killed and 4% buffered glutaraldehyde was used for 30 min to fix the loop. The tissue was then finely diced and post-fixed by buffered 2% osmium tetroxide for 1 h. The blocks were then dehydrated and embedded in Epon by the usual techniques. Sections were stained with lead citrate.

Results. The epithelial cells at the distal ends of the villi (Figure 1) had numerous particles of ferritin between their long microvilli. There were occasional small invaginations at the bases of the microvilli; some of these contained ferritin. Small vesicles in the cells also sometimes contained a few molecules of ferritin. They were also present occasionally throughout the cells' membrane systems and, extracellularly, at the base and sides of the cells.

The epithelial cells near the proximal ends of the villi (Figure 2) had much less ferritin adjacent to their small and infrequent microvilli. However, in these younger cells, there were many more small invaginations – perhaps resulting from the much less pronounced terminal web. Hence there were almost as many ferritin molecules in the invaginations and small vesicles in these cells as in the more distal ones. It should be emphasized, however, that in both of these sites the amount of ferritin in the cells was very small, much less than the amount of lipid which can enter the cells.

One could tell that the ferritin was not substantially degraded by observing the micelles, present in the molecules, under high magnification.

Conclusions. A small proportion of intact protein molecules can enter adult rat jejunal epithelial cells, via small vesicles, and pass through them into the body. This presumably is the basis of intestinal allergic phenomena. CLARK's[4] results showed that the numbers of molecules which are ingested in this way are much reduced in the adult as compared with the new-born animal. However, he was incorrect in saying that none can enter in this way.

The small amount of intracellular ferritin found in these experiments also supports ROSTGAARD and BARRNETT[2] when they suggest that the passage of lipid via vesicles is relatively much less than directly through the plasma membranes of the microvilli. One cannot, of course, exclude some selective mechanism which would allow much more lipid than ferritin to enter the invaginations. However, it seems unlikely. Indeed, considering the relative sizes of the particles, ferritin should enter them more often than the lipid droplets.

Résumé. On a étudié la pénétration de la ferritine dans les cellules épithéliales du jejunum de rats adultes. Quelques molécules ont passé dans les cellules grâce aux petites vésicules. Ce processus est, peut-être, à la base de l'allergie intestinale.

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Mechanical Prerequisites for Effective Uterine Work[1]

The human uterus is continuously contracting. The contractions accomplish useful mechanical work only if the uterine cavity is sufficiently filled with an incompressible material.

Under normal conditions the intrauterine volume is a variable which influences the uterine performance. The correlation between the intrauterine volume and the uterine performance can be defined with a work diagram. As with the heart muscle[2], this diagram consists of curves for the resting tension, active pressure, and for volume output. The work diagram characterizes the uterine performance even under extreme conditions. In experiments it will be demonstrated that, as the volume is increased, a point is reached at which the prerequisites for effective uterine work are satisfied. Our studies were designed to compare the conditions for the effective work by the pregnant and by the non-pregnant human uteri.

The experiments were performed on a total of 7 pregnant and on 12 non-pregnant uteri obtained by hysterectomy. The uteri were continuously perfused through their normal vascular systems with oxygenated physiological solution containing: NaCl 8.0, KCl 0.4, $CaCl_2$ 0.2, $MgCl_2$ 0.1, $NaHCO_3$ 1.0, NaH_2PO_4 0.05, dextrose 2.0 g aqua dest. ad 1000.0 ml.

The perfusion pressure was kept constant at 200 cm water. At 37 °C the uteri survived for as long as 40 h. A thin-walled rubber balloon was filled with water and inserted into the uterine cavity. The volume of water in the balloon was increased in steps. The intrauterine resting and active pressures were recorded alternately by an electro-mechanical transducer and the volume output was estimated gravimetrically using an electronic balance. The first parameter was measured at constant volume so that the uterus was under isometric tension, and the latter one at constant pressure, i.e. under isotonic conditions. The maximal uterine contractions were induced every 5 min by intraarterial administration of 100 μg acetycholine[3].

In non-pregnant uteri the work diagram was obtained by expansion of the residual volume. Because of the resistance of the uterine muscle to stretch, the resting tension curve was relatively steep. The isometrically measured active pressure reached its maximal value with normal filling. The isotonically determined output volumes were small; they varied from 3 to 5 ml. Additional filling increase the resting pressure, but the active pressure and the output volumes were reduced. In non-pregnant uteri the mechanical work can always be obtained with the residual filling (see Figure).

In early and midterm pregnancy, a uterus containing only the products of conception does not perform any external mechanical work. However, an experimental work diagram can be constructed if the uterine volume is further expanded. Because of increased extensibility of the uterine wall the resting tension curve is considerably flatter. The isometrical work tension reaches its maximal value only with additional volume. The volumes expelled during contractions are larger than in the non-pregnant

[1] Mit Unterstützung der Deutschen Forschungsgemeinschaft.

[2] O. FRANK, Z. Biol. *32*, 370 (1895).

[3] K. H. MOSLER, Arch. Gynäk. *202*, 487 (1965).

