REPORTS

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REPORT ON THE PATHOLOGY OF INFANTILE MARASMUS.

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PROGRESSIVE wasting of the tissues of the body in infancy may be due to many different causes. In some cases the symptom arises from some constitutional affection, such as rickets or syphilis. In other instances tuberculosis is directly responsible for the loss of flesh; while in others, again, actual want of food, or starvation, is the sole cause of the emaciation. But perhaps the most interesting variety of infantile atrophy is that which ensues from the habitual administration of certain deleterious substances, misnamed "foods," which from their chemical composition are incapable of adequate digestion and absorption by the immature digestive apparatus of the child, and not only fail to supply the amount of nutriment required by the growing tissues, but by exciting an insidious disease of the alimentary tract effectually prevent the beneficial results which might be expected to accrue from remedial treatment.

It is with this latter form of the complaint, which is so extremely common among the children of the poor as to constitute the bulk of the cases attending the outpatient department of a children's hospital, that the few remarks I have to make are immediately concerned.

Parrot, in his monograph upon *Athrepsie*, was the first to describe the microscopical features presented by the stomach and intestines in infants who had succumbed from progressive emaciation. Since the appearance of that work several writers have confirmed and amplified the statements of Parrot concerning the existence of catarrhal changes in the mucous membrane of the intestines, and at least one modern authority upon diseases of children (Ashby and Wright) appears to have discarded the objectionable title of *Infantile Atrophy* in favour of the more appropriate designation of chronic gastro-intestinal catarrh. It is with a view of showing that in most cases of the so-called "simple atrophy" or "marasmus" of infancy an organic and often incurable lesion of the alimentary canal is responsible for the failure of nutrition, that the following paper has been compiled.

The description of the histological appearances of the various tissues is based upon an examination of 16 fatal cases of the disease which have come under the notice of the writer during the last three or four years.

General Appearances.—In every instance the stomach shows signs of dilatation when examined after death, and in many cases the lower border of the organ is found to extend below the level of the umbilicus. When the stomach is opened and cleansed from the thick layer of mucus which covers its inner surface, the mucous membrane is found to present a dead white and opaque appearance, and to be more firmly adherent to the subjacent tissues than under normal circumstances. In very chronic cases, where the body exhibits an extreme degree of emaciation, the coats of the viscus are often so remarkably thin and transparent as to closely resemble tissue-paper in appearance. In the majority of the cases where the microscope demonstrates the existence of severe inflammation, the macroscopic signs of the disease are either entirely wanting, or, at most, consist of a little patchy congestion in the fundus of the organ. Occasionally, however, the surface of the mucous membrane presents a brownish or slate-coloured tinge from chronic congestion, or minute hæmorrhages from the same cause may be observed in the region of the lesser curvature. Only in rare cases can

a form of rudimentary mamillation be detected in the pyloric region. As a rule the intestines are collapsed and empty, but in some cases the transverse and descending portions of the larger bowel may be found to be distended with gas. The naked-eye appearances of the mucous membrane of the small intestine closely resemble those already described, but occasionally an irregular and superficial form of ulceration is present in the lower end of the ileum just above the valve. The most characteristic feature in the large intestine consists of small patches of brown pigment, which, by the help of a lens, are seen to be composed of a large number of discrete spots of pigment situated in the superficial portions of the mucous membrane. Follicular ulceration of the mucous membrane is observed in about 62 per cent. of the cases, the disease being usually situated in the transverse and descending colon and in the rectum. With the exception of certain secondary phenomena, like bronchopneumonia and congestion of the lungs or meninges, no other noteworthy appearances are worthy of special notice in the other tissues of the body at the necropsy.

Legendre was the first to show that fatty degeneration of the liver is a frequent result of chronic diarrhoea in children. This condition was observed in 3 out of the 16 cases to which allusion has been made, but in these the morbid appearance was almost entirely confined to the cells situated at the circumference of the lobules. Owing to the stress which has been laid upon the occurrence of nephritis as a complication of chronic gastro-intestinal catarrh in infancy, the kidneys of the various cases were also submitted to careful microscopical examination, with the result that in only one instance were any changes of a catarrhal nature observed in the renal epithelium. In 2 cases fatty degeneration of the epithelium of the convolute tubules was observed, and in 4 cases the uratic infarcts described by Parrot were also detected. In 1 case slight fatty degeneration of the muscular papillares and of the tissue of the left ventricle was noted.

