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Poliomyelitis Vaccine

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Staff Meeting Report

Some Comments on Polyps of the Rectum and Colon*

Richard B. Capek, M.D.†

William C. Bernstein, M.D.‡

Introduction

During the past decade, cancer detection centers and other diagnostic clinics in all parts of the United States have contributed an enormous amount of data relating to tumors of the large intestine, much of it concerned directly with polyps of the colon and rectum.

Although polyps of the rectum and colon had been described in the literature by Virchow, Luschka, and others as early as 1861, very little interest in the subject was manifested in the United States until after the mid-twenties. One of the earliest papers of this new "polyp era" was written by Erdmann and Morris¹ in 1925. In 1926, C. E. Dukes² described tumors of the large intestine and their relations to cancer. It is interesting that many of the early papers on this subject originated in the midwestern part of the United States. Papers by Hullsiek³ (1928), by Bargaen and Comfort⁴ (1930), and by Buie and Brust⁵ (1935) are examples. In 1937, Buie⁶ published his textbook, *Practical Proctology*, in which he reviewed the literature on polyps and added his own findings on the subject. Among the early leaders in proctology to call attention to the importance of rectal and colonic adenomas as precancerous lesions were Fansler of Minneapolis, Hirschman of Detroit, and Rosser of Dallas.

In 1936, D. C. McKenny⁷ called attention to the tendency of this disease to occur in families. It was McKenny's paper, probably more than any other single contribution, that alerted the profession to the seriousness of rectal and colonic polyps and started a trend toward the early recognition and removal of these so-called benign tumors.

At the University of Minnesota Hospitals the first comprehensive review of the subject of rectal and colonic polyps was presented to the staff in 1941 by Bernstein.⁸ At that time, all polyps within reach

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on November 29, 1957.

†Medical Fellow, Division of Proctology

‡Clinical Associate Professor, Division of Proctology

of the sigmoidoscope were routinely removed, while polyps above the reach of the sigmoidoscope were "watched" by x-ray and were not removed unless the radiologist suspected malignancy or could demonstrate evidence of polyp growth. Since 1941, the subject of polyps has been investigated intensively in the University Hospitals, the outpatient clinic, and the Cancer Detection Center. The approach to treatment of polyps has changed from the conservative attitude described above to the aggressive approach advocated by Lillehei and Wangenstein,⁹ who said in 1955, "This experience would appear to indicate that total or subtotal colectomy is an acceptable operation for all lesions of the colon in which no ileum, or a very short segment thereof, needs to be removed." Their experience indicated that 38 per cent of patients with an initial diagnosis of carcinoma and/or polyps of the colon had additional polyps in a portion of the colon that preoperatively was believed to be uninvolved.

The purpose of this presentation is to clarify if possible some of the attitudes towards polyps of the rectum and colon.

Definition and Incidence

Before discussing the incidence of rectal and colonic polyps, one must have a definite idea of their nature. The term "polyp" has been used very loosely in this and other clinics, and much misunderstanding and misinterpretation of figures have resulted. In reviewing the literature, one is struck with the wide discrepancy in the reports published by various authors. Most of the confusion that results can be attributed to the lack of agreement on the definition of the word "polyp." If every elevation of mucous membrane, regardless of size and the nature of the elevation, is called a polyp, then the incidence of polyps will be exceedingly high. It is altogether likely that the single word "polyp" is inadequate to describe a clinical entity, and that a descriptive adjective or adjectives should be used to precede the word. While most clinicians will agree that the ordinary rectal or colonic polyp is an adenoma, the term "polyp" continues to be used for most other types of small growth in the bowel.

Turell and Wilkinson¹⁰ described an adenoma as a "pedunculated or sessile glandular structure which exhibits proliferation of colonic epithelium without invasion of the intestinal wall." Bacon¹¹ stated that an adenomatous polyp is "a sessile or pedunculated benign tumor of glandular origin." Hellwig¹² described an adenoma as "a sessile or pedunculated benign tumor of glandular origin." The first two of these definitions were written by clinicians, while the third was written

by a well-known pathologist with a deep interest in rectal and colonic polyps. It is clearly the adenoma that distinguishes the common rectal polyp, and unless the tumor exhibits evidence of glandular proliferation it should not be referred to as a rectal polyp.

Blakiston's *New Gould Medical Dictionary*, on the other hand, describes a polyp as, "a pedunculated mass composed of neoplastic tissue or other structures, found especially on mucous membranes." It is easy to understand how the incidence of polyps would be exaggerated if every minute elevation of mucous membrane were to be classified as a rectal or colonic polyp. The fact is well established and has been observed often enough to warrant particular mention that many small mucosal elevations or excrescences appear and later disappear without any treatment. The exact nature of these elevations has not been definitely established. Indeed, some of these tiny areas cannot even be classified as elevations but rather as minute plaques. The supposition is that these elevations or excrescences may be the result of inflammatory reaction in the lymphoid follicles of the submucosal layer. In biopsies of these areas the enlarged lymphoid follicles are sometimes visible but not uniformly enough to prove the point. Many times the biopsy specimens from patients with such excrescences reveal perfectly normal mucosal and submucosal patterns. Wilson, Dale, and Brines¹³ in 1955 reported the results of 20,847 sigmoidoscopic examinations. They reserved the word "polyp" for the adenomatous polyp or adenoma, and not for any other protrusion of the intestinal mucosa—inflammatory or otherwise—which might be encountered in that area. The incidence of polyps in patients over the age of forty in their series was 3.95 per cent. This contrasts with the figures of 16 per cent and higher at the Cancer Detection Center at the University of Minnesota and of 12 per cent reported by Jackman and Mayo.¹⁴ Turrell and Wilkinson,¹⁰ limiting the term "polyp" or "adenoma" to the definition previously mentioned (and excluding the so-called mucosal excrescences), found an incidence of 6.9 per cent in patients with average ages of 50 years or more and with intestinal symptoms. In a group of asymptomatic individuals under the age of 45 the incidence of polyps was 1.81 per cent. Scarborough and Klein¹⁵ reported an incidence of 4.6 per cent in a series of 10,000 sigmoidoscopic examinations.

The identification of a true polyp or adenoma on sigmoidoscopic examination need not be difficult. If the tumor is pink to red in color and exhibits solid or fleshy characteristics it is probably a true polyp. If, however, the elevation under consideration presents a clear or

translucent appearance and resembles a tiny bleb or plaque on the mucosal surface, it should not be classified as a polyp but rather as a mucosal excrescence. In view of the extensive experience of the many cancer detection centers, it seems reasonable to expect that rigid standards of definition regarding pathologic classification should be set up in the near future.

A very valid reason for limiting the term "polyp" to the true adenomas is that patients are aware that they harbor precancerous lesions in their large intestine when polyps are detected. The mucosal excrescences referred to above, are not precancerous and therefore should not be put into the same category as the true polyp.

Polyps and Cancer Found at Autopsy

It is extremely difficult to obtain reliable and accurate figures of the number of polyps and cancers of the rectum and colon found at autopsy. Some pathologists do not routinely open and inspect the colons. In some hospitals colons are opened by an attendant, and if no gross cancers or large polyps are seen, no other examination is performed. Edwards¹⁶ stated that in 802 autopsies performed during 1951, polyps of the large bowel and rectum were found in 77, or 9.6 per cent. In 25 of these cases, or 34 per cent of the 77 with unsuspected adenomatous polyps, microscopic diagnosis of Grade I adenocarcinoma in an adenoma was made. In four cases (approximately 0.4 per cent of the 802 cases and 3 per cent of the patients with unsuspected lesions) an adenocarcinoma of Grade II or higher was found. At the University of Minnesota Hospitals 2,012 autopsies were performed between January 1, 1951, and December 31, 1955; in this series 35 colons were found to contain unsuspected tumors, seven of which were actual cancers.

Malignancy in Polyps

That polyps of the rectum and colon are premalignant lesions, no one will dispute. There is an overwhelming amount of factual data based on long experience to prove this point. Two questions remain unanswered, however. The first is whether or not all polyps will undergo malignant change if left untreated; the second is how to determine which polyps already have undergone malignant change. Unfortunately, there is not much agreement among pathologists on what constitutes malignancy in polyps. Swinton and Warren¹⁷ have stated that "If one accepts three important criteria of malignancy, namely, anaplasia, irregularity of architecture, and invasion—it is nec-

essary to have at least two of these three factors present before making a diagnosis of malignant growth." Rosenberg¹⁸ submitted these criteria to a large group of prominent pathologists in different parts of the country and learned that while most pathologists agreed that invasion was important, there was much argument about the other two criteria.