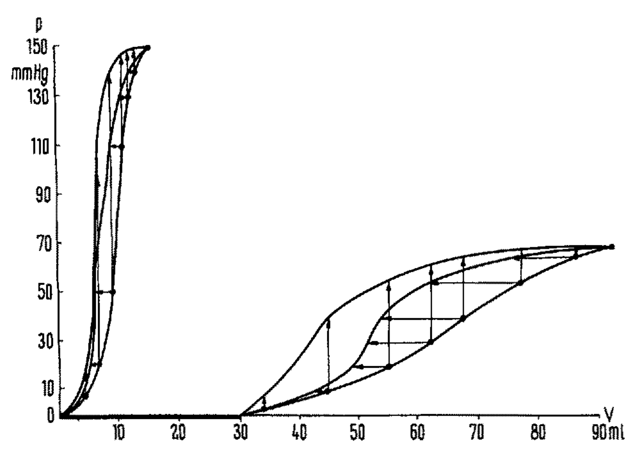
uterus. In the 2nd and 3rd months of pregnancy, they reach 15 to 20 ml and increase further as pregnancy continues. The external work of the pregnant uterus is larger than that of the non-pregnant uterus (see Figure).

Our experiments demonstrate that the simple filling of the uterine cavity of a non-pregnant uterus initiates external work. A similar condition exists also in the menstrual phase of the normal cycle or in the presence of a submucous myoma or endometrial polyps: the uterus tries to expell its contents[4].

Our experimental findings on uteri from the 2nd, 3rd, 6th and 8th months of pregnancy indicate that the intrauterine volumes are not large enough to perform external mechanical work. Only after an increase of its volume is a work diagram obtainable. There exists, therefore, during normal pregnancy a natural defence mechanism against the premature delivery[4].

Under pathological conditions, a rapidly growing intrauterine volume leads to a premature expulsion of the uterine contents. Abortion is associated with an increase of this volume caused by intrauterine bleeding. A hydatidiform mole grows more rapidly than a normal pregnancy, and is usually expelled early. Multiple pregnancy or polyhydramnios often leads to premature delivery. In pregnant but otherwise normal women, abortions can be induced by infusions of isotonic or hypertonic solutions into the uterine cavity. The size of the required infusion volume is dependent on the duration of the pregnancy and increases with the diameter of the uterus. The larger the diameter of the uterus – as any spherical vessel – the greater volume is required to cause a unit increase in wall tension.

In our study of uterine mechanics, the tension of the wall is the important factor in controlling uterine activity. We are assuming that the uterus at term is at the optimal working conditions for the given volume of the products of conception. At this point the tension of the uterine wall reaches its maximal value. The relationship between the uterine diameter, the intrauterine pressure and the tension of the uterine wall can be calculated with the



Work diagrams of human uteri. On the left is shown the diagram of a non-pregnant, and on the right, of an 8 weeks pregnant uterus. The baseline represents resting pressure as related to the corresponding intrauterine volumes (Ruhedehnungskurve). The vertical arrows represent the active pressure (isometrische Maxima). The horizontal arrows represent the volume output (isotonische Maxima). The curve indicates that the pregnant human uterus performs mechanical work only if the intrauterine volume exceeds the corresponding volume of the product of conception, 30 ml in this case. The spontaneous active pressure – not shown in this curve – is very small. It amounts to approximately 25% of the induced active pressures.

equation of LAPLACE if it is assumed that the uterus resembles a sphere:

$$T = \frac{r}{2} \cdot p \text{ [dyn/cm]}.$$

According to this equation, the tension of the uterine wall increases both with an increase in the intrauterine pressure and with the radius of the uterus. In pregnancy the resting pressure is constant at a low level. Therefore the wall tension is directly proportional to the increasing radius of the uterus[4]. At the end of pregnancy, the increasing resting pressure exerts an additional influence. At this time, the uterine wall undergoes structural changes, and the individual muscle fibres reach their optimal tension for shortening[4].

It can be demonstrated that as the volume is varied the dynamics of the uterine muscle are changed. If the volume is increased in any stage of pregnancy, a point is reached at which maximal external work can be done. Furthermore, the changing volume may influence the efficiency of this organ in the following manner. With the gradually expanding volume (increasing radius and/or pressure) the tension of uterine wall is increased (LAPLACE). The muscle fibres of the uterine wall will be stretched[4]. It is known that changes in the tension of smooth muscle alter the electrical properties of the cell membrane: its excitability is increased[5]. Both the spontaneous electrical and mechanical activity of the uterine muscle are enhanced. The spontaneous contractions become more frequent; this is associated with an improvement of the efficiency of the muscle, as indicated by an increase in the volume output per unit of time[4].

From the mechanical aspect it appears that the spontaneous onset of labour occurs only if a critical tension of the uterine wall is exceeded by the additional filling of the uterine cavity beyond its normal capacity at any given stage of the pregnancy. The pregnant uterus filled only with the volume of the products of conception does perform intrinsic but no external mechanical work. In this uterus a further increase of the volume is needed for effective work. Normally this point is reached by the active growth of the products of conception. At the same time the wall tension is at its optimum; hence activity is induced by muscle stretch. Only if these 2 mechanical prerequisites are simultaneously met can active labour begin, and the effective expulsion of the uterine contents be achieved.

Zusammenfassung. Von ganzen überlebenden Uteri des Menschen werden Arbeitsdiagramme gewonnen. Der nichtgravide Uterus leistet schon mit dem Residualvolumen äussere Arbeit, während der gravide Uterus mit dem gegebenen Fruchtvolumen nur Verformungsarbeit leisten kann. Das für den graviden Uterus jeweils zu geringe Volumen stellt einen natürlichen Mechanismus zur Erhaltung der Schwangerschaft dar. Die Geburt beginnt, wenn eine kritische Uteruswandspannung überschritten wird. Die Verformungsarbeit geht dann kontinuierlich in äussere Arbeit über.

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26. Januar 1967.

[4] K. H. MOSLER, Habilitationsschrift med. Fakult. Universität Würzburg (1965).

[5] E. BÜLBRING, Pflügers Arch. ges. Physiol. *1*, 273 (1961).

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