Summary and Conclusions.

The local tissue response to implanted crystals and pellets is a typical non-specific foreign body reaction. Following the implantation of crystals of a-estradiol and a-estradiol benzoate, the tissue surrounding the crystals responds by the formation of tiny nodules. In contrast to this type of reaction, a thick avascular capsule forms about the pellets of the implanted hormone. It is important to note that the epidermis overlying the implants showed no evidence of cellular atypism and, similarly, in no instance did the subcutaneous tissues in contact with, and adjacent to, the implanted hormone show any abnormal cellular proliferation.

A significant observation which emerges from this study is the probable effect that the thick avascular capsule has on the absorption rate of the estrogenic substances employed. It was noted that the crystals had a strikingly more prolonged therapeutic and physiologic effect than the pellets composed of the same estrogenic substance and of comparable weight. It would appear, therefore, that the capsule might have a marked retarding effect on the rate of absorption of the hormone. Apparently, with the passage of time, the absorption rate is progressively diminished by the growing thickness of the capsule around the pellet. After a period of approximately 3 months, absorption is either completely stopped or so reduced as to have no demonstrable physiologic or therapeutic effect. It seems, therefore, that for purposes of implantation, pellets of a-estradiol and a-estradiol benzoate are not as efficient as crystals of the same chemical constitution.

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Portals of Entry of Poliomyelitis Virus in the Chimpanzee.*

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The lack of any direct evidence concerning the portal of entry of poliomyelitis virus in man has led to many animal experiments. The use of the resistant rhesus monkey and of "monkey strains" of virus in this problem, however, is open to the objection that the experimental conditions at the outset are widely divergent from those under which the disease takes place in human beings. A closer approxima-

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tion to the actual situation of the epidemic may be obtained by the use of human stools as a source of virus and the chimpanzee as a near substitute for man. The chimpanzee was selected for this purpose because of its phylogenetic relationship to man and because of a report by Müller[1] that during an outbreak of poliomyelitis in Cologne, Germany, 2 chimpanzees in a children's zoo apparently contracted the disease by natural contagion. One of these animals subsequently died and an examination of the central nervous system by Spielmeyer revealed lesions characteristic of poliomyelitis.

Five chimpanzees were inoculated with a pool of 7 different untreated human stools each of which had previously been found positive by intranasal inoculation into rhesus monkeys.[2] The results are briefly summarized in Table I. Three animals received large inoculations on 5 successive days by stomach tube, while the other two were given 2 cc of untreated stool intranasally and by mouth, respectively, on 3 successive days. In each instance special care was taken to exclude portals other than the one inoculated, and in the case of the last animals (A105, A106), both olfactory tracts had been sectioned intracranially 4 and 5 days previously. All animals except the first (A48, which received stool by stomach tube) contracted typical flaccid paralysis of the left arm. The animal with cut olfactory tracts which received stool by mouth had an initial right facial paralysis which later extended also to the left arm. In all, sections of the cervical cord showed heavy poliomyelitic lesions. Cord and stools from A83 and A105 reproduced the disease in rhesus monkeys. Despite the typical form of the paralysis and lesions in A71, virus could not be demonstrated in either the cord or stools. The stools and cord of A106 have not been tested for virus as yet.

The olfactory bulbs of A83 (inoculated intranasally) showed maximal perivascular cuffing, neuronophagia and cellular infiltration. In contrast to this the olfactory bulbs of A71, the normal animal receiving stool by stomach tube, showed no signs of virus invasion. There was evidence of a meningitis around the olfactory nerve fila which was in keeping with the generalized meningitis over all exposed pial surfaces of the brain. The bulbs of the animal subjected to bilateral olfactory tract section (A105) showed similar changes. There was a generalized meningitis (the spinal fluid white cell count was 900 per cu mm). There were also slight infiltrations of lympho-

[1] Müller, W., *Monatschr. f. Kinderheilk.*, 1935, **63**, 134.

[2] Howe, Howard A., and Bodian, David, *J. Infect. Dis.*, 1940, in press.

TABLE I.

Chimpanzee	Mode of inoculation (untreated stool pool)	Intranasal rhesus controls	Incubation period from day of 1st inoculation	Lesions		Cord passage
				Olf. bulbs	Spinal cord	
A48, *ca.* 5 yrs	Stomach tube, 95 cc stool pool	Prostrate	No paralysis			
A71, " 4½ "	Stomach tube, 250 cc stool pool	"	14 days, lt. arm paralysed	Neg.	4 +	Neg.
A83, " 6-7 "	Intranasal, 6 cc stool pool	"	8 days, lt. arm paralysed	4 +	4 +	Pos.
A105, " 3½ "	Olf. tracts cut, stomach tube, 235 cc stool pool	"	9 days, lt. arm paralysed	Neg.	4 +	Pos.
A106, " 3½ "	Olf. tracts cut, 6 cc stool pool by mouth	"	15 days, rt. face, lt. arm paralysed	Neg.	4 +	

cytes and losses of mitral cells which were probably the result of retrograde changes following the tract sections. The olfactory bulbs of A106 showed no inflammatory infiltrations. The completeness of the olfactory tract section in these cases rules out any possibility of virus having reached the brain by this route.[3] †

The failure of chimpanzee A48 to contract poliomyelitis cannot readily be explained, since 2 intranasal rhesus controls were paralyzed in 10 days. A period of 10 days elapsed between the first and second stomach tube inoculations of 25 cc of stool. This was a relatively small dose as compared with those given by the same method to the other animals. On the sixth day following the first inoculation the animal's temperature rose from 100.4° to 104.6° but on the next day had dropped to its former level. The animal has remained entirely well for 6 months. Whether this fever indicated an abortive attack of poliomyelitis cannot be stated. In contrast with this is the finding that A106, a younger animal, became paralyzed after receiving only 6 cc of stool by mouth. The fact that the initial paralysis was bulbar suggests the oral cavity and pharynx as a portal of lower threshold than the gastrointestinal tract.

Summary. Typical poliomyelitis has been produced in 4 chimpanzees by the intranasal, intragastric, and oral inoculation of untreated human stools. In 2 instances the olfactory portal was ruled out by section of both olfactory tracts.

[3] Brodie, M., and Elvidge, A. R., *Science*, 1934, **79**, 235; Schultz, E. W., and Gebhardt, L. P., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 728; Howe, Howard A., and Ecke, Robert S., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 125.

†Vignec, Paul and Trask's[4] feeding experiments on monkeys unfortunately do not exclude this possibility.

[4] Vignec, A. J., Paul, J. R., and Trask, J. D., PROC. SOC. EXP. BIOL. AND MED., 1939, **41**, 246.