Microscopical Appearances.—In every one of the 16 cases examined changes of an inflammatory nature were observed in the mucous membrane of the stomach and intestines, although in many instances the symptoms which are supposed to accompany chronic catarrh of the digestive organs were but little in evidence during life.

Stomach.—The first sign of the disease in the stomach consists of an infiltration of small round cells into the interstitial connective tissue immediately beneath the superficial epithelium, and around the mouths of the ducts. This exudation gradually increases in amount, and extends in the direction of the muscularis mucosæ until the spaces between the gastric glands become closely packed with deeply staining nuclei, among which the original connective tissue elements can often be discerned in a state of active proliferation. The columnar epithelium which normally covers the surface of the mucous membrane undergoes a series of changes as the disease progresses, the cells being at first converted into goblet cells, and afterwards becoming granular and shrunken preparatory to being detached from their basement membrane. The engorgement of the capillaries which ramify in the mucous membrane tends to increase the pressure already exerted upon the gastric glands, so that the tubules often appear twisted or displaced, and their outlines obscured. The solitary lymphatic glands undergo a considerable increase in size, and tend to encroach upon the free surface of the mucous membrane. (Fig. 2.)

The second stage of the process is characterised by the gradual organisation of the inflammatory products effused into the interstitial tissue. The surface of the mucous membrane now exhibits a jagged and uneven appearance owing to the irregular contraction of the newly-formed fibrous tissue, while instead of pursuing a straight course, the tubules are seen to be distorted and their lumina occluded by detached cells and epithelial debris. The glands themselves appear to be separated from one another by bands of fibrous tissue, the density of which varies considerably at different spots. The basement membranes are thickened, and the secretory epithelium undergoes a series of changes as the result of interference with its nutrition. In the cardiac two-thirds of the organ, where the tubular glands are comparatively short and straight, the peptic cells at first proliferate in an active manner, and completely block the lumen

of the tube. At a later period they undergo fatty or other degenerative changes, so that eventually the glands become irregularly distended by the accumulation of their degenerated contents. In the pyloric region, on the other hand, where the glands are of greater length and much convoluted, the first effect of the pressure exerted upon them by the contraction of the interstitial fibrous tissue is to constrict the tubules and to retard the evacuation of their secretion. As a result of this the lower ends of the glands dilate, and eventually become converted into retention cysts, the walls of which are lined by a single layer of cubical cells. The

brane becomes the seat of an extensive cirrhosis attended by complete destruction of its glandular structures. In many cases the surface of the section presents a peculiar papillary or villous appearance, which at first glance may cause it to be mistaken for small intestine. These spurious villi are due to the accumulation of inflammatory products between the mouths of the ducts, and consist entirely of round and spindle cells along with capillary vessels of new formation. The gradual contraction of the interstitial tissue has given rise to a more or less complete atrophy of the parenchyma, so that the greater portion of the section appears to be com-

Fig. 1.—Drawing of the mucous membrane of the stomach of a healthy infant. ($\times 80$.)

submucous coat of the stomach also participates in the inflammatory disease, and presents a general engorgement of its blood vessels with a considerable increase in the number of nuclei scattered through its tissue. The muscularis mucosæ is densely infiltrated with small round cells, and in many places its contractile fibres show signs of compression

Fig. 2.—Drawing of the mucous membrane of the stomach in the first stage of chronic catarrh, showing the exudation of round cells between the gastric glands. ($\times 80$.)

by the newly formed fibrous elements. The muscular coat proper is seldom affected to any noticeable extent. (Fig. 3.) In the third and last stage of the disease the mucous mem-

Fig. 3.—Photomicrograph of the stomach in a case of marasmus, showing the formation of fibrous tissue between the glands—second stage of interstitial gastritis. ($\times 80$.)

posed of a mass of fibrous tissue in which lie embedded the remnants of such tubules as have hitherto escaped obliteration. The cirrhotic tissue is extremely vascular, and when artificially injected displays numerous newly-formed vessels, a fact which probably accounts for the absence of any notable signs of disease when the tissue is viewed with the naked eye. At this stage the muscularis mucosæ is almost com-

Fig. 4.—Photomicrograph of the stomach in a case of marasmus, showing complete cirrhosis of the mucous membrane with obliteration of the glands. Third stage of interstitial gastritis. ($\times 80$.)

pletely destroyed, and the few fibres which remain usually show signs of fatty degeneration. The submucous coat is much thickened and condensed, while the arterioles which pass obliquely upwards to supply the mucous membrane ex-

hibit sclerotic changes in their inner and middle coats, and are not infrequently obstructed by thrombi of old formation. The muscular coat of the organ is closely intersected by bands of fibrous tissue, and its fibres often appear granular and fatty (Fig. 4).

