Foundation, but so far without astonishing success. Needed is a chemical medium that prevents the cells from reverting as they do with maddening routine to a primitive, unrecognizable state.

But metabolic studies are beginning to emerge from the what-goes-in-what comes-out stage into the what-happens-inside phase.

Dr. Donald S. Layne of Canada's Food and Drug Directorate, Ottawa (a counterpart of the U.S.'s FDA), is examining changes in the chemical structure of progestins by some inherent action in the tissues that localize them (liver, kidney, and target organs).

He has found, in one study, that norethynodrel is peroxidized in the blood stream shortly after administration. "This could implicate the blood as an important site of metabolism of norethynodrel," he reported recently. "Further," he says, "the hydroperoxy intermediate has recently been shown to be as potent an ovulation inhibitor as norethynodrel itself, although it has little progesterone-like activity. This indicates that classical progestogenic action is not necessary for contraceptive action."

Work on how the steroids affect the structural chemistry of target tissue has come out of the U.S. Naval Hospital in San Diego, Calif., under Dr. Thomas B. Lebherz. His group has found, for example, that the normal bnildup of endometrium involves polymerization of acid mucopolysacharides, the so-called "ground substance" material that structurally fortifies living tissue. Such a physical framework is needed to support the thickening web of blood vessels that bring nourishment to the fertilized egg after implantation.

With progesterone, Dr. Lebherz has found, the ground substance depolymerizes, a sol state ensues, and the softened endometrium (also undergoing a phase of intense secretion) facilitates implantation of the fertilized egg. Dr. Lebherz theorizes that with oral contraceptive progestins, which in low doses apparently prevent implantation, the sol-gel effect via the acid mucopolysaccharides is thrown out of phase so that, before the sol effect sets in, the egg has already arrived and failed to implant.

FDA's Bureau of Science (now in the process of redefining its mission) is making modest efforts toward getting at some of the scientific issues that could lead to a deeper insight into mechanisms. But much of this work is preliminary and is hindered by FDA's notorious manpower shortage. Anyway, under Dr. Ernest Umberger at the Bureau of Science, scientists are beginning to look into such areas as the effects of steroids on liver enzymes, the role of receptor protein in estrogen and progesterone metabolism, and uptake of estrogen by the hypothalamus. In a study on hamster ovulation, Dr. Umberger's group has found that monoamine oxidase prevents ovulation at the hypothalamus level by blocking release of the luteinizing hormone releasing factor. Several laboratories, incidentally, have tried to characterize this factor but so far can do no better than call it a protein.

SEVEN DRUG FIRMS MARKET ORAL CONTRACEPTIVES UNDER EIGHT BRAND NAMES

| Product | Manufacturer | FDA clearance | Progestin | | Estrogen | |
|---|---|---|---|---|---|---|
| Enovid | G. D. Searle | June 1960 | Norethynodrel | 9.85 mg | Mestranol | 0.15 mg. |
| Do | do | March 1961 | do | 5 mg | do | 0.075 mg. |
| Enovid-E | do | February 1964 | do | 2.5 mg | do | 0.1 mg. |
| Ortho-Novum | Ortho pharmaceutical. | May 1962 | Norethindrone | 10 mg | do | 0.06 mg. |
| Do | do | October 1963 | do | 2 mg | do | 0.1 mg. |
| Norinyl | Syntex | March 1964 | do | 2 mg | do | 0.1 mg. |
| Norlestrin | Parke-Davis | March 1964 | Norethindrone acetate. | 2.5 mg | Ethynyl-estradiol | 0.05 mg. |
| Provest | Upjohn | August 1964 | Medorxyprogesterone acetate. | 10 mg | do | 0.05 mg. |
| Oracon [1] | Mead Johnson | April 1965 | Dimethisterone | 25 mg | do | 0.1 mg. |
| C-Quens [1] | Eli Lilly | April 1965 | Chlormadinone acetate. | 2.0 mg | Mestranol | 0.08 mg. |
| Ovulen | G. D. Searle | March 1966 | Ethynodiol diacetate. | 1 mg | do | 0.1 mg. |
| Ortho-Novum SQ.[1] | Ortho pharmaceutical. | December 1966 | Norethindrone | 2 mg | do | 0.08 mg. |
| Ortho-Novum-1 | do | February 1967 | do | 1.0 mg | do | 0.05 mg. |
| Norinyl-1 | Syntex | February 1967 | do | 1.0 mg | do | 0.05 mg. |

[1] Sequential; all others are combination type.