (for example, *JP*). (Oil immersion; hematoxylin-eosin.) (About × 800) [Free Hospital for Women, Brookline, Mass.]

acid phenomena have been observed by these investigators in endometrial carcinoma (*6*) and in cervical epidermoid carcinoma (7). Kopac and Mateyko have confirmed and extended these observations in tissue culture studies of ovarian carcinoma (*8*).

Recent studies of Feulgen-reacted gynecological material have shown localization of deoxyribonucleic-acid aggregates around the sites of nucleolar-chromosomal junction points and the presence of minute deoxyribonucleic-acid compounds in cytoplasm. As in amphibian renal adenocarcinoma, such activity was limited to scattered foci within each tumor and was observed predominantly in tumors of the highest grade of malignancy (Figs. 1 and 2).

Localized nests of cells in a 2100-gram adenocarcinoma of the kidney were found to contain all stages of enlarged eosinophilic inclusions in the nucleus, up to 11 microns in diameter. Many examples of intranuclear eosinophilic material containing presumable ribonucleic acid were observed in such areas escaping into the cytoplasm. Occasional cytoplasmic deoxyribonucleic acid granules (0.5 to 1.5 μ) could be identified. The unusual characteristics of these cells deserve attention and suggest that further search of other renal tumors be made, beyond the preliminary exploration which has yielded a small number of comparable cases (Figs. 3 and 4).

In another patient with a presumably benign hydatidiform mole (Hertig group II), focal groups of cells were found showing all stages of enlarged nuclei (up to 25 μ) with large eosinophilic intranuclear masses (up to 18 μ). Stages of massive nucleolar ribonucleic acid escaping into the cytoplasm were observed. It is of interest that no cytoplasmic deoxyribonucleic acid was demonstrable.

In a case of grade I adenocarcinoma of the large intestine, a Feulgen-stained section showed packed nuclei, highly variable in size, with indications of marked nucleolar hyperactivity. There were many examples of intranuclear ribonucleic-acid inclusions and some "new" deoxyribonucleic acid granules. An average of two mitoses per high-power field indicated rapid growth rate. It is of interest that inclusions containing deoxyribonucleic acid were also noted on occasion in the cytoplasm of closely adjacent colon gland cells (Fig. 5). The latter cells of the colon wall illustrate large Feulgen-positive inclusions (2 to 3 μ) in the cytoplasm similar to those noted by Helwig (*9*) and others.

Another case of primary ovarian adenocarcinoma yielded exceptionally clear examples of tumor nodules with Feulgen-positive bodies situated inside and outside the nuclear membrane (Fig. 6).

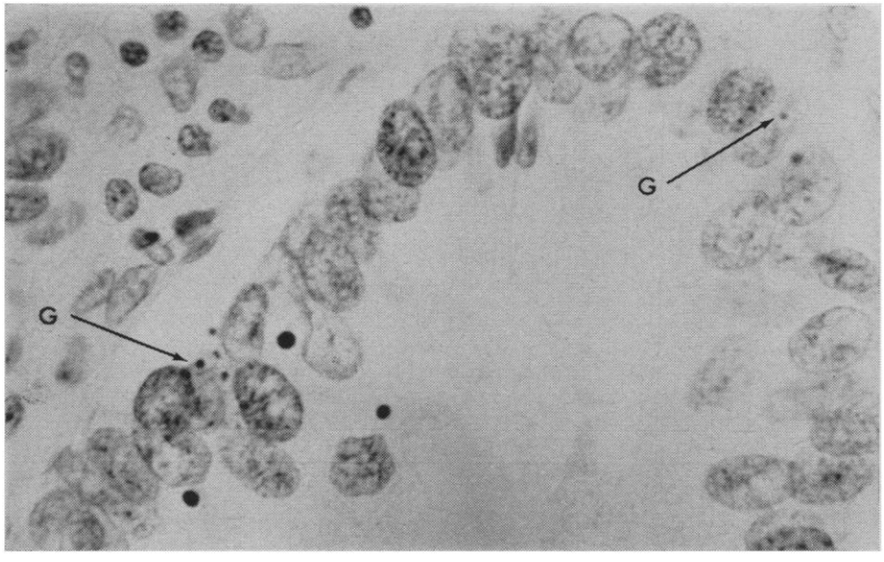


Fig. 5. Early cellular changes in a human colon gland closely adjacent to adenocarcinoma, grade 1 (G-7923, F.D.). Deoxyribonucleic acid granules (*G*) are extruded from the nuclei. (Oil immersion; Feulgen–fast green FCF.) (About × 900) [George Washington University Hospital]

