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Experimental Studies on the Regenerative Process of Rabbit-caecum

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Abstract

After the experimental removal of the most part of caecum of rabbit, when it is bred over 100 days, the remained portion of the caecum is enlarged distinctly and not only the spiral plicae increases its number but it is partly formed a peculiar caecal-dilatation, projecting against the colon-side. The muscular layer of caecum-wall is generally thickened, especially the epithelium is markedly proliferated. This is a regenerative phenomenon on the caecum of which damaged portion is to be filled and partly regains the characteristic shape of caecum and at the same time shows the systematical changes on the whole caecum-tissue. Consequently it may be admitted that these changes are not merely the regeneration of tissue of caecum but it is a regenerative process as an organ. However, literature on this subject hold the same view that each tissue of intestinal canals of mammalia is independently regenerated but the regeneration of an organ is not acknowledged. Korschelt states in his book that " Die ausgebildeten Wirbeltiere zeigen keine eigentliche Regeneration der einzelnen Abschnitte des Darmkanals. Wenn von einer solchen die Rede ist, handelt es sich nur um den Ersatz von Teilen der Schleimhaut, die sowohl im Magen, wie in den darauffolgenden Darmpartien stattfindet . . . ". On the other hand, the fact shown by my experimental results on mammalia such as rabbit, proved the regenerative process of intestinal canals, and I believe that it is a new information which overthrows the old established view. On the subject of caecumregeneration, Schmalhausen and others have alreacly pointed out that the morphotgenesis of the regenerated organ or tissue is closely connected with the function or its mechanical element, and in case of the regenerative process of rabbit-caecum, its functional relation is undoubtedly the important factor. There are many theories on the caecum-function and caecum of herbivorous animal such as rabbit plays an important role on the digestion and resorption of cellulose as it has been hitherto marked by Tullberg Ustjnzezw Elllenberger and others. Any herbivorcus animal which takes food which is rich with cellulose, posseses the large caecum, and it is a well known fact that Such food taken is stored in the caecum for a long while and sufficient liquid and putrefactive action decompose the cellulose and completely digests. The remained portion of the excised caecum of rabbit partly regains its peculiar cul-de-sac which is physiologically formed as above described, and at least it may be said that the anatomical structure of caecum in which the intestinal contents isolated from the main intestinal canals is stored for a long while which signifies an importance of its function and again a part of the morphological changes in caecum-regeneration is probably a functional adaptation concerning the digestion and resorption of cellulose. Among the intestinal-tissues, the mucous membrane manifests most distinctly its regenerative activity and

also the epithelium of mucous membrane on the originally remained portion of caecum is remarkably proliferated. Thus the defect of the caecum-tisseue is compensated by the hypertrophy. Such proliferation is not observed in all the intestinal canals except the caecum alone. Therefore, the epithelium of the caecum appears to monopolize this special function which the small intestines and colon are unable to compensate.

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Introduction.

It is well acknowledged that the tissues of mammalia such as epithelium, connective tissue, osteogenetic tissue, etc., possess the remarkable regenerative activity but the activity of various organs as a whole is little recognized and limited to a certain extent. Although numerous literature hitherto are found as to the regenerative phenomenon of each tissue of the mucous membrane or muscular layer of intestinal canals of mammalia, that of the regeneration of the intestinal canal itself as organ is quite rarely seen. It is, howerer, a well known fact that the wound of the intestinal canal of human-being or mammalia carries out a particular process of healing. When both ends of the intestinal canal of human-being or dog, which were operatively amputated are caecally satured, after a certain period, the both caecal canals are anastomosed and reopened. This fact was already proven by *Heller*, *Seidel*, *Tietze* and others. *Tietze* considered this phenomenon as "a complicated regenerative process", but his view is very uncertain whether the regeneration of intestinal canal was really performed or not.

