EXPERIMENTAL STUDIES RELATING TO SHIP-BERI-BERI AND SCURVY.

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(Plates XVII and XVIII.)

II. ON THE ETIOLOGY OF SCURVY.

(1) **On the macroscopical alterations in the tissues of guinea-pigs which had been fed exclusively on bread, groats, and unpeeled grain.*

By experimenting with the "one-sided" diets which were used in the experiments, mentioned in the foregoing paper on polyneuritis in poultry, we found that guinea-pigs also contract a disease, and that this disease is accompanied by very characteristic changes.

These alterations however do not as a rule develop until from three to four weeks after the beginning of the experiment. Young animals, weighing less than 150—200 gms. could not be used because they died in one or two weeks, and although older guinea-pigs, especially at the beginning of our experiments, remained alive for a longer period, we frequently lost these animals within a fortnight. This happened especially when they were fed on ordinary rice. These rice-animals as well as all guinea-pigs fed on other sorts of grains which died within 14 days, will be briefly mentioned in the 3rd section of this article.

The present section of our paper deals with the 64 animals that died in 18 days or more when fed on ground or unground oats, barley, rye, or wheat and water. To these we add one animal fed on rye-bread that died in 15 days. The weight of the animals was usually 300—600 gms. Apart from two guinea-pigs fed on a mixture of oats and rye-bread, each animal received one single nutriment only.

We commence with the introductory information given in Table I.

https://doi.org/10.1017/S0022172400033623 Published online by Cambridge University Press

TABLE I.

Nutriment	Effect on pigeons	Effect on guinea-pigs	Number of examined animals	Molar teeth: Examined in number of animals	Molar teeth: Found loose in number of animals	Number of animals the osseous system of which was examined microscopically
Oats	0	Death after 22–28 days	4	4	4	4
Rye	Not examined	24–28 ,,	4	4	4	4
Wheat	0	25–29 ,,	4	4	4	4
Barley	0	26–46 ,,	7	3	3	3
Oaten groats	0	28–33 ,,	9	9	9	9
Barley groats	Death after on an average 5 weeks	21–41 ,,	13	2	2	2
Rye-bread baked with yeast	In some cases some loss of weight; but otherwise no effect after 4 months	15–46 ,,	10	6	6	9
Do. baked with baking-powder	Do.	32–37 ,,	4	0	0	3
Rye-bread baked with yeast, and oats	Not examined	27–29 ,,	2	2	2	2
Wheat-bread baked with yeast	Death after 3–3½ months	23–36 ,,	6	4	4	4
Do. baked with baking-powder	In most cases death after 30–51 days, in some cases after about 3 months	33 ,,	2	0	0	0
		Total	65	36	36	44

This table shows, that whereas only barley groats and wheat bread—or in other words certain kinds of ground grain—were observed to have a marked effect on pigeons, *the results with guinea-pigs were quite otherwise.* These animals invariably died, no matter whether the grains were ground or not. In the 65 animals, death occurred, on an average, after 30 days.

During the experiment the animals became emaciated, the corresponding total loss of weight being, on an average, 40 % of the weight at the beginning of the experiment. In some cases the weight decreased uniformly, but as a rule the animals at first lost weight, then either increased or remained unchanged for 3—14 days, and finally exhibited a definite decrease in weight during the week or so preceding death.

Moreover, these experiments afforded, in other respects, quite different results to those obtained with pigeons. In the first place it must be pointed out that the majority of the guinea-pigs exhibited, at the post-mortem, *pronounced haemorrhages.* These haemorrhages appeared most frequently in the muscles of the hind-limbs, where they sometimes infiltrated large portions of both thighs and legs. In other cases the

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haemorrhages were found only in one thigh and one leg. In the legs they appeared as a rule in the upper part of the peroneal muscles from which they often spread to the fascia round the knee-joint. In the deeper layers they could often be traced to the periosteal tissue around the epiphyseal lines of the tibia and fibula. At the same time, there were frequently to be observed haemorrhages in other muscles, particularly in the intercostal muscles around more or less numerous junctions between the ribs and their cartilages. Sometimes all the ribs were affected in this manner, and some haemorrhages in this locality were almost constant. The same observation applies to haemorrhages in the deeper muscular layers and in the periosteal tissue at the inside of the lower jaw. Finally there appeared in several cases, haemorrhages in the muscles of the fore-limbs, of the back, and of the abdomen.

In addition to these muscular haemorrhages we observed often, although far less frequently, subcutaneous haemorrhages. These also appeared, as a rule, on the hind-limbs.

In all, we noted haemorrhages of the kinds mentioned in 51 of our 65 animals (about 80 %). It is probable however that they occurred more often, because observations of those localities in which the haemorrhages appear, were not made with equal accuracy throughout the entire course of our experiments. In particular, we did not during the first period regularly seek for haemorrhages around the foremost ends of the ribs, and at the inside of the lower jaw. Yet subsequent investigations showed us that these localities are particularly instructive in this respect.