According to the practice of the pathology department at the University of Minnesota, a polyp is not described as malignant unless, in addition to irregularity of glands, deep staining cells, and mitotic figures, it shows some evidence of the penetration or invasion of the muscularis mucosa by the cellular or glandular elements of the epithelium. At the Mayo Clinic Grade I adenocarcinoma is a frequently used classification. Edwards¹⁶ described this lesion as:

an adenomatous polyp which has undergone pre-cancerous changes. The acini show a greater irregularity and the cells are hypertrophied, elongated and compressed. The nuclei are elongated, longer and stain more deeply than in the pure adenoma. There is a migration of the nuclei from the base of the cell. Mitotic figures occur with increased frequency. Small hemorrhages may occur.

Thus in two large clinics and teaching centers the basic criteria for diagnosing malignancy in polyps differ considerably. This represents another reason for the discrepancies in figures on the incidence of cancer.

Biopsy of Polyps

The practice of removing a small portion of a polyp for biopsy deserves comment because it is fraught with danger and leads in many cases to an incorrect diagnosis. If one removes only a small fragment of the tumor, areas of malignancy may be missed, causing the pathologist to render a report of benign tissue. In the case of a sessile or pedunculated polyp reported as malignant, it may well be that if this fragment were seen in relation to the entire polyp the diagnosis would be different. Since it is almost always possible to remove the entire polyp for microscopic diagnosis, a plea must be made for physicians to perfect their technics so that better specimens can be given to the pathologists for diagnosis.

Most pedunculated polyps within reach of the proctoscope can be removed effectively with the electric snare. Most sessile polyps within the rectum proper can be excised in their entirety under anesthesia. For large sessile polyps—villous papillomas, for instance, which are often attached by wide, strap-like bases—it may be necessary to split the rectum from the anus to the coccyx in order to obtain good ex-

posure and to remove the tumor completely; since most of these tumors are benign, this procedure (referred to as the Harrison-Cripps operation) is curative as well as diagnostic. Another technic for total biopsy of doubtful polypoid growths of the lowest large bowel segment has been described by Crowley and Davis.¹⁹ They make an incision between the coccyx and the outer edge of the sphincter ani muscle without severing the muscle. Through this incision they expose the posterior wall of the rectum. They then incise the posterior wall of the rectum and gain access to the polyp, which can be excised completely. Once the pathologist has the total polyp he can make sections through several portions of the tumor and render a precise diagnosis.

Etiology

Factual information on the etiology of adenomas of the colon and rectum is nonexistent. Evidence on why most polyps and cancers of the large bowel appear in the lower sigmoid colon and rectum is also lacking. During the past ten years several cases have been encountered at the University of Minnesota Hospitals which raised the question of whether or not some hormonal influence affected the production of polyps. In two women patients upon whom a subtotal colectomy with low ileosigmoid anastomosis had been performed it was observed that between the time of the resection of the major part of the colon and the time set for the fulguration of the remaining rectal polyps a marked reduction in the number and size of rectal polyps had occurred. It is not clear whether this diminution was caused by the removal of the parent organ itself or by the alteration or reduction of some hormonal secretion as a result of the surgery. Speculation on this problem increased when another patient, who had undergone subtotal colectomy and ileoproctostomy in 1950 and had returned for regular examinations, came in again in 1957 and reported that she was three months pregnant. Since the time of her surgery new polyps had developed in her rectum at the rate of two to ten per year, all of which had been destroyed by fulguration. At the time of the patient's first visit during pregnancy, the rectal mucosa was studded with new, small polyps. Many were destroyed, and the patient was told to return at monthly intervals. At each subsequent visit it was observed that the rectal mucosa was again studded with new polyps. When the patient had entered the sixth month of her pregnancy a proctoscopic examination revealed innumerable small polyps covering the rectal mucosa. Destruction of all the polyps would

have been impossible. It was decided not to carry out further treatment during pregnancy. The patient was asked to return for another examination 6 weeks after the birth of her baby. The clinicians felt that at that time it would be necessary to remove the rectum and establish an ileostomy. When the patient returned for this examination, it was noted that practically all the polyps had disappeared and that the mucous membrane had returned to the status observed before pregnancy. Observations such as these have not been reported in the literature before. The possibility of a hormonal relationship to cancer has been discussed at length in Bacon's textbook.¹¹ In this last case one must certainly suspect the operation of a hormonal influence, which disappeared after the completion of the pregnancy.

Polyps and the Cancer Problem

General agreement exists that rectal and colonic polyps undergo malignant degeneration. Evidence supports the statement that some cancers of the large bowel begin as very small malignant tumors. Several actual cancers of not more than 3 to 4 mm. have been found in specimens removed at the University Hospitals and at the Veterans Hospital in Minneapolis. Evidence is lacking, however, as to the actual *percentage* of polyps that undergo malignant degeneration. Jackman and Mayo¹⁴ have stated that "in our opinion, polyps of the large intestine, if given sufficient time, will develop into carcinomas."

The 1956 monograph on *Cancer of the Colon and Rectum*, published by the American Cancer Society, Inc., and written by Frederick A. Collier,²⁰ contains the following paragraph:

An accurate estimate of the true incidence of polyps depends on the source or nature of the material studied. According to data from cancer detection centers, 2 to 7 per cent of the population has undetected polyps. In 1843 autopsies, Swinton and Haug found 311 cases of benign polyps, or an incidence of 7 per cent. In 42 per cent of these cases the polyps were multiple. Polyps are present in 7 per cent of patients with definite rectal symptoms. After the age of 20, the incidence of adenomatous polyps of the colon and rectum increases with each decade. The average age of patients with benign polyps is about ten years less than that of cancer patients. Fifteen to thirty per cent of polyps become carcinomatous. These data emphasize the value and importance of sigmoidoscopic and barium-enema roentgenological examination of the colon as a part of a complete diagnostic survey, especially in patients at or beyond middle age.

But these official figures published by the American Cancer Society differ widely from figures published by the United States Department of Health, Education, and Welfare, whose *Vital Statistics of the*

*United States*²¹ in 1955 listed the death rate from all malignant tumors of the colon and rectum as 22 per 100,000 population. If the figure of 7 per cent is used to indicate the incidence of polyps in the adult population, then 7,000 out of every 100,000 adults would have polyps. If 15 to 30 per cent of all polyps become carcinomatous, as stated by the American Cancer Society, then the incidence of cancer of the colon and rectum would exceed 1,000 per 100,000 adults, even after taking into account the fact that multiple polyps occur in many people. As stated above, the death rate from all cancers of the colon in 1955 was 22 per 100,000. This figure appears to indicate that too many lesions of the colon and rectum are being wrongly classified as polyps, or that the percentage of polyps which undergo malignant degeneration is much smaller than the estimate given above.

Dr. Leo G. Rigler, former Professor of Radiology at the University of Minnesota, has been discussing this question of the importance of polyps as related to the cancer problem for some time. In a recent letter to the authors, he wrote:²²

The basic point that I made was that if we assume that 10 per cent of the population over the age of 45 have polyps, either in the colon or in the rectum, which appears to be a fairly conservative estimate in the light of what is found in the Cancer Detection Center, this would indicate 10,000 polypi per 100,000 population. So far as we can determine from the best statistics, the figure of 200 per 100,000 population indicates the incidence of cancer of the colon. Since not all of these 200 arise from polypi, the tremendous discrepancy between 10,000 and either 200 or 100 makes one wonder as to the importance of these polypi; even though we all admit that some cancers arise from them.

Part of this I am sure is due to the excessive number which are reported by proctologists and which are excrescences on the mucous membrane rather than true tumors but which can hardly be distinguished either pathologically or otherwise when they are small in size.