Portier extirpated a vermiform appendix of rabbit and after 3 months he affirmed its regenerative phenomenon although it was opposed by *Okano* on the similar experiment. In other words except the vermiform appendix, the regeneration of any parts of intestinal canals of mammalia has not ever been observed, and the statement that "intestinal canal of higher vertebrate animal does not regenerate", seems to be an established view nowadays. On the studies of caecumfunction of rabbit, I happened to discover the remarkable regenerative phenomenon on the caecum, and by repeating systematical experiments, it was affirmed by the author that the intestinal canals, particularly, its caecum characteristically possesses regenerative activity. Such research work has not been hitherto attempted so far as the author is aware.

Method of Experiments.

A male rabbit weighted ca. 2 kg was used for the experiment. The most part of caecum and its vermiform appendix were aseptically excised and after a long breeding the remained portion of caecum was examined. The amputation of caecum was made at a point connected with sacculus rotundus near the opening of ileo-caecum, and the transitional portion from this point to colon was left only consisting of the sac-form-portion and tubular portion (transitional portion to the colon). The length of this remained caecum measured 3.5 to 5.0 cm and the number of spiral plicae was 1 to 2. The length of extirpated caecum measured 29 to 34 cm. The whole length of rabbit-caecum is usually 30 to 40 cm, and the number of spiral plicae existed to its wall is ca. 25, so that by the above operation the caecum is excised over its 90 per cent. The caecum-extirpated rabbit went almost without food for a few days after operation and after 3 days gradually began to take food a little until it reached to the normal amount. The animal, at the begining had loose bowels and passed some mucous only, but after 1 week, the excreats became a little hard and after 2 weeks restored to the normal condition. The body-weight gradually decreased and after 2 weeks it lost nearly 500 to 700 g at the maximum but afterwards it gradually recovered. The animal was fed mainly with "Tofu-kasu" made of beans. Totally 40 rabbits were extirpated their caecum for this experiment, but the majority of them died within 2 weeks after operation and are excluded here; 8 of them survived for relatively long period (51 to 400 days) and they were examined microscopically and macroscopically as to their remained portion of caecum. The material was placed into 10% solution of formol, embedded with paraffin and the sections were stained with hematoxylin-eosin and *van Gieson*'s stain.

Results of Experiment.

A. Gross-findings of the remained portion of caecum after it was excised.

The remained portion of caecum immediately after the operation presented a shortened oval globule between the ileo-caecal-opening and the colon, and the length was 3.5 to 5.0 cm. The number of its spiral plicae measured 1 to 2 as described above (Figure 1). One case which survived for 51 days after the operation exhibited tight fibrinous adhesions between the rest of extirpated caecum and the adjacent tissue, and the condition of the remained portion of caecum was not so differentiated from that of the pre-operated caecum as to its shape and

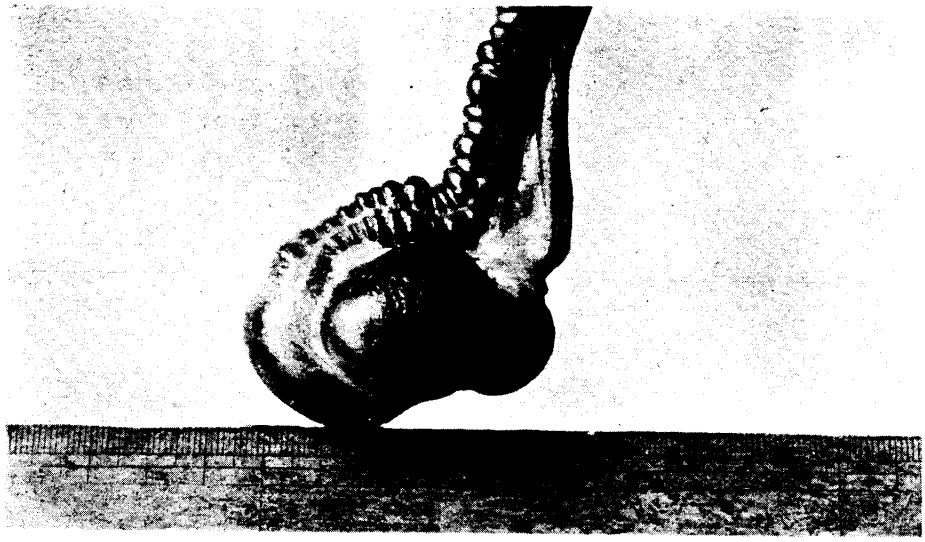

Fig. 1. The remained portion of immediately after caecum-excision.