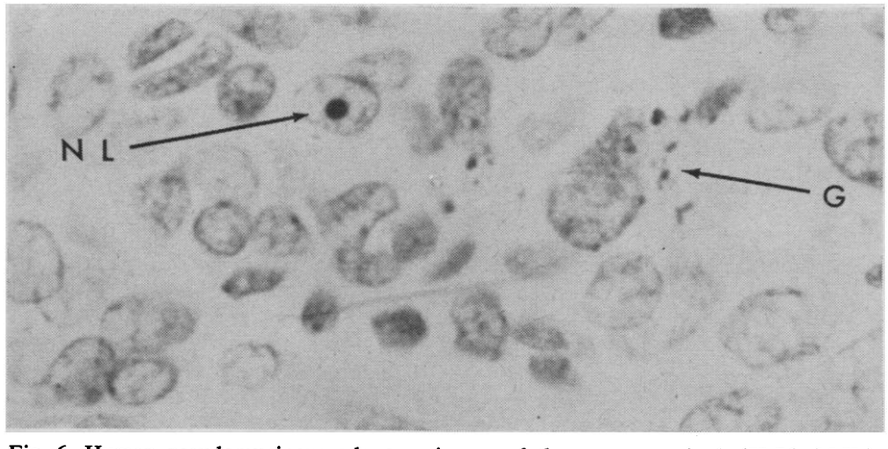
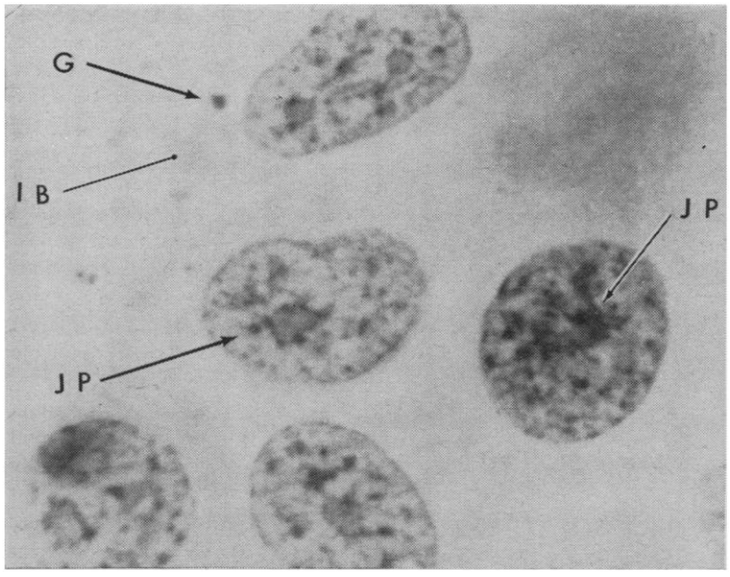


Fig. 6. Human pseudomucinous adenocarcinoma of the ovary, grade 1 (H-76, M.K.). Granules containing deoxyribonucleic acid (*G*) may be seen escaping from nuclei together with a small amount of ribonucleic acid. A hyperactive nucleolus (*NL*) has a Feulgen-positive capsule. (Oil immersion; Feulgen–fast green FCF.) (About × 1160) [George Washington University Hospital]

Spontaneous and Experimental Amphibian Tumors

In comparable ways spontaneous and virus-induced amphibian renal adenocarcinomas agreed in showing deoxyribonucleic acid granules from the nucleus escaping into the cytoplasm. Sections of spontaneous and experimental frog tumors demonstrated clearly that acini of primary renal adenocarcinoma were derived directly from transformed kidney tubules. In the majority of over a hundred cases studied, numerous tubules per kidney were involved, giving clear proof of the multicentric origin of this tumor. Close examination of transforming tubules frequently showed great numbers of infected nuclei with "new" deoxyribonucleic acid granules around the nucleolus. Release of ribonucleic acid from the nucleus allowed the deoxyri-