Although the whole of the organ is affected in a similar manner, the inflammatory disease is usually observed to vary in intensity at different spots. As a rule, its effects are most apparent in the region of the lesser curvature, in the neighbourhood of the pylorus. In other parts of the viscus the disease exhibits a more irregular distribution, so that it may often be observed that while the mucous membrane at one spot is already in an advanced state of cirrhosis, at another in its immediate neighbourhood the inflammatory process has only attained its second stage.

Small Intestine.—The small intestine presents the same general morbid appearances as have already been described in the case of the stomach. The vascular injection that accompanies the initial stage of the inflammatory process is associated with an infiltration of round cells into the connective tissue of the villi and into that which separates the tubular glands from one another. The columnar epithelium which covers the surface of the bowel is detached at an early period, and the villi tend to become adherent at their free extremities. Thus it happens that in many sections the surface of the mucous membrane presents a series of hoops or arches; while in others, where the contiguous villi have become united along their lateral margins, the distinctive features of the tissue are completely obliterated.

Fig. 5.—Photomicrograph of the small intestine showing obliteration of the glands as a result of chronic inflammation. ($\times 80$.)

As a rule the epithelium of Lieberkühn's glands desquamates early, and the ducts become blocked with granular and fatty plugs; but occasionally these tubular structures maintained their normal appearance until a late period of the disease. When organisation of the exudation takes place, the newly-formed fibrous tissue compresses the ducts of the gland, so that the fundi of the tubules dilate and are eventually converted into small retention cysts similar in structure to those found in the pyloric end of the stomach. (Fig. 5.)

The epithelium of Brunner's glands usually shows signs of catarrh at an early stage of the disease, the cells at first being detached from the basement membrane and afterwards undergoing fatty degeneration. Finally, when the submucous coat of the duodenum becomes involved in the inflammatory process, these convoluted glands are gradually obliterated by the contraction of the cirrhotic tissue which surrounds them.

Large Intestine.—In the large intestine the first signs of inflammation are to be observed in the middle third of the mucous membrane, and in sections made from this part of the bowel the tubular glands appear to be divided by an horizontal band of round cells. The superficial epithelium persists for a considerable length of time, so that it is by no means unusual to observe large areas of diseased tissue still covered by goblet cells or shrunken cells of columnar form. In the second stage of the disease the organisation of

the inflammatory exudation causes compression of the central portions of the glands, the ducts of which are subsequently dilated in a mechanical manner, while their blind extremities are converted into globular or flask-shaped retention cysts. (Fig. 6.)

Fig. 6.—Photomicrograph of the caecum showing the effects of chronic inflammation upon the glands of the mucous membrane. ($\times 80$.)

In the descending colon and rectum it is not unusual to find the glandular ducts occupied by opaque plugs of degenerated epithelium, which are gradually extruded from the tubules by the surrounding pressure. In the final stage of the disease, when the mucous membrane is in a state of extensive cirrhosis, numerous thin-walled vessels may be seen pursuing an irregular course through the fibrotic tissue, while here and there large sinuses appear to lie in close proximity to the surface. It is probably on account of this remarkable degree of vascularity that hæmorrhage so often takes place in cases of chronic intestinal catarrh during the act of defæcation. (Fig. 7.)

Fig. 7.—Photomicrograph of the descending colon from a case of chronic marasmus, showing partial obliteration of the glands of the mucous membrane. ($\times 80$.)

Chemical Examination of the Contents of the Stomach.—Although the stomach at birth is equipped with the physiological powers necessary to ensure the digestion of suitable milk, it does not exhibit the same degree of activity as in adult life. In order, therefore, to appreciate the changes which occur in the gastric secretion as the result of disease,

it is necessary to comprehend the manner in which the process of digestion is carried out in a healthy infant's stomach, and the variations to which it is liable under normal circumstances. It is allowed by all that hydrochloric acid is secreted by the stomach coincidentally with the introduction of its first meal, but concerning the presence of free acid in the contents of the organ many contradictory statements have been made. Thus, while certain writers affirm that the free acid is never found during the process of digestion (Einhorn), others believe that its presence can be often detected (Heubner, Wohlman, Leo).