size. However, the other case which survived for 98 days showed not only remarkable enlargement but peculiar changes on the remained portion of caecum, increasing the number of spiral plicae 3 to 5, viz., at the point of amputation, there appeared still enlarged caecal swelling, and the wall and cavity of caecum which were lost by operation regained partly (Figure 2). Its cavity was filled with brown greenish paplike

Fig. 2. The remained portion of caecum, 300 days after caecum-excision.

contents, watery and gaseous, and appeared nearly similar to that of normal caecum.

The results of the gross-findings are outlined in the following table:

Table 1.

Nos. of Cases	Nos. of animal	Sex	Body-weight		Appearance of remained portion of caecum, immediately after excision		Appearance of remained portion of caecum after long breeding				
			at the begining of operation (g)	at the time of death (g)	Length (cm)	Number of spiral plicae	Feeding days	Length (cm)	Width (cm)	Thickness (cm)	Number of spiral plicae
1	22	Male	2430	1200	4.5	2	51	5.5	—	—	2
2	14	Male	2375	2150	4.0	2	98	13.0	5.0	4.0	4
3	20	Male	2160	2020	3.5	2	100	8.0	4.0	3.0	3
4	16	Male	2150	1990	4.2	2	208	10.0	4.0	3.5	4
5	38	Male	1870	2250	3.8	2	250	12.0	4.8	3.2	5
6	40	Male	1720	2380	4.5	2	280	11.5	3.7	3.8	5
7	37	Male	1820	2600	3.5	1	300	10.0	6.0	5.8	5
8	6	Male	2260	2360	5.0	2	400	13.2	5.5	4.2	5

B. Microscopic appearances of the remained portion of caecum after it was excised.

Prior to the description of the above subject, a word on the caecum of normal rabbit will be given. The caecum of normal rabbit be generally very thin wall, and composed of 4 layers, namely mucous, submucous, muscular, and serous. The mucous membrane is covered with a single layer of columnar epithelium and mostly appears irregular superficial wavy plicae or flattened ramified, villous or convexed processes. The thickness measured 0.1 to 0.2 mm. The submucous membrane is extremely thin. The thickness of muscular layer is 0.1 to 0.15 mm (Figure 3). Such condition is nearly similar at any portions of