Even if we cut this figure down to five per cent there is the tremendous difference between perhaps 100 cancers of the colon per 100,000 population due to polypi and 5,000 polyps. Through such circumstances one may well question whether drastic treatment of an individual small polyp is justified. I would be the last to want to delay in the treatment of polypi which are large, are growing, are very multiple, or are associated with a carcinoma either previously or presently present in the colon. But most of the cases that we see are not of this kind, now that many apparently normal people are being examined.

I think in the Bulletin of the Cancer Detection Center the ratio between polypi discovered and cancers discovered in the same group of the population bears out fairly well the figures that I have

given. I would certainly advocate following every patient in whom a polyp has been found most carefully, but I am questioning whether they should be operated upon or anything else very radical done.

Judging from the obvious discrepancies cited above, it would appear that the time has come when a series of 100 to 500 patients with rectal and colonic polyps should be studied for a period of five to ten years without treatment unless findings indicated a change in the picture of the polyps suggesting malignancy. Until such a study is undertaken little will be added to our knowledge of polyps and their potentialities for malignancy.

Diagnosis

The fact has been well established that the sigmoidoscopic examination is the only accurate method of identifying polyps of the rectum and lower sigmoid colon. The barium enema x-ray of the colon, which is the only means at our disposal to find polyps above the sigmoidoscopic level prior to surgery, leaves much to be desired in the identification of a large percentage of the polyps of one cm. or smaller. The most important reason for the failure to obtain a good barium enema x-ray examination appears to be inadequate cleansing of the bowel, for if solid feces are present, an accurate diagnosis of polyps cannot be made. Adequate cleansing of the bowel with enemas and castor oil, plus abstinence from all solid food for 24 to 48 hours prior to the examination may help answer this disturbing problem. Overlapping of loops of bowel and inadequate filling or emptying of the barium during the examination are other technical factors that complicate the procedure. Endoscopic examination of the entire colon through several colotomy incisions during laparotomy is a very valuable procedure and is completely safe in competent hands.

Treatment

The treatment of benign polyps of the colon and rectum appears to be well established in most medical centers. All small sessile polyps can be destroyed adequately by fulguration if they are within reach of the sigmoidoscope. Large sessile growths below the rectosigmoid area can usually be totally excised from below. Pedunculated polyps can be removed by means of the electric snare passed through the sigmoidoscope. Through a scope of 1 in., 1½ ins. or 1¾ ins. in calibre, large pedunculated polyps can be successfully removed from the upper rectum and lower sigmoid regions.

The treatment of polyps above the sigmoidoscopic level requires

that the abdomen be opened and that either a colotomy and polypectomy or a colon resection be performed. Most authorities agree that a subtotal colectomy and ileoproctostomy are indicated if there are three or more polyps located in different segments of the colon. The performance of a subtotal colectomy for a single benign polyp does not appear to be justified in the light of existing knowledge of this disease.

When the question of malignancy in a polyp exists, the operation should be one for cancer and not for benign polyp.

Summary and Conclusions

1. The term rectal or colonic polyp should be reserved for the true adenomas.

2. Statistics concerning the incidence of polyps differ greatly in the various reports and have led to much confusion in the literature.

3. Statistics concerning the incidence of cancer of the rectum and colon do not bear out the contention that most polyps will undergo malignant change.

4. A controlled series of untreated polyps is needed to provide reliable data on the relationship of polyps to cancer of the rectum and colon.

5. Clinical observations suggest the possibility of a hormonal influence in the genesis of some polyps.

6. The detection of polyps by sigmoidoscopy and by improved colon x-rays remains a most valuable part of the complete physical examination.

7. More complete biopsy specimens should be submitted to the pathologists in order to improve the accuracy of diagnosis.

Note: The Annie and Louis Paper Fellowship in Proctology was established at the University of Minnesota Hospitals in 1950. It has been my good fortune to hold this fellowship between July 1, 1956 and June 30, 1958. I am most grateful to the donors of the Paper Fellowship in Proctology for the opportunity afforded to obtain training at the University of Minnesota. The present study and other, similar studies, have been made possible through this fellowship.—Richard B. Capek.

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Staff Meeting Report

Studies of Orally Administered Attenuated Live Virus Poliomyelitis Vaccine in Newborns and Infants under Six Months*†

Mauricio Martins da Silva, M.D.‡

John L. McKelvey, M.D.§

Henry Bauer, Ph.D.¶

Konald A. Prem, M.D.**

Marion K. Cooney, M.S.††

Eugene A. Johnson, Ph.D.‡‡

The development of an inactivated virus vaccine against poliomyelitis—the Salk Vaccine—constituted an important step toward the control of this disease. For the first time in its long history some direct measure of control could be exercised against the poliovirus itself.¹ The protective effect of the new vaccine against paralytic poliomyelitis has been reported to be 83.1 per cent among individuals receiving two doses.² The duration of the immunity produced by the vaccine is not known, but evidence presented by some investigators, including the unpublished observations made by one of the authors (M.M.S.) on the antigenic potency of the vaccine in infants and children with no previous immunizing experience, seems to suggest that “booster” injections will be required at regular intervals, probably yearly, to maintain measurable levels of circulating antibodies. The inability of Salk vaccine to prevent infection of the intestinal tract by virulent or attenuated poliovirus or even to reduce the amount or duration of virus excretion in the stool has been well established^{3,4,5} and is further confirmed by the present study. These considerations, as well as the necessity for administering the vaccine by injection and

*This report was given at the Staff Meeting of the University of Minnesota Hospitals on December 6, 1957.

†The authors are indebted to Dr. Herald R. Cox and associates of the Viral and Rickettsial Research Division of American Cyanamid Company, Pearl River, New York, for the testing in monkeys of the excreted viruses.

‡Assistant Professor, Department of Pediatrics, University of Minnesota. Present address: Pan American Sanitary Bureau/World Health Organization, Washington 6, D. C.

§Professor and Head, Department of Obstetrics and Gynecology, University of Minnesota

¶Director, Division of Medical Laboratories, Minnesota Department of Health, Minneapolis

**Instructor, Department of Obstetrics and Gynecology, University of Minnesota

††Chief, Section of Viral and Rickettsial Diseases, Division of Medical Laboratories, Minnesota Department of Health

‡‡Assistant Professor, School of Public Health, University of Minnesota

the fact that its manufacture is technically complicated and expensive for most countries of the world, have kept alive the search for better types of poliomyelitis vaccine.

It is an accepted observation in immunology that the most effective protection against a virus disease is attained through acquiring the disease and recovering from it (influenza and the common cold, of course, being notable exceptions). In this regard, it should be remembered that a mild, controlled, or modified infection provides as effective an immunity as does a strong one. Duplicating this type of convalescent immunity is, indeed, the aim of immunologists in developing vaccines.⁶ The best vaccines currently available against virus diseases are live virus vaccines prepared as attenuated strains. Outstanding examples of such vaccines for use in man are those for smallpox and yellow fever. Notable in the field of veterinary medicine, among others, is the Flury strain used in rabies vaccination.

An attenuated live virus poliomyelitis vaccine administered by mouth and capable of reproducing the long-lasting immunity conferred by the natural infection was made available to us for investigative purposes in January, 1957. This study summarizes the results obtained to date with this vaccine in a group of twenty-five families in which infants below the age of six months received orally, in succession, types I, III, and II. The fate of the viruses within the family unit was followed by serial stool cultures and serum antibody determinations in the infants and members of their families. This is believed to be the first such study using the three types of attenuated poliovirus in families living in their natural settings.

MATERIALS AND METHODS

*History of the Attenuated Strains**

The SM strain used in this study started as a mixture of the Sickle and Mahoney strains of type I virus,⁷ first adapted from monkey kidney tissue culture to the spinal cord tissue of mice and cotton rats (Figure 1). It was carried for 27 consecutive intraspinal passages in Princeton Rockefeller Institute mice followed by 14 serial passages in minced chick embryo tissue cultures of the Maitland type. The strain was next plaqued out by the Dulbecco technique on monkey kidney monolayer plates according to the method recommended by Dulbecco and Vogt.⁸ The plaqued material was next carried by making five alternating passages between monkey kidney and minced

*These viruses were supplied to the investigators by Lederle Laboratories Division of American Cyanamid Company.