With a view of testing this and other disputed points, a series of observations were made upon healthy children, some of whom were fed exclusively upon the breast, while others received either cow's milk or some form of farinaceous food. The same quantity of food was administered on each occasion, and after a definite interval of time the stomach was emptied and its contents submitted to chemical analysis, the methods employed being always of the same kind. In this manner a series of results were obtained which permit of the following conclusions being drawn:

1. The quantity of hydrochloric acid secreted during the course of digestion varies in the same child from day to day and from meal to meal, even when the food on each occasion is identical both in quantity and quality.

2. In healthy children at the breast the milk is found to be curdled after a residence of eight to fifteen minutes in the stomach, a result which depends upon the presence of rennet ferment in the gastric secretion.

3. The acidity of the gastric contents steadily increases during the progress of digestion, and finally attains its maximum within an hour and a-half from the commencement of the meal.

4. The average total acidity calculated as hydrochloric acid at the end of the first fifteen minutes is about 0.028 per cent.; at the end of one hour, 0.06 per cent. to 0.072 per cent.; and at the end of one hour and a-half about 0.135 per cent. It is to be noted that the usual method of filtration lessens the acidity of the gastric contents very considerably, the difference between the filtrate and the crude material often amounting to as much as 0.06 per cent.

4. Free hydrochloric acid can never be detected in the contents of the stomach until after the lapse of eighty minutes from the commencement of the meal; but it can often be found between this time and the termination of the process of digestion.

5. Pepsine and rennet are invariably present as long as the secretion contains a trace of the mineral acid.

6. Lactic and other secondary acids do not occur as normal products of digestion, and their appearance must therefore be regarded as evidence of fermentation.

7. In children who are fed upon cow's milk the total acidity is much greater than in the case of breast-fed infants (0.18 per cent., 0.195 per cent.).

8. Free hydrochloric acid can almost always be detected towards the latter end of digestion. In a large proportion of cases small quantities of lactic acid are also present.

9. In infants who are fed upon farinaceous foods the total acidity of the gastric contents is invariably diminished, and may not exceed half the normal. In many cases where a trial meal was composed of oatmeal gruel the contents of the organ extracted at the end of an hour were found to be neutral or only faintly acid to litmus paper.

10. In breast-fed infants the process of gastric digestion is usually completed and the stomach void of food at the end of an hour and a-half. In infants fed upon cow's milk from two to two hours and a-quarter usually elapse before the organ is empty.

Turning now to the peculiarities of gastric digestion in cases of chronic catarrh of the stomach, the first point to observe is the comparative stagnation which the food undergoes in the organ owing to the damage inflicted upon its mucous and muscular coats. Thus, in 8 cases where the symptoms of the complaint were stated to have existed for two to four weeks, the stomach was found to contain curdled milk from two and a-half to two and three-quarter hours after the administration of 3 ounces of milk and water. In 23 instances where the disease had existed for from six to twelve weeks the stomach was seldom empty until after the lapse of

three hours and a-quarter; while in 9 cases which exhibited a duration of more than three months the organ often contained the remnants of the meal five hours after it had been taken. In most of the very chronic cases physical examination demonstrated the existence of dilatation of the stomach. One of the principal objective features of the semidigested material extracted from the stomach is its extreme viscosity from admixture with mucus. In most cases the material is distinctly acid to litmus paper, but the tests for the presence of free hydrochloric acid invariably give a negative result. By a careful comparison of the results of a chemical examination of the contents of the stomach with the appearances presented by the mucous membrane after death, in conjunction with numerous other observations conducted upon cases of varying severity which eventually made a more or less complete recovery, the following general facts have been arrived at, and may be accepted as approximately correct.

In the first stage of the disease (Fig. 2) the contents of the stomach when extracted one hour and a-half after a test meal of milk and water, contain an excess of mucus, and possess an acid reaction. Free hydrochloric acid is uniformly absent, and the total acidity calculated as hydrochloric acid varies between 0.135 per cent. and 0.094 per cent. Uffelmann's test gives a positive reaction for the presence of lactic acid, and occasionally butyric acid can also be detected.

In the second stage of the complaint where the gastric glands are suffering compression from the organisation of the interstitial exudation, the contents of the organ still contain a large amount of mucus, and possess an acid reaction. Free hydrochloric acid is invariably wanting, and the quantity of combined acid as estimated by the process of Hehner and Seeman seldom exceeds 0.026 per cent., although the total acidity may sometimes reach 0.057 per cent., owing to the presence of secondary organic acids.