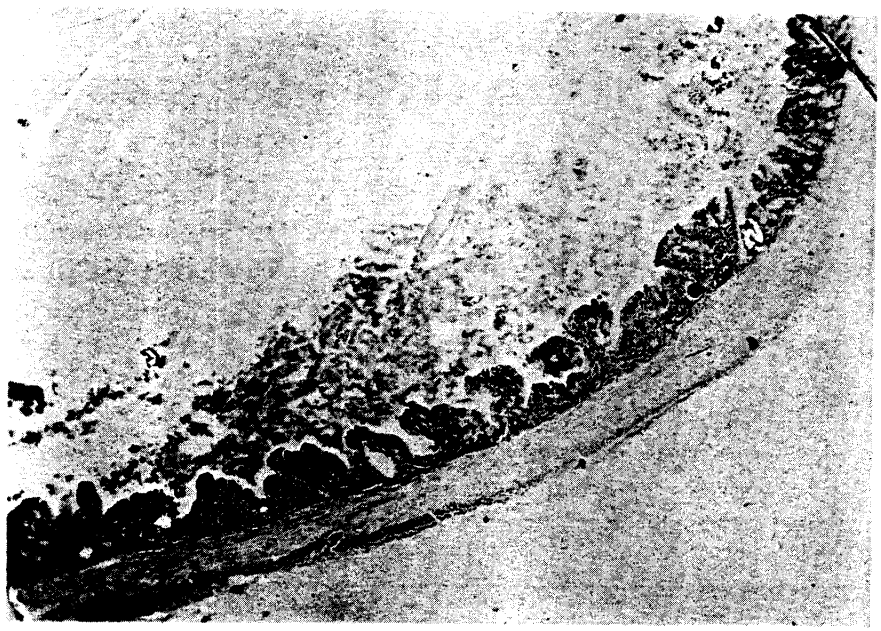

Fig. 3. Normal caecum-wall; × 34

whole caecum-wall and there is no difference even between the opening to the ileum and transitional portion to the colon. It is here excluded such rabbits as Cases 1 & 2 which died within 100 days as there is no particular appearance and such cases only those which alived over 100 days will be described in detail. The remained portion of caecum was divided into caecal-swelling-portion and originally remained portion (see previous chapter) and the latter was observed as to its sac-form-portion and tubular portion (transitional portion to colon) respectively.

Case 3 (100 days after experiment).

a. Caecal-swelling-portion:— The muscular layer is generally

thickened, measuring 0.6 mm, at the vicinity of cul-de-sac and 0.3 mm at the central area. Some submucous layer is projected distinctly and shows wrinkle-like appearance. The mucous membrane mostly exhibits a little flattened villous processes. Some of its tunica propria are rich of abundant and fresh hemorrhage. The epithelial cell is cylindrical and the thickness of mucous membrane is 0.25 to 0.30 mm.

b. Originally remained portion:— (1). Sac-form-portion. The thickness of muscular layer and mucous membrane is 0.4 to 0.5 mm, and 0.4 to 0.8 mm, respectively. The mucous membrane shows ramified processes remarkably. The epithelium is cylindrical and foamy, and many possess chromatin-poor-nuclei. The submucous membrane is hyperemic. The tunica propria is rich of lymphatic cells slightly sufficient. (2). Tubular portion. The thickness of muscular layer is 0.1 to 0.7 mm. The tunica propria of mucous membrane is well developed. The thickness of mucous membrane is 0.3 to 0.8 mm. It forms flattened convexed processes, villous or ramify.

Case 4 (208 days after experiment).

a. Caecal-swelling-portion:— At the point of cul-de-sac, the thickness of muscular layer is 0.3 to 0.6 mm. The mucous membrane uniformly projects villous processes and its thickness is mostly 0.25 to 0.30 mm. The tunica propria is pretty well developed and some possess remakable groups of lymphatic cells. The epithelium is cylindrical and many contain foamy chromatin-poor-nuclei. At the central area, the thickness of muscular layer is 0.3 to 0.7 mm and especially the circular muscle is thickened to 0.5 mm. The mucous membrane shows villous processes and its height reaches to 0.6 mm. The tunica propria is relatively poorly seated.

b. Originally remained portion:— (1). Sac-form-portion. The thickness of muscular layer is 0.3 to 0.7 mm. The mucous membrane shows convexed or villous processes and its height mostly reaches from 0.25 to 0.30 mm. The tunica propria is relatively poorly developed and is covered with a single layer of columnar epithelium. (2). Tubular portion. The thickness of muscular layer is 0.2 to 0.7 mm. The mucous membrane is poorly exhibited its tunica propria and in contact with the muscular layer, some are arranged with a single layer of columnar epithelium and among them villous or ramified processes are observed and are generally measured 0.3 to 0.5 mm.