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chick embryo tissue cultures and was again plaqued out on monkey kidney monolayer plates three consecutive times. The material finally used in the study represented the first passage in minced chick embryo tissue culture from monkey kidney tissue culture material. The strain is cytopathogenic for monkey kidney epithelial tissue and may be assayed either in monkey kidney tissue culture roller tubes or on monolayers of monkey kidney epithelial cells. The SM strain is non-

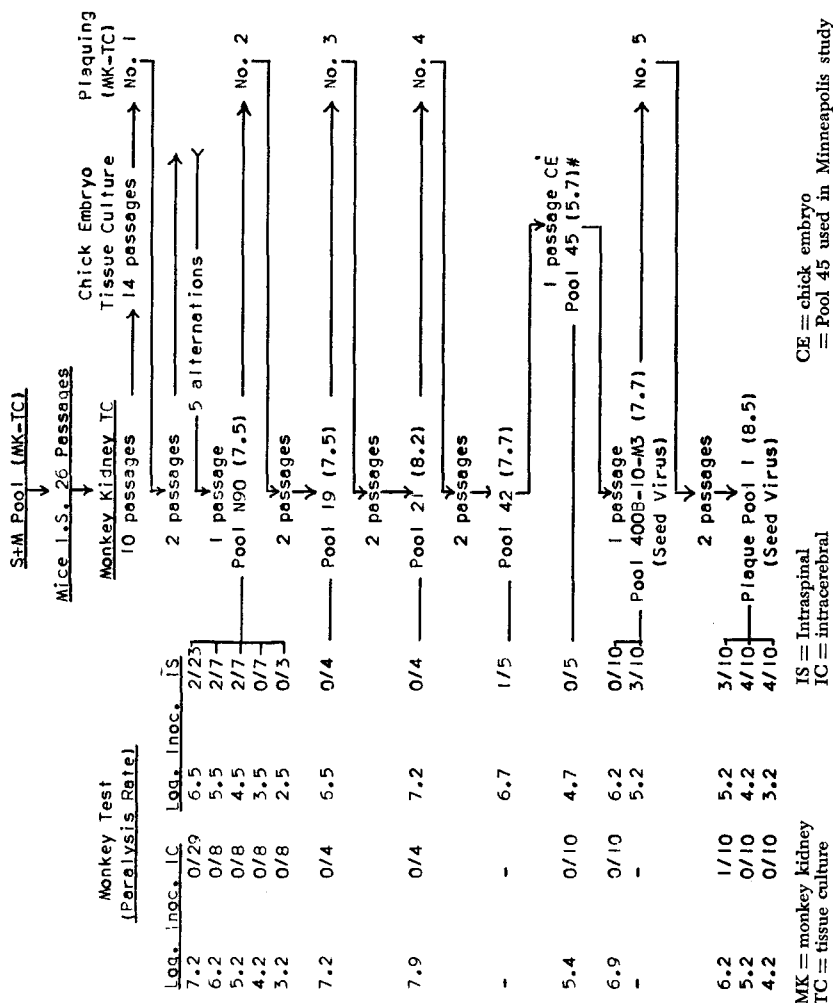
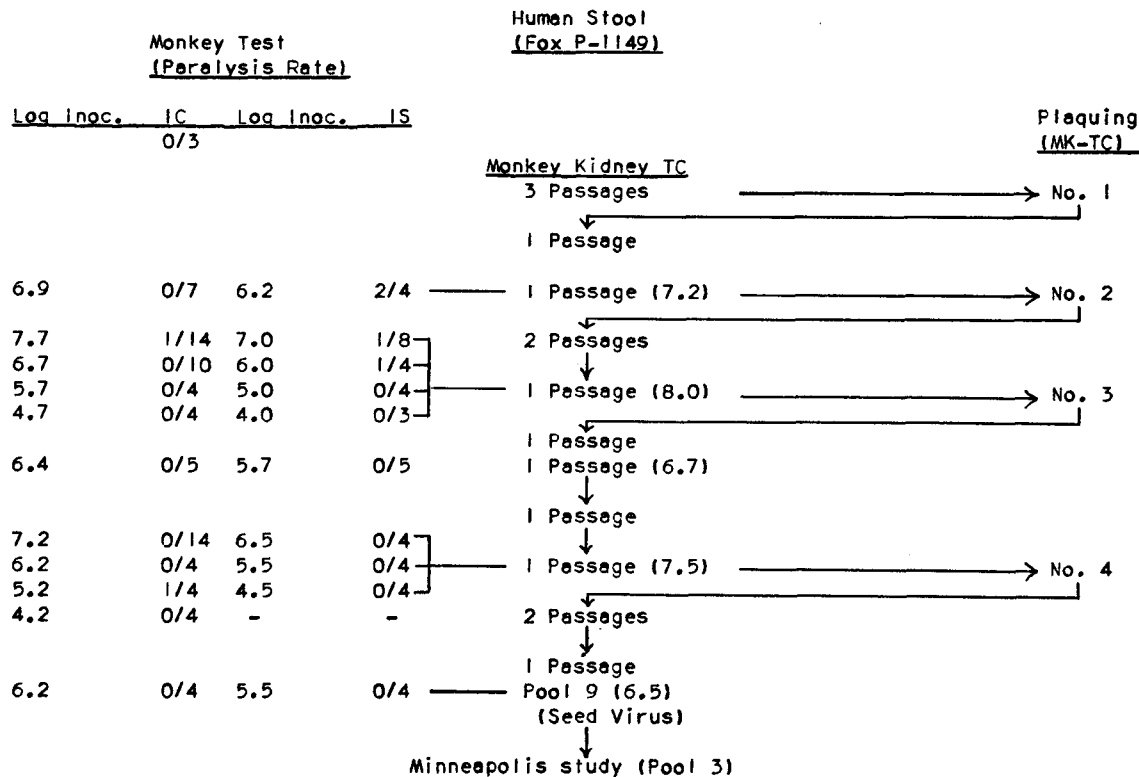


Fig. 1. Passage History of SM Virus (Type I): Origin of Pool 45 Seed

pathogenic for monkeys inoculated intracerebrally but does cause paralysis in some monkeys inoculated intraspinally, particularly in the higher concentrations.

The Fox strain, type III, was isolated from a one-year old child with nonparalytic poliomyelitis by Dr. John Fox of Tulane University (Figure 2). It has thus far been grown only in monkey kidney tissue culture and has been purified by being plaqued out four consecutive times by the Dulbecco technique. While highly cytopathogenic for monkey kidney tissue culture cells, it is nonpathogenic for cynomolgus monkeys inoculated intracerebrally or intramuscularly. Intraspinal inoculations in high concentrations will produce paralysis only occasionally. The material used in this study was grown in monkey kidney tissue (cynomolgus) in Povitsky bottles.

The MEF₁ Type II material was grown in chick embryo tissue. This strain was adapted from the central nervous tissue of mice first to the central nervous tissue of weaning hamsters then to suckling hamsters (Figure 3). The virus was carried for 119 serial passages in suckling 7- to 10-day old hamsters, followed by three passages in young adult white mice, one passage in developing chick embryos, another single passage in white mice, and finally, 33 consecutive passages in developing chick embryos. The culture and growth characteristics of this strain have been well described by Roca-Garcia, Moyer, and Cox⁹ and by Cabasso and his associates.^{10,11} This is the only strain of poliovirus that has been fully adapted to grow in the chick embryo. Roca-Garcia and Jervis¹² have shown that the strain produced a mild attack of poliomyelitis in only one of 35 cynomolgus monkeys inoculated intracerebrally with high concentrations of virus. Slight cord lesions were found upon histological examination in only eight of 35 monkeys inoculated intracerebrally. No paralysis was observed in eight monkeys given intraspinal injections of 10^{4.5} to 10^{4.9} PD₅₀ of virus, and a slight cord lesion was found in only one of these monkeys. Cynomolgus monkeys which repeatedly received large doses by the intramuscular route showed no symptoms, but specific neutralizing antibodies were developed in them. Similarly, chimpanzees inoculated intramuscularly or fed orally were found to have antibodies although they did not become fecal carriers or show any signs of illness. The MEF₁ strain is almost completely noncytopathogenic for monkey kidney cells but retains its ability to kill mice and hamsters inoculated intracerebrally even after more than 150 serial passages in chick embryos. All of these characteristics indicate that this strain of virus is greatly altered, and that a number of biological