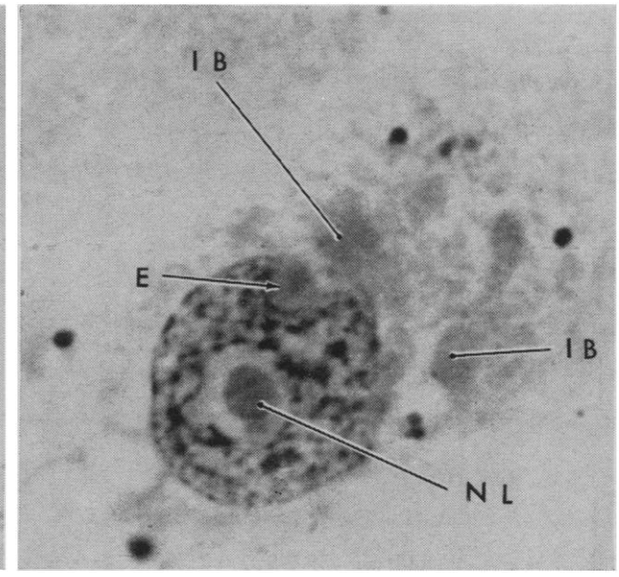


Fig. 7 (left). Frog renal adenocarcinoma nuclei in tissue culture. The arrows indicate a deoxyribonucleic acid granule (*G*) outside of the nucleus; a ribonucleic acid cytoplasmic inclusion body (*IB*) in the cytoplasm; and a hyperactive nucleolus developing at the nucleolar-chromosomal junction point (*JP*), together with additional deoxyribonucleic acid. (Oil immersion; Feulgen–fast green FCF.) (About × 2100) Fig. 8 (right). Frog adenocarcinoma cell nucleus in tissue culture. Note the ribonucleic acid inclusion bodies in the cytoplasm (*IB*), one escaping from the nucleus (*E*), and the ribonucleic acid in the enlarged core of the nucleolus (*NL*). (Oil immersion; Feulgen–fast green FCF.) (About × 2700) [George Washington University School of Medicine]

bonucleic acid granules (presumably virus) to escape also. Strong evidence for the transformation of normal tubules into malignant tissue immediately adjacent to active tumor masses was noted (see Figs. 7–9).

Conclusions

As indicated in the opening statement, histological and cytological features common to all of these human malignant tumors are (i) marked increase in Feulgen-positive granules (deoxyribonucleic acid) around the nucleolus; (ii) increase in the size, and evidence of extreme hyperactivity of the nucleolar machinery, leading to greater than normal extrusion of ribonucleic acid into the nucleoplasm and cytoplasm; (iii) resultant accumulation of nucleolar ribonucleic-acid and occasional deoxyribonucleic acid aggregates in cytoplasm. (Occasional massive cytoplasmic ribonucleic acid inclusion bodies and small "bursts" of deoxyribonucleic acid into extracellular areas are characteristic only of the most malignant grades.)

These findings are compatible with and extend the "cytogenetic" virus concept of Furth (*10*). There is clear evidence that the genetic machinery of an amphibian cell [that is, the deoxyribonucleic acid templates (*11*) of a gene locus on a chromosome] not only can organize nucleolar ribonucleic acid but, under unusual stimulus, can fragment itself (*3, 4*). Stimulation of normal nucleolar machinery of the cell to a highly abnormal or malignant degree by a cytogenetic infecting virus (*10*) is evident in various animal tumors and is consistent with previous, poorly understood, observations on human tumors. The purpose of this article has been to emphasize that these essential features may be experimentally ap-