Case 5 (250 days after experiment).

a. Caecal-swelling-portion:— At the point of cul-de-sac, the thickness of muscular layer is 0.4 to 0.8 mm and this mucous membrane exhibits slender villous or ramified processes. The development of crypts is distinct. Remarkably grouped lymphatic cells are seen in

some places. The mucous membrane is covered with higher columnar epithelium and its height is generally 0.4 to 0.7 mm. The development of tunica propria of mucous membrane is not distinct and in some places it is edematous. At the central area, the thickness of muscular layer measured 0.25 to 0.30 mm. The mucous membrane is rather minutely villous and its height is 0.3 to 0.7 mm. The tunica propria is poorly developed and mostly delicate but also seen slightly edematous portion. The epithelium is a single layer of higher columnar epithelium and shows remarkable development of crypts.

b. Originally remained portion:— (1). Sac-form-portion. The thickness of muscular layer is 0.2 to 0.3 mm. The mucous membrane generally shows only slightly flattened villous or convexed processes and its height is 0.2 mm. The tunica propria is poor and crypts are also very few. (2). Tubular portion. The thickness of muscular layer measures 0.2 to 0.3 mm. The mucous membrane shows very minute ramified processes. The development of tunica propria and crypts is remarkable. It is covered with slightly flattened single layer of columnar epithelium.

Case 6 (280 days after experiment).

a. Caecal-swelling-portion:— At the cul-de-sac, the thickness of muscular layer is 0.2 to 0.3 mm. The mucous membrane shows flattened convexed or villous processes and its elevation is 0.2 to 0.5 mm. The tunica propria is pretty well developed. The epithelium is higher cylindrical but mostly contains chromatin-rich-nuclei. The development of crypts is remarkably poor. At the central area, the thickness of muscular layer measures 0.2 mm, and the tunica propria of mucous membrane is poorly formed, showing convexed or villous processes and its elevation is 0.2 to 0.4 mm. The development of crypts is relatively poor.

b. Originally remained portion:— (1). Sac-form-portion. The thickness of muscular layer is 0.3 mm. The tunica propria of mucous membrane shows poor and loose villous processes and it is mostly 0.3 to 0.4 mm in elevation. The epithelium is higher cylindrical and the development of crypts is not distinct. (2). Tubular portion. The muscular layer is 0.2 to 0.5 mm in thickness. The tunica propria is rather remarkably developed and is convexed, villous or ramified. Its thickness reaches from 0.5 to 0.7 mm. Some are strongly grouped with lymphatic cells. The epithelium is higher cylindrical and the development of crypts is distinct.

Case 7 (300 days after experiment).

a. Caecal-swelling-portion (Figure 4):— At the cul-de-sac, the thickness of muscular layer is 0.3 to 0.5 mm. The tunica propria of mucous membrane is well developed and projected villously and ramifiedly. Its height is generally 0.4 to 0.7 mm, but some reach from