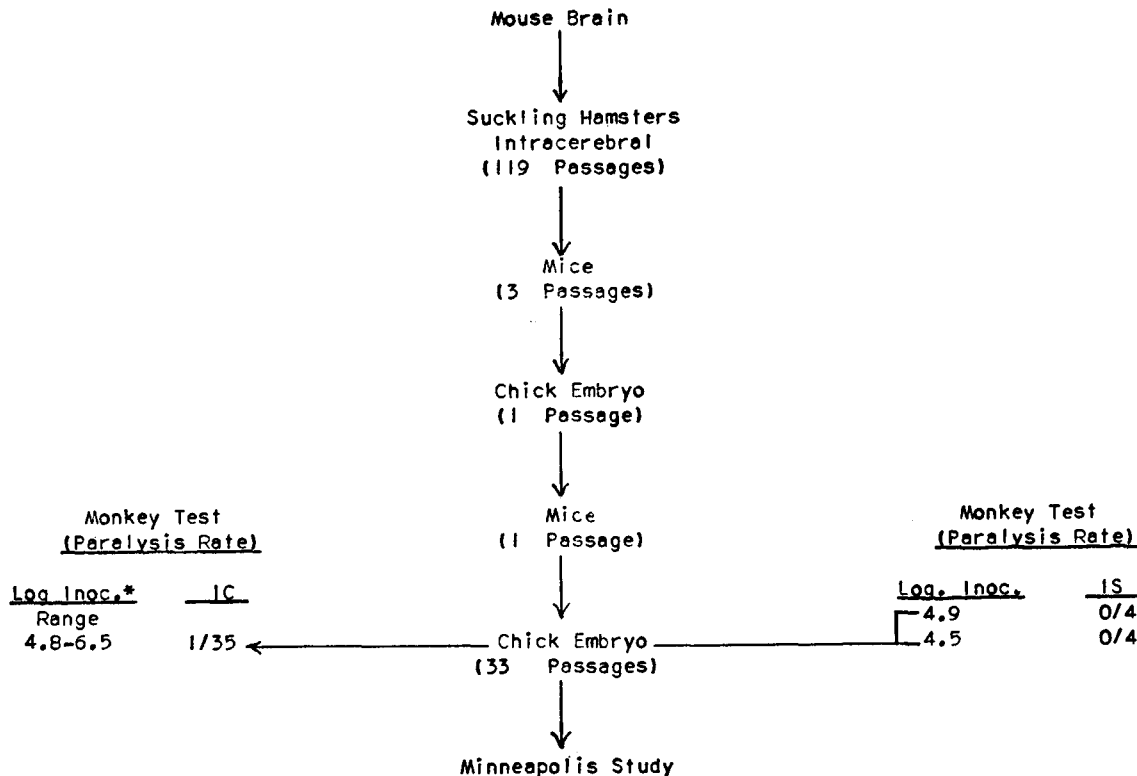
IC = intracerebral

IS = intraspinal

TC = tissue culture

MK = monkey kidney

Fig. 2. Passage History of Fox Virus (Type III): Origin of Pool 9 Seed



*Expressed in mouse lethal doses (LD₅₀) log to base 10
 IS = Intraspinal inoculum: 0.10 ml. 20 per cent chick embryo suspension
 IC = Intracerebral

Fig. 3. Passage History of MEF₁ (Type II) Virus Chick Embryo Line

tags or markers differentiate it from the naturally occurring strains.

Method of Study

Twenty-five infants delivered at the University of Minnesota Hospitals, ranging in age from four days to six months (born of mothers immunized during pregnancy with two doses of Salk vaccine given three to four weeks apart), were selected for vaccination by the oral route. Clinic and private patients comprised this group in about equal numbers. A thorough explanation of all aspects and objectives of the study was given to the parents, and written consent for vaccination of the infant was obtained from each family. Babies with high titers at birth of passively transferred poliomyelitis antibodies were chosen for vaccination in order to test the immunizing capacity of the strains used in the presence of circulating homologous antibodies and also to insure parent cooperation.

A stool specimen for virus assay and a blood sample for poliomyelitis antibody titration were obtained from each infant and from every member of his family before feeding the vaccine to the index child. Subsequent stool specimens were secured from all members of the household at weekly intervals for five to 12 consecutive weeks. After the first virus feeding, blood samples were collected from the infant and all family members at approximately three-month intervals.

The SM strain, type I virus, was administered first with $10^{4.2}$ TCD₅₀ of the virus mixed in approximately 2 oz. of nursery formula and fed to the baby in a regular three-ounce nursing bottle. Breast-fed babies were removed from the breast for this one feeding to eliminate possible neutralization of the virus by antibodies present in breast milk. To prevent fecal spread in the hospital nursery the virus was given on the day of dismissal from the hospital, usually the fifth, day of life. Three to eleven weeks later $10^{5.3}$ TCD₅₀ of type III virus (Fox strain) was given, followed in three more weeks by $10^{5.2}$ to $10^{5.5}$ PD₅₀ of type II virus (MEF₁ strain) as a 20 per cent chick embryo suspension. The three different strains were administered separately to avoid the interference phenomenon described by Koprowski⁸ and Sabin.¹³ The feeding of types III and II virus (as well as the feeding of type I in older infants) was given in the pediatric outpatient department or in the home. Parents were asked to note any reactions to the vaccination; on subsequent visits, a brief physical examination of each infant was made and abnormal symptoms exhibited by the infant after vaccination were recorded and evaluated (by M.M.S.).

Blood specimens (6 to 8 ml. each) from the infants in the study, obtained by puncturing the internal jugular vein, were collected in sterile tubes without anticoagulant; older children and adults were bled from antecubital veins. All blood and stool specimens were sent to the Minnesota State Board of Health Laboratories for antibody and virus studies. The technique used for isolating polio virus from stools and for the neutralization test for antibody titration in the serum was essentially that described previously by Martins da Silva and Syverton¹⁴ and by Syverton and others.¹⁵ The serum was separated from the clot within 24 hours after collection and kept frozen at -20° C. until tested. Quantitative assay for neutralizing antibodies in the sera was effected through use of HeLa cell cultures. Serum specimens to be tested were thawed, diluted 1:4, and heated at 56° C. for 30 minutes. Six serial four-fold dilutions (1:4 to 1:4096) were prepared with BSS (Hanks balanced salt solution). Three tubes each containing 0.15 ml. of each serum dilution were prepared. One hundred and fifty TCD₅₀ (0.15 ml.) of each poliomyelitis virus, type I (Mahoney), type II (MEF₁), and type III (Saukett) were added to each set of serum dilutions for each serum specimen and allowed to stand at room temperature for one hour. Two-tenths ml. of this virus-serum mixture was transferred to HeLa cell culture tubes and incubated at 37° C. The end point of the titration was determined by microscopic observation on the third and fourth day after inoculation, the last serum dilution showing complete protection from the cytopathic effect of the virus being taken as the end point.

RESULTS

Clinical Observations

Ten families reported slight gastrointestinal symptoms such as loose stools or occasional vomiting, or both. One mother reported infant colic. All of these lasted only one or two days, and the complaints are probably no more numerous than they would be during a comparable period with unvaccinated infants, particularly since mothers were warned to be especially observant.

Response of Vaccinated Infants

Antibody responses in the index children are shown in Table 1. In four of the 25 infants vaccinated, antibody titers to type II were not measurable before and after feeding, and hence these cases were counted as failures. A similar failure of response to vaccination by type III was observed. Of those whose antibody responses were

measurable, the geometric average of the estimated fold increase was calculated. Comparisons of the average fold increase for all three types for a group of newborns inoculated with Salk vaccine and the infants fed oral vaccine are included in this table: The result for type III oral vaccine was very good; the response to type I was at least as good for the oral as for the Salk vaccine; the antibody response to type II oral vaccine was poor. The estimation of fold increase took into account the anticipated exponential drop in antibody titer due to passive immunity. The half-life of passive poliomyelitis antibodies has been variously estimated by Streat and his associates¹⁶ as between five and eight weeks. In computing the fold increase for the reported cases an estimated half-life of five weeks was used.