In the last stage of the disease when the mucous membrane of the stomach is in a condition of atrophy (Fig. 4), the remains of the test meal after a residence in the organ of an hour and a-half may only possess a slight degree of acidity. The secretion of mucus also fails, and the quantity of combined hydrochloric acid is too insignificant to allow of accurate estimation. The peptic ferment is deficient in quantity, but if the stomach be washed out with a dilute solution of hydrochloric acid, both it and the milk-curdling ferment can be recognised in the acid fluid.

In every case the blood deteriorates in quality during the progress of the disease, and the infants often exhibit a severe and progressive form of anæmia. An exact examination of the blood is, however, a matter of some difficulty, and the results obtained are at all times open to question, owing to the depletion of the system by the diarrhoea which usually exists. In 23 of the cases where the contents of the stomach were examined, the blood was also made the subject of investigation. In early cases, before the secretion of hydrochloric acid had undergone any permanent diminution, the red corpuscles were usually found to vary between 80 per cent. and 94 per cent., and the hæmoglobin between 65 per cent. and 78 per cent.; while in one case where the stomach after death presented a condition similar to that depicted in Fig. 3, an examination of the blood the day before death gave the percentage value of the corpuscles as 78, and that of the hæmoglobin as 66. As soon as the complaint has reached an incurable stage, both the corpuscular elements and the colouring matter of the blood diminish in quantity week by week; and in four instances where the chronicity of the primary disease, combined with severe anæmia and an absence of all digestive power on the part of the stomach appeared to indicate atrophy of the gastric mucous membrane, the final examination of the blood demonstrated the presence of from 48 per cent. to 54 per cent. of red corpuscles, and 37 per cent. to 45 per cent. of hæmoglobin. It may perhaps be added that no case was ever observed to recover in which the quantity of hæmoglobin fell below 45 per cent.

Remarks.—The observations just recorded, although comparatively few in number, and perhaps also lacking in novelty, are sufficient to illustrate several important practical points. It is usually supposed that as soon as a child has recovered from the immediate effects of chronic catarrh of its digestive organs it will rapidly and completely regain its former state of health. Far from this being

the case, however, the period of convalescence is fraught with considerable danger to life, and even in the most favourable cases is often protracted for several months, and not infrequently marked by serious relapses. Thus I find that among 100 consecutive cases of chronic gastro-intestinal catarrh in infants which have come under my care at the Evelina Hospital and elsewhere, no fewer than 24 died after the symptoms of the primary disease had apparently subsided. Of this number 13 succumbed to an attack of whooping-cough (9) or measles (4), 6 died either from broncho-pneumonia or tuberculosis, while the remaining 5 were subsequently attacked by acute intestinal catarrh, which proved rapidly fatal.

Another point of interest is to be found in the tardy and incomplete recovery which is made by some of the victims of the complaint, who remain thin and weakly for many years, and apt to suffer from attacks of subacute catarrh of the stomach or bowels from trivial causes. Even those children who apparently recover completely from the disease often exhibit a remarkably slow growth, and are apt to remain stunted in stature or backward in mental development for several years. These facts suggest a question as to how far chronic inflammation of the stomach and bowels in infancy can influence the digestive functions in adult life, and although I am not prepared as yet to answer this question in a decisive manner, there are yet a few facts in this connection which are worthy of consideration.

A few years ago, when engaged upon a microscopical examination of the digestive organs of persons who had died of various diseases, I was struck by the occasional appearance of small patches of cirrhosis in the mucous membrane of the stomach near the lesser curvature. I have since observed similar appearances in the stomachs of children whose history indicated that they had suffered from gastro-intestinal catarrh in infancy.

It has already been stated that catarrhal inflammation of the stomach seldom presents a uniform distribution, but that in certain districts, and notably in the pyloric region near the smaller curvature, the disease attains its fullest degree of development more speedily than elsewhere. And since after the second year of life the increase in the size of the stomach is chiefly confined to the fundus and along the line of the great curvature, it is obvious that should any relics of inflammatory mischief persist to adult life, they will be found in that part of the viscus which has undergone the least structural change, namely, the pyloric.