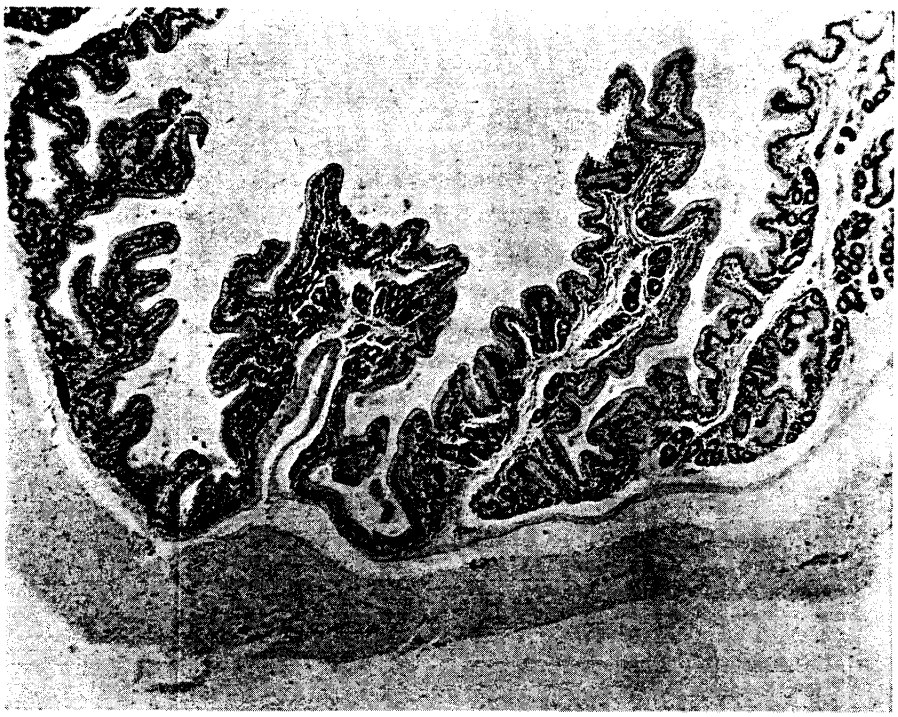

Fig. 4. The proliferation of mucous membrane on the regenerated portion of caecum, 300 days after caecum-excision; × 34.

1.2 to 1.7 mm. It is mostly very dense and the appearance of lymphatic cells is relatively noticeable and some are remarkably edematous. The epithelium is higher cylindrical and some possess vesicular nuclei or slender and dense nuclei. The goblet-cells are observed there occasionally. The development of crypts is very distinct. At the central area, the muscular layer is 0.4 to 0.6 mm in height. The tunica propria and submucosa are remarkably edematous and exhibit irregular and flattened villous or ramified processes. There is also seen a large protuberance of mucous membrane which is formed by projecting the wrinkled submucous membrane and it reaches to 1.8 mm in elevation. The rest of the mucous membrane is generally 0.3 to 0.5 mm in elevation. The epithelial cell is a little flattened cylindrical and the development of crypts is good.

b. Originally remained portion:— (1). Sac-form-portion. The thickness of muscular layer is 0.3 to 0.6 mm. Some of the submucous membrane are strongly edematous. The tunica propria of mucous membrane is partly edematous but mostly shows dense villous or ramified processes. The elevation of mucous membrane is generally 0.3 to 0.6 mm. The epithelium is mostly a little flattened cylindrical and

the crypts are developed but weaker than the other portion. (2). Tubular portion (Figure 5). The thickness of muscular layer is 0.3 to

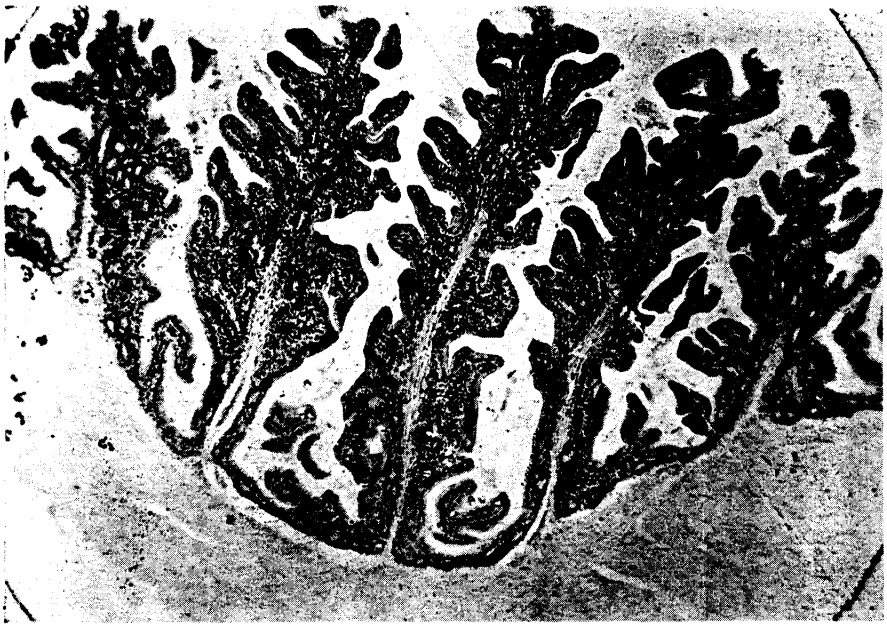

Fig. 5. The proliferation of mucous membrane on the originally remained portion; × 34.