Subsequently the antibody titer to type I in one of the infants did not remain measurable. A final count of those failing to respond to oral vaccination is as follows: one failed to respond to type I, four to type II, and one to type III.

Fourteen infants, vaccinated against all three types shortly after birth, demonstrated satisfactory antibody responses as measured at approximately two months of age.

TABLE 1

GEOMETRIC AVERAGE OF ESTIMATED* FOLD INCREASE IN ANTIBODY TITER
AMONG INFANTS GIVEN SALK VACCINE† AND ORAL VACCINE‡
(Number of observations in each average given in the parentheses below the average.)

	Type I	Type II	Type III
Salk	6.07 (53)	8.60 (68)	7.45 (58)
Oral	8.10 (25)	3.70 (21)	126. (24)

*This estimation took into account the expected exponential drop in passive antibody titer in infants.

†Infants had no previous immunizing experience. They received intramuscular injections, 1 ml. each, four weeks apart, of commercially available Salk vaccine.

‡Attenuated live virus poliomyelitis vaccine amounts fed included in tables.

The distribution of time intervals between feeding and the last virus isolation are given in Table 2. The results show 72 per cent, 4 per cent, and 44 per cent isolation for types I, II, and III respectively. The low recovery rate of type II virus was attributed to the use of a tissue culture technique not particularly suitable for the isolation of the noncytopathogenic type II strain.

The maximum length of time of virus multiplication in the intestinal tract for any type was seven weeks. There was no apparent

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association between the length of time the virus was present in the intestinal tract and the magnitude of the antibody rise.

TABLE 2
DISTRIBUTION OF TIME INTERVALS BETWEEN FEEDING AND THE LAST
VIRUS ISOLATIONS IN THE STOOLS OF 25 INFANTS

		Number of Infants		
		Type I	Type II	Type III
Time in Weeks	0°	7	24	14
	1	4	0	3
	2	2	1	2
	3	3	0	1
	4	3	0	2
	5	5	0	0
	6	1	0	2
	7	0	0	1
Totals		25	25	25

*Zero indicates no isolations.

Contact Infections in the Family

Of the 26 siblings involved in the study, one had been given a third Salk injection during the course of the study and was therefore excluded from the evaluation. Every mother and 22 of the siblings had received at least two injections of Salk vaccine before the initial feeding of the infant. The pre-feeding antibody status of these contacts is presented in Table 3.

TABLE 3
DISTRIBUTION OF ANTIBODY TITERS OF
25 MOTHERS AND 22 SIBLINGS OF THE FED INFANTS*

	All Three Types Less Than 4	Mixture	All Three Types Greater Than 4
Mothers	0 per cent	12 per cent	88 per cent
Siblings	4.5 per cent	50 per cent	45.5 per cent

*These were mothers and siblings who had had at least two Salk vaccine injections. Blood was taken before the index infant was fed.

Evidence concerning spread to the mother and siblings is presented in Tables 4, 5, and 6. A positive stool, or a 16-fold increase in antibody titer following feeding of the index child was considered evidence of contact infection. Using this criterion, 68 per cent of the siblings and 8 per cent of the mothers acquired contact infections to type I; 16 per cent of the siblings and none of the mothers, to

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TABLE 4
EVIDENCE OF SPREAD TO CONTACTS OF INFANTS FED $10^{4.2}$ TCD₅₀
TYPE I (SM STRAIN) VIRUS

	Siblings			Mothers		
	Virus Isolation	No Virus Isolation	Totals	Virus Isolation	No Virus Isolation	Totals
Antibody rise (at least 16-fold increase)	11	4	15	0	1	1
No antibody rise	2	8	10	1	23	24
Totals	13	12	25	1	24	25

TABLE 5
EVIDENCE OF SPREAD TO CONTACTS OF INFANTS FED $10^{5.2}$ PD₅₀
TYPE II (MEF₁ STRAIN) VIRUS

	Siblings			Mothers		
	Virus Isolation	No Virus Isolation	Totals	Virus Isolation	No Virus Isolation	Totals
Antibody rise (at least 16-fold increase)	0	4	4	0	0	0
No antibody rise	0	21	21	0	25	25
Totals	0	25	25	0	25	25

TABLE 6
EVIDENCE OF SPREAD TO CONTACTS OF INFANTS FED $10^{5.3}$ TCD₅₀
TYPE III (FOX STRAIN) VIRUS

	Siblings			Mothers		
	Virus Isolation	No Virus Isolation	Totals	Virus Isolation	No Virus Isolation	Totals
Antibody rise (at least 16-fold increase)	12	2	14	3	7	10
No antibody rise	1	10	11	1	14	15
Totals	13	12	25	4	21	25

type II, and 60 per cent of the siblings and 44 per cent of the mothers, to type III.

As the study was terminated some of the subjects with contact infection were still eliminating virus from the intestinal tract five weeks after the first isolation. This indicated an intestinal infection of at least five weeks duration, since the exact initial date of infection was unknown.

A graphic chronological representation of responses of members of two families to the three strains used in the study is given in Figures 4, 5, and 6 (pp. 144-145).

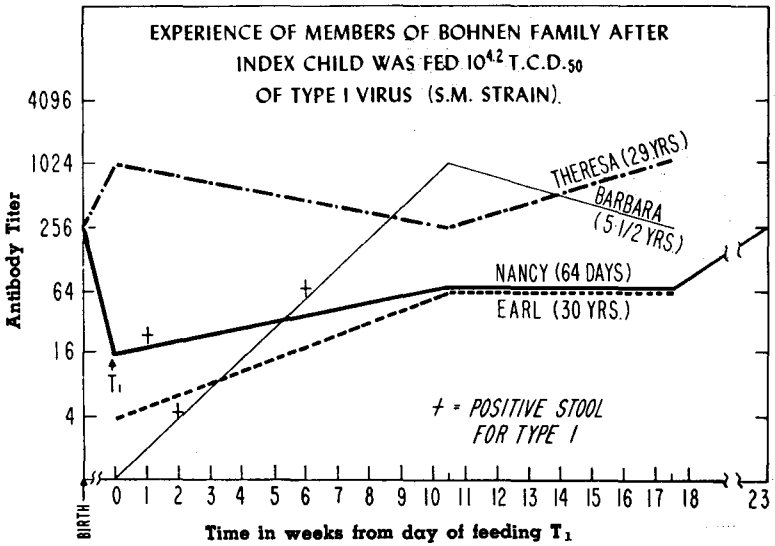


Fig. 4.

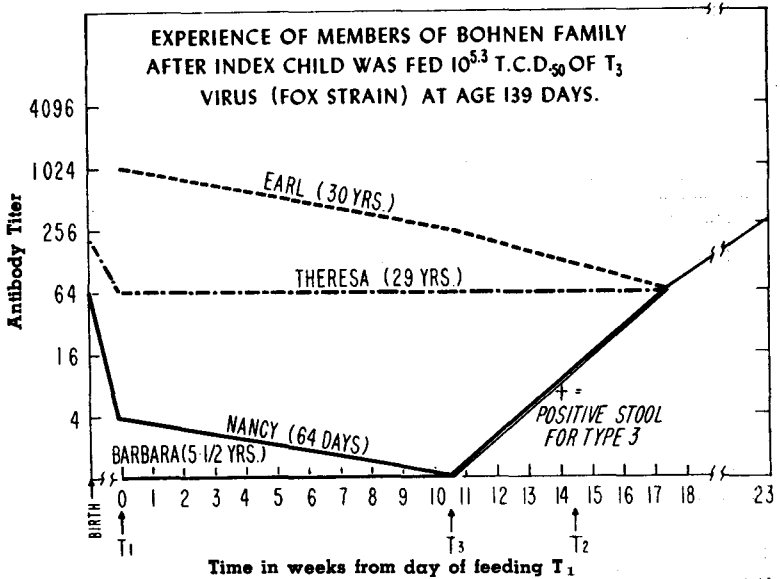


Fig. 5.