Lastly, there is a certain form of habitual dyspepsia in which the complaint invariably commences about the time that the body attains its full development. The victims of this troublesome disorder have almost always displayed an abnormally rapid growth after the age of puberty, and consequently the loss of digestive power is commonly ascribed to the phenomenon of "outgrowing the strength." But in many of these cases, at any rate, careful inquiry will elicit the fact that as a child the patient had always been puny and delicate, and had suffered severely from vomiting or diarrhoea. Putting these different facts together, it does not seem improbable that organic mischief wrought in the mucous membrane of the stomach in infancy may persist through the whole life, and exert a permanent and deleterious effect upon the functional activity of the organ should the requirements of the system expose it to exceptional strain.

The fact that the secretion of hydrochloric acid fails in cases of catarrh of the gastric mucous membrane affords a certain amount of help both in the diagnosis and prognosis of the chronic disease of infancy. In out-patient practice, where it is common to find extreme degrees of emaciation arising from criminal neglect, I have often found the stomach tube of the greatest value in checking the statements of parents and nurses, for by its help the stomach can be easily evacuated, and its contents submitted to immediate examination. Thus I have often demonstrated an absolutely empty stomach in an infant which was supposed to have recently enjoyed a full meal, or the presence in the organ of some article of adult diet the administration of which had just been strenuously denied. In these cases of starvation, also, the stomach, even when devoid of food, usually contains a small amount of fluid in which both hydrochloric acid and pepsin are present; and since the acid in a free state is seldom encountered in the

diseased condition of the organ, we have at our hand a ready method of distinguishing between cases of wasting of the body arising from want and that which results from disease. As an aid to prognosis the method is, perhaps, less valuable owing to the difficulty of performing an accurate examination of the gastric contents in ordinary practice. It may, however, be said that the reappearance of free acid in the stomach is a sure sign that, with ordinary care, the child will recover its flesh and strength. Even in those cases where free acid continues absent for a length of time, there is always hope as long as the contents of the organ after a test meal contain an excess of mucus, and possess an appreciable quantity of combined hydrochloric acid. In those chronic and severe cases, on the other hand, where the contents of the stomach hardly exhibit any acidity at all, and obvious dilatation of the organ exists with a marked diminution in the hæmoglobin of the blood, a fatal termination of the disease is the only one which can be expected.

REPORT ON INFECTION AND IMMUNITY.

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Owing to the difficulty of obtaining pure vaccine material and the impediment which at the outset confronts one when experimenting with this material, caused by the fact that practically only calves can be used for inoculation purposes, I have directed my attention to investigating the question as to whether animals which are not normally affected by a specific disease germ could not, under certain abnormal conditions, be rendered more or less susceptible. I hoped to overcome this difficulty by subjecting the animal to those general and local conditions which have been recognised as increasing the virulence of infection. I shall consider these conditions and their effects briefly under the headings of constitutional and local.

It has long been recognised that an infection may be rendered much more acute when complicated with the presence of another micro-organism. It was subsequently shown that the sterile products of other microbes could exert the same influence, and this knowledge has been taken advantage of for laboratory purposes in regaining or increasing the virulence of pathogenic micro-organisms. Thus streptococcus erysipelas when grown on our ordinary cultivation media frequently loses its pathogenicity, and as it no longer is able to give rise to reaction in rabbits, the possibility of its regaining its virulence by passage through animals is completely obviated. If, however, the rabbit receives at the same time an injection elsewhere of the sterilised products of bacillus prodigiosus or some other organism the microbe of erysipelas gives rise usually to marked local reaction at the point of inoculation, from which the organism may be easily obtained for further transmission through animals, the animal not infrequently succumbing to the disease which has thus been induced. The cultivation of the organism obtained from this first animal is now usually capable of setting up a local process in a fresh rabbit, but its power is still further increased when aided by the presence of the other microbe, the virulence of the erysipelas being also increased by this process. It has been shown that the products of quite a number of different organisms can exert this "summative" influence on the process of infection, while some well-defined chemical substances can even be used for this purpose, and these include some of our best known antiseptics. It is certain, however, that this is not a mere general constitutional influence which subjects the animal equally to all species of infection, but that it is quite specific in its working.

Thus it has been found that the products of certain microbes, when introduced into an infected animal tend to arrest the process and cure the animal, exerting what we may term a "dissipative" action as regards another pathogenic micro-organism. The explanation of this circumstance is in all probability to be ascribed to the interaction of the two sets of toxic products on the cells of the animal undergoing infection. Thus, if the effect on the cells of the sterile bacterial