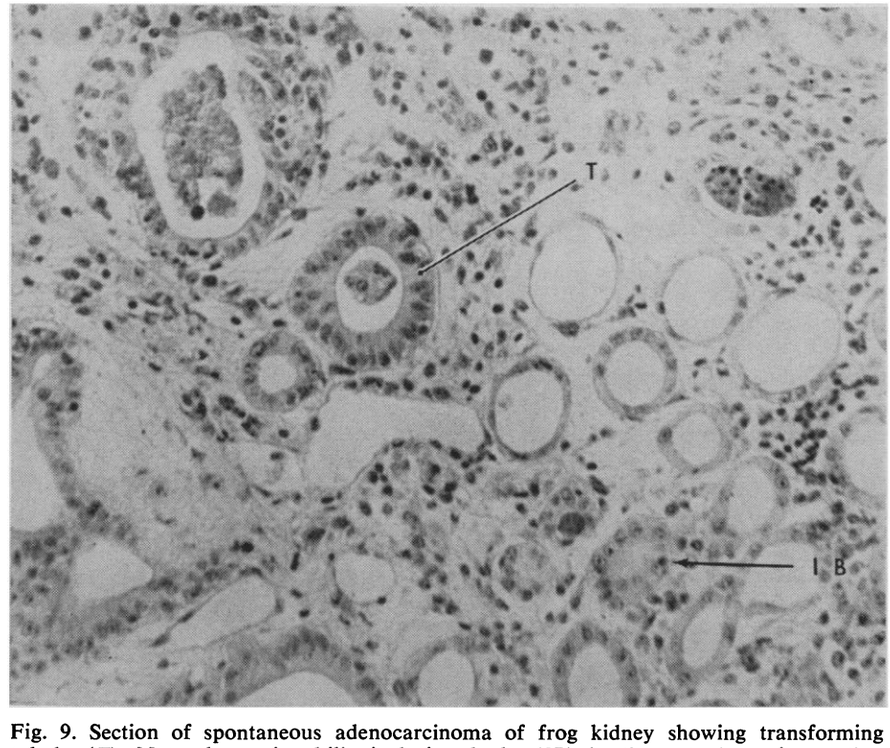


Fig. 9. Section of spontaneous adenocarcinoma of frog kidney showing transforming tubule (*T*). Note the eosinophilic inclusion body (*IB*) in the cytoplasm in another tubule. (Hematoxylin-eosin.) (About × 230) [George Washington University School of Medicine]

proached in the test animal and therefore may be compared with malignant cytology in human beings. A parallelism may throw light on possible conditions of carcinogenesis in human beings, but certainly parallelisms are no proof, and no direct implication that human tumors are virus-induced is allowed or intended. However, it is noteworthy that all the foregoing details in stained frog-kidney sections may be observed in comparable living cell nuclei in tissue culture under the highest powers of phase-contrast microscopy, and it may be pointed out that tissue-cultures of human malignant cells have, in many instances, exhibited nucleolar abnormalities identical with those described in this preliminary presentation (*12*).

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12. The experimental portion of the work on amphibian material was supported by funds from the U.S. Public Health Service (C-2754) and the Damon Runyon Memorial Fund (DRG-437) and by a grant from Mr. and Mrs. Robert B. Flint. The studies of tumors in human beings carried out at Columbia University were supported in part by grants from the Damon Runyon Fund (DRG-413) and from the National Cancer Institute, Bethesda, Md. (C-2428).

Introducing Modern Medicine in a Navajo Community

Physicians and anthropologists are cooperating in this study of changing patterns of culture and disease. The second of two parts.

Walsh McDermott, Kurt Deuschle, John Adair, Hugh Fulmer, Bernice Loughlin

In part I of this article (see last week's issue of *Science*) were presented the background, the goals, and certain of the preliminary findings of a joint medical-anthropologic research program on cross-cultural technologic development in the field of health. The studies are being conducted with the cooperation of the Navajo Tribe and the U.S. Public Health Service in an 800-square-mile area situated in the approximate center of the Navajo land in the southwestern United States.

Few better illustrations of the significance of cross-cultural matters in medicine can be cited from the present study than the situation observed with respect to congenital dislocation of the hip. Indeed the experience has been an excellent lesson in the basic principle that what constitutes a "disease" in one culture does not necessarily constitute a "disease" in another culture.

The authors are affiliated with the Department of Public Health and Preventive Medicine of the New York Hospital–Cornell University Medical Center, New York, N.Y. Miss Loughlin is also affiliated with the School of Nursing. This article is adapted in part from the Edward Jenner memorial lecture delivered by Dr. McDermott at St. George's Hospital Medical College, London, 1 July 1958.

"Congenital" Hip

As had been expected, the prevalence of congenital dislocation of the hip at Manyfarms-Rough Rock was found to be quite high. Indeed the number of cases found represents a prevalence rate of 1090 persons afflicted per 100,000 population, in contrast to a rate of 3.8 persons per 100,000 in New York City. To what extent this disease is truly hereditary has never been precisely established, although it is generally designated as a congenital disorder. It has also been strongly suspected that cultural factors, notably the use of cradleboards, contribute substantially either to the condition itself or to the degree of permanent disability resulting from it. For, on the cradleboard, the infant is securely laced with the outstretched legs bound together in a position that does not favor continued insertion of the head of the femur in the pelvic joint.

Irrespective of the relative roles of genes and culture in causation, there is an increasing body of evidence that the major portion of the disability in congenital hip disease can be prevented if the condition is discovered and appropriate nonsurgical treatment is started during the first year, or at most the first two years, of life. During the next two years (ages three and four), the only satisfactory treatment is surgical and consists of exposing the joint and inserting the femur in its proper location. Once the child has attained the age of five or six years (school age), the only treatments available are the more elaborate surgical procedures of attempting to create a "shelf" of bone, or, if this fails, fusing the hip joint. The latter operation is seldom employed as the initial treatment unless the child has reached the age of 12 or 13 years, and the operation results in a completely stiff and "frozen" hip joint. The reason for purposely producing the obvious physical handicap of a completely fused hip joint is that unless this is done, the patient runs a considerable risk of having a chronically painful traumatic arthritis of the hip when he or she attains the age of 40 or 45.