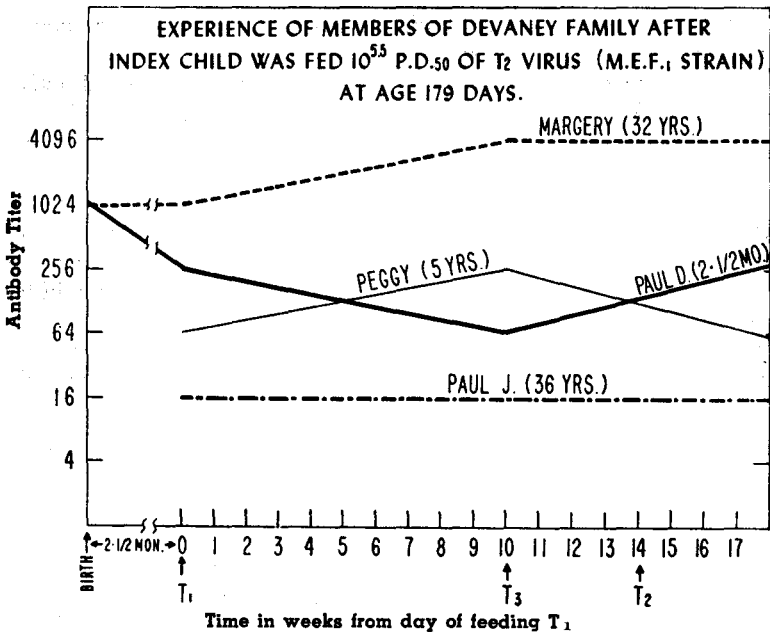


Fig. 6.

Intracerebral Activity in Monkeys of the Excreted Viruses

The stools found to be positive for polio viruses were sent to Dr. Herald R. Cox for further study. Virus was reisolated from these stools, passed through three monkey kidney tissue cultures to raise the virus titer, and 10^6 TCD₅₀ of the virus was inoculated intracerebrally in cynomolgus monkeys (0.5 ml. into the thalamic area of each hemisphere). Monkeys—four for each stool—were observed for 18 days and then sacrificed for histopathological study.

The results of these monkey tests completed to date for infants fed the type I virus are presented in Table 7, which gives the age of each infant at feeding and the interval between feeding and stool collection; the virus titers of the stool collected at this interval and the titers after three monkey kidney tissue culture passages; and the intracerebral activity (paralysis rate) of the virus after injection into the monkey. Similar results are shown in Table 8 for the contact infections. These results show no consistent enhancement of virulence with prolonged intestinal infection. The final summary of results for all isolations tested to date for type I is presented in Table 9. There was

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no evidence that a second intestinal passage had increased the neurotropism of the virus in monkeys.

Only nine stools have been tested to date for intracerebral activities in monkeys of the infected type III virus, and the results are presented in Table 10. (The histopathological examination has not been completed for these monkeys.)

Type II virus was isolated from the stool of only one vaccinated infant. One-half ml. of a 20 per cent extract of the stool of this infant injected intracerebrally into five monkeys and 0.1 ml. injected intraspinally into five monkeys produced no paralysis or significant histopathology. After the virus was passed through six consecutive monkey kidney tissue cultures, $10^{6.7}$ TCD₅₀ of virus was injected intracerebrally into each of five monkeys; one had slight paralysis of one limb.

TABLE 7
FATE OF MONKEYS INOCULATED INTRACEREBRALLY WITH 10^6 TCD₅₀*
OF VIRUS CULTURED FROM STOOLS OF INFANTS FED THE SM STRAIN OF
ATTENUATED TYPE I POLIO VIRUS
(Data supplied by Dr. Herald R. Cox)

Family No.	Name	Age (days)	Stool		TCD ₅₀ /ml. 3rd MK Passage	Result in †‡ Each Monkey
			Days Post-Feeding	TCD ₅₀ /Gm.		
1.	N.B.	64	6	5.2	8.5	0, 0, 0, 0
			6	3.7	8.0	0, 0, 0, 0
			14	3.2	8.3	0, 0, 0, 14
2.	M.B.	32	21	3.7	7.7	0, 0, 0, 15
			46	2.7	7.7	0, 0, 13, 13
			8	5.5	7.6	0, 0, 0, 0
			13	4.5	7.6	0, 0, 7, 9
3.	Ma.B.	5	22	4.5	8.5	0, 0, 0, 12**
			17	4.5	7.7	0, 0, 0, 9
			4	5.2	8.5	0, 0, 10, 10
4.	P.D.	75	14	5.5	8.3	0, 0, 0, 0
			22	2.2	7.6	0, 13, 18, 18
5.	E.H.	182	7	5.2	7.5	0, 0, 0, 10
			7	2.5	7.8	0, 0, 0, 0
6.	E.M.	53	14	3.2	8.5	0, 0, 10, 11
			7	4.5	7.5	0, 0, 0, 0
7.	B.P.	169	15	3.5	8.3	0, 7, 12, 17
			7	5.2	7.7	0, 0, 0, 0
8.	S.R.	7	13	5.5	7.7	0, 0, 0, 10**
			21	3.2	8.0	0, 0, 0, 13
			28	4.2	7.5	0, 0, 11, 12
			35	3.7	7.6	0, 0, 0, 0
9.	K.S.‡	17	8	3.5	8.5	0, 0, 0, 0**
			11	4.0	8.0	0, 0, 0, 0**
10.	M.W.	113	15	1.5	7.6	0, 0, 0, 10**
			<1:5-5.5 Range			
			7.5-8.5 Range			
			24/100 Paralyzed			

*TCD₅₀ = tissue culture dose expressed as log₁₀

†All abnormal clinical observations confirmed by histopathology, except when indicated by**

‡Numbers are incubation period (days) in paralyzed monkeys. 0 = no paralysis

§ Premature infant

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TABLE 8

FATE OF MONKEYS INJECTED INTRACEREBRALLY WITH 10^6 TCD₅₀* OF VIRUS CULTURED FROM STOOLS OF SIBLINGS OF THE CHILD FED THE SM STRAIN OF ATTENUATED TYPE I POLIO VIRUS† (Data supplied by Dr. Herald R. Cox)

Family No.	Name	Age (yrs.)	Stool		TCD ₅₀ /ml. 3rd MK Passage	Result in‡§ Each Monkey
			Days Post-Feeding	Index Child TCD ₅₀ /Gm.		
1.	E.B., Jr.	11	42	4.7	7.6	0, 0, 0, 8
			13	5.5	7.3	0, 0, 0, 13
	B.B.	5½	37	3.7	8.5	0, 0, 0, 0
			42	3.5	8.3	0, 0, 0, 0
			13	4.2	8.0	0, 0, 0, 0
			42	3.5	8.0	0, 0, 0, 0
	J.B.	4	13	4.2	8.0	0, 0, 0, 0
			42	3.5	8.0	0, 0, 0, 0
	K.B.	2½	6	3.2	7.5	0, 0, 0, 0
			15	5.5	8.3	0, 0, 0, 0
36			4.2	7.7	0, 0, 0, 0	
42			2.7	8.3	0, 0, 0, 13	
14			5.2	7.7	0, 0, 0, 0	
2.	G.B.	2	21	5.5	7.7	0, 0, 14, 14
			28	4.7	8.3	0, 0, 0, 13
			35	4.7	9.0	0, 0, 0, 0
			44	3.7	8.5	8, 8, 14, 14
			14	5.2	7.7	0, 0, 0, 0
	M.B.	4	14	4.5	8.0	0, 0, 0, 0
			21	4.2	7.5	0, 0, 0, 11
3.	M.B.	1	8	3.7	7.6	0, 0, 0, 0
			13	3.7	8.3	0, 12, 13, 17
			21	3.7	8.3	0, 0, 0, 0
			27	3.2	8.0	0, 0, 0, 0
14.	G.N.	2¾	35	5.0	8.5	0, 0, 0, 0**
15.	G.N.	2	22	5.5	8.5	0, 0, 0, 14**
			2.7-5.5 Range		7.3-9.0 Range	15/92 Paralyzed

*TCD₅₀ = tissue culture dose expressed as log₁₀

†Contact infections represent at least two intestinal passages of the virus.