0.7 mm. The submucous membrane is pretty well developed, wrinkled and projected into the cavity. Its elevation reaches to ca. 1.3 mm. The tunica propria of mucous membrane is well developed, especially at the wrinkled part of submucous membrane above mentioned. The elevation of mucous membrane is mostly 0.4 to 0.7 mm. The epithelium is formed of a little flattened cylindrical cells and the crypts are very well developed.

Case 8 (400 days after experiment).

a. Caecal-swelling-portion :— The thickness of muscular layer is 0.3 mm. The tunica propria of mucous membrane shows convexed or villous processes. The elevation of mucous membrane is 0.2 to 0.3 mm. The epithelium is rich with chromatin and dense nuclei. The crypts are relatively well developed. The thickness of muscular layer at the central area is 0.3 to 0.5 mm. The mucous membrane shows villous processes and its elevation is mostly 0.3 mm. The tunica propria is relatively well developed and the groups of lymphatic cells are observed. The crypts are poorly developed.

b. Originally remained portion :— (1). Sac-form-portion. The thickness of muscular layer is 0.3 mm. The mucous membrane mostly

shows villous and ramified processes and its elevation is 0.3 to 0.5 mm. The tunica propria is scanty, and the crypts are also very few. (2). Tubular portion. The thickness of muscular layer is 0.2 to 0.5 mm. The submucous membrane is well developed and partly wrinkled. The mucous membrane is very complicately remified. There are many lymphatic-cell-groups. The crypts are well developed.

Summarizing the appearance of the above cases, the conditions of the caecum-wall are more or less different to some extent although both of caecal-swelling-portion and originally remained portion are nearly similar, viz., the both of mucous membrane and muscular layer are remarkably thickened and the most of them are nearly 3 times thicker than those of normal rabbit-caecum-wall. Generally, the mucous membrane shows remarkably complicated and enlarged villous or ramified processes. The epithelium is rich with the crypts and the proliferation of epithelial cells is distinct. Still, no abnormality is discovered in the mucous membrane of small intestinal canals and colon nor regeneration of vermiform appendix-tissue.

Summary and Discussion.

After the experimental removal of the most part of caecum of rabbit, when it is bred over 100 days, the remained portion of the caecum is enlarged distinctly and not only the spiral plicae increases its number but it is partly formed a peculiar caecal-dilatation, projecting against the colon-side. The muscular layer of caecum-wall is generally thickened, especially the epithelium is markedly proliferated. This is a regenerative phenomenon on the caecum of which damaged portion is to be filled and partly regains the characteristic shape of caecum and at the same time shows the systematical changes on the whole caecum-tissue. Consequently it may be admitted that these changes are not merely the regeneration of tissue of caecum but it is a regenerative process as an organ. However, literature on this subject hold the same view that each tissue of intestinal canals of mammalia is independently regenerated but the regeneration of an organ is not acknowledged. *Korschelt* states in his book that "Die ausgebildeten Wirbeltiere zeigen keine eigentliche Regeneration der einzelnen Abschnitte des Darmkanals. Wenn von einer solchen die Rede ist, handelt es sich nur um den Ersatz von Teilen der Schleimhaut, die sowohl im Magen, wie in den darauffolgenden Darmpartien stattfindet ...". On the other hand, the fact shown by my experimental results on mammalia such as rabbit proved the regenerative process of intestinal canals, and I believe that it is a new information

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Conclusions.

1. When the large portion of caecum of rabbit is experimentally removed, the remained portion of caecum partly regains its peculiar form and the mucous membrane is remarkably proliferated and the muscular layer is thickened.

2. The rabbit-caecum possesses the regenerative activity as an organ.

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