‡All abnormal clinical observations confirmed by histopathology, except when indicated by**

§Numbers are incubation period (days) in paralyzed monkey. 0 = no paralysis

TABLE 9

INTRACEREBRAL VIRULENCE OF TYPE I (SM STRAIN) POLIO VIRUS TO MONKEYS AFTER ONE OR MORE INTESTINAL PASSAGE IN THE HUMAN (Data supplied by Dr. Herald R. Cox)

	Fed (one passage)	Contact (two or more passages)
No. of individuals tested	13	9
No. of stools examined	25	23
Monkey paralysis rate	24/100 (24.0 per cent)	15/92 (16.3 per cent)
No. of stools with:		
0/4 paralysis rate	10 (40 per cent)	14 (60.9 per cent)
1/4 " "	8 (32 per cent)	6 (21.7 per cent)
2/4 " "	5 (20 per cent)	1 (4.3 per cent)
3/4 " "	2 (8 per cent)	1 (4.3 per cent)
4/4 " "	0—	1 (4.3 per cent)

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TABLE 10
 FATE OF MONKEYS INJECTED INTRACEREBRALLY WITH 10^8 TCD₅₀* OF VIRUS
 CULTURED FROM STOOLS OF SIX INFANTS FED FOX STRAIN OF
 ATTENUATED TYPE III POLIO VIRUS AND ONE FAMILY CONTACT
 (Data supplied by Dr. Herald R. Cox)

Family No.	Name	Age (days)	Stool Days		TCD ₅₀ /ml. 3rd MK Passage	Result in Each Monkey†	
			Post-Feeding	TCD ₅₀ /Gm.			
3.	M.B.	44	4	4.2	8.8	0, 0, 0, 0	
			10	<1:5	8.3	0, 0, 0, 0	
			17	<1:5	7.5	0, 0, 0, 0	
5.	E.H.	254	27	<1:5	8.6	0, 0, 0, 0	
8.	S.R.	49	8	4.2	8.3	0, 0, 0, 4‡	
9.	K.S.	53	15	<1:5	8.3	0, 0, 0, 0	
11.	D.S.	47	9	4.2	8.8	0, 0, 0, 0	
12.	T.K.	44	9	5.0	7.5	0, 0, 0, 0	
					<1:5-5.0 Range	7.5-8.8 Range	1‡/32 Paralyzed
3.	M.T.B. (contact)	1 yr.	16	<1:5	8.3	0, 0, 0, 0	

*TCD₅₀ = tissue culture dose expressed as log₁₀

†0 indicates no analysis.

‡Monkey died on the fourth day after injection, presumably from something other than polio.

SUMMARY AND CONCLUSIONS

Twenty-five infants (born of mothers immunized during pregnancy with two doses of Salk vaccine given three to four weeks apart) ranging in age from four days to six months, were fed in succession living attenuated poliomyelitis virus, type I (SM strain), type III (Fox strain), and type II (MEF₁ strain) at intervals varying from three to eleven weeks. Fourteen infants, less than two weeks of age, were vaccinated against all three types of polio virus. All demonstrated a satisfactory antibody response as measured at approximately two months of age. There were no significant untoward reactions directly attributable to the administration of these strains.

The stools of these infants and of the members of their families were examined for the presence of virus before the index child received type I virus and at weekly intervals thereafter for five to twelve weeks.

Antibody titers were determined in all members of the family before and at approximately three month intervals after vaccination.

When the group vaccinated orally was compared to a similar group of infants inoculated with Salk vaccine, the antibody response to the attenuated virus was found to be as good or better for types I and III but poorer for type II.

Virus was recovered from the stool of vaccinated infants in 72 per cent, 4 per cent, and 44 per cent of infants given types I, II, and III strains respectively.

Evidence of spread to other members of the family, excluding the father, was determined by significant antibody rise or isolation of virus from the stool. These criteria showed spread to siblings to the extent of 68 per cent for type I, 16 per cent for type II, and 60 per cent for type III.

Some viruses were present in the stools for as long as seven weeks after oral vaccination, and for at least five weeks in some contact infections. The biological characteristics of the excreted viruses are being evaluated and compared with the original strains used for vaccination.

Type I virus recovered from the stools of the vaccinated infants (one passage) showed evidence of increased neurotropism in monkeys when compared to the original strain. However, there was no consistent indication that prolonged multiplication or a second passage through the human intestine further increases neurotropism.

The type III virus isolated from nine stools (including one contact) showed no increased neurotropism when compared with the vaccine strain.

The only type II isolation tested to date showed slight paralysis in one of five monkeys after intracerebral injection of large amounts of the virus.

The extent to which the general population was seeded by carriers is a possible measure of community safety for the strains used. For instance, 17 infants, 14 mothers, and nine siblings were known to be excreting large amounts of type I virus for an extended period, yet there have been no reported contact cases of poliomyelitis, despite the fact that many of these families lived under crowded conditions highly favorable for spread of the disease.

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Editorial

The Interrelationship of Postgraduate and Undergraduate Medical Education

That we believe firmly in postgraduate or continuation medical education will come as no surprise to our readers. We are convinced that the good physician will remain a student throughout his professional career and that suitable opportunities should be provided for him to do so.

But, in our opinion, the good physician is much more than a frequently seen face in the crowd at postgraduate courses. He is, first of all, a person of good intellectual capacity, sincerely motivated, idealistic, curious, imaginative. Next, he is a person whose formal medical education has provided a solid background for the development of clinical skill. Particular stress must be laid on his knowledge of the basic medical sciences. Our good physician demonstrates mastery of these subjects. These lessons must be learned during school years; it is the rare physician, indeed, who returns after graduation to acquire such knowledge in depth.

His medical school must also have taught him well how to approach clinical problems of a wide variety. Taking a meaningful history, and performing a careful, complete physical examination will be part of his nature, thanks in large measure to the efforts of his early mentors. He will have learned about the laboratory and how it can best serve him for the benefit of his patients. His concept of medicine will be broad, and he will have a full appreciation of the role of research within that concept.

With this background and training, our good physician will be a "natural" for postgraduate medical education. Not only will he attend gladly — and frequently, but he will be able to profit from his participation, to add effectively to his knowledge and skill. The physician who lacks such a background will gain from attending postgraduate courses little more than the certificates with which he can line his office walls.

R. B. H.

Coming Events

- January 6-11 Continuation Course in Ophthalmology for Specialists
- January 9 PHI DELTA EPSILON LECTURE: *Formation, Character, and Drainage of Aqueous Humor*; Dr. Hermann M. Burian, Professor of Ophthalmology, State University of Iowa College of Medicine, Iowa City; Mayo Memorial Auditorium; 11:00 a.m.
- January 9-11 Continuation Course in The Newer Drugs in General Practice
- January 30-
February 1 Continuation Course in Emergency Surgery for General Physicians
- February 6-8 Continuation Course in Cardiovascular Diseases for General Physicians
- February 10-15 Continuation Course in Neurology for General Physicians

WEEKLY CONFERENCES OF GENERAL INTEREST

Physicians Welcome

- Monday, 9:00 to 10:50 A.M. OBSTETRICS AND GYNECOLOGY
Old Nursery, Station 57
University Hospitals
- 12:30 to 1:30 P.M. PHYSIOLOGY-
PHYSIOLOGICAL CHEMISTRY
214 Millard Hall
- 4:00 to 6:00 P.M. ANESTHESIOLOGY
Classroom 100
Mayo Memorial
- Tuesday, 12:30 to 1:20 P.M. PATHOLOGY
104 Jackson Hall
- Thursday, 11:30 A.M. to 12:30 P.M. TUMOR
Todd Amphitheater
University Hospitals
- Friday, 7:45 to 9:00 A.M. PEDIATRICS
McQuarrie Pediatric Library,
1450 Mayo Memorial
- 8:00 to 10:00 A.M. NEUROLOGY
Station 50, University Hospitals
- 9:00 to 10:00 A.M. MEDICINE
Todd Amphitheater,
University Hospitals
- 1:30 to 2:30 P.M. DERMATOLOGY
Eustis Amphitheater
University Hospitals
- Saturday, 7:45 to 9:00 A.M. ORTHOPEDICS
Powell Hall Amphitheater
- 9:15 to 11:30 A.M. SURGERY
Todd Amphitheater,
University Hospitals

For detailed information concerning all conferences, seminars, and ward rounds at University Hospitals, Ancker Hospital, Minneapolis General Hospitals, and the Minneapolis Veterans Administration Hospital, write to the Editor of the BULLETIN, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minnesota.