Below we further illustrate the occurrence of haemorrhages by means of some examples taken from the journal of our post-mortem examinations; but before doing so we desire to mention a number of additional points.

We observed in our animals petechiae in the skin. With one exception however (where they occurred in the skin of the abdomen) they were to be found only in the follicles of the vibrissae of the lips and muzzle. Here they seemed to be constant.

Small haemorrhages from the mucous membrane of the stomach were to be met with rather frequently. The same remark applies also to a diffuse injection—with or without bloody contents—of the small intestine, and also minute haemorrhages of its peritoneal cover. These peritoneal haemorrhages, in conjunction with a pronounced injection, were especially frequent in the duodenum. The latter in some cases

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also showed ulcers in the mucous membrane, and occasionally these had perforated and caused a peritonitis.

We also in some cases noted haemorrhages in the kidneys, the liver, the spleen, and the lungs. The two first named had in other respects a normal appearance. The spleen was usually small. Sometimes the haemorrhages were so extensive that the liver, for instance, appeared excessively anaemic. This was especially so in the case of animals fed on oaten groats.

In addition to the haemorrhages there occurred a subcutaneous oedema. This however was not frequent, and was nearly always limited in extent. It appeared, for instance, in the paws, on one or even both thighs, in the axillae or on the lower jaw. In the experiments here described we only once saw a universal anasarca. In other cases where no subcutaneous oedema could be seen, we found some oedema of the muscles.

We further found at the post-mortem, a pronounced fragility of the bones. This remark applies in several instances to the tubular bones, and repeatedly when removed from the body the upper epiphyses of one or even both humeri or tibiae, or the lower epiphyses of one or both femora, separated from the corresponding shafts. Microscopic examination proved that this was due to fractures of the shafts just below the intermediate cartilages. As will be shown in the next section of this article, we have, in other cases where no macroscopical separations of this nature took place, found microscopically smaller or larger fissures passing horizontally through the shafts just below the epiphyseal lines, but without laceration of the periosteum: or there appeared microscopical fractures of the cortical substance. We have therefore concluded that the macroscopical separations between the epiphyses and the shafts existed *intra vitam*, but that the intact periosteum kept the fractured bones *in situ*. On several occasions we were able to prove the correctness of this view at the post-mortem, for after removing the periosteum it was sometimes easy to observe that the epiphyseal ends of the ribs were fractured and separated from their cartilages in correspondence with the haemorrhages in these localities as described above. [See the 4th animal, the post-mortem of which is described in detail below. See also some of the records of the animals in Table III, section 4.] In one instance we also found after a careful preparation of both tibiae, that the upper epiphyses of these bones lay movable on the top of the shafts, and were only connected with the latter by the periosteum.

When closely examined the surface of the tubular bones was found

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to be rougher than is the case normally. This modification was especially remarkable at the surroundings of the epiphyseal lines. Here also the marrow shone through the cortical substance with a more reddish appearance than in the control animals. Sometimes we found holes, the size of a pin's head, in the cortical substance when the periosteum lay in direct contact with the marrow. The osseous *trabeculae* of the spongy substance of the long bones were, when compared with those of control animals, nearly always markedly rarefied. This was particularly noticeable when cutting through the upper ends of the tibiae.

A pronounced fragility was also repeatedly observed in the lower maxilla. In many cases the hind part of this bone fractured with remarkable ease when we attempted to remove it. Sometimes it actually crumbled between the fingers. In one instance the hind part of this bone was fractured *intra vitam* with a considerable amount of surrounding haemorrhage. Another animal showed fractures of both *rami ascendentes* just beneath the articulations. We also very often observed macroscopical defects of the osseous substance of the lower jaw. In one case its hind portion was perforated by numerous minute holes, but as a rule the defects appeared on the outer surface of the bone. The largest were the size of a hemp seed, and we further observed that in advanced cases the openings took a horse-shoe form. They corresponded to the root-tips of the molar teeth. We also frequently observed similarly situated defects in the upper maxilla. In this locality they were found at the base of the *antrum Highmori.*

Not only where these defects were pronounced, but in all cases examined in this direction, we found without a single exception more or less looseness of the molar teeth. Usually most of the molars were affected: more rarely only one or two were loose. In some instances they could with ease be removed by the fingers, and in pronounced cases after a careful preparation a gap between the teeth and the walls of their alveoli might be observed. In other words the latter had become too wide for the teeth.

On the other hand we have in only a few instances found the incisors loose. The reason probably is, that the incisors have long curved roots, and therefore do not so easily lose their hold.

Whilst discussing the teeth we may mention that they nearly always had a somewhat greenish-grey colour, whereas under normal conditions the teeth of guinea-pigs are pearly white. We also observed that in one case the pulp of a molar tooth, and in another instance

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the pulp of both incisors, could be seen through the intact enamel as a dark red substance. Microscopical examination proved that this was due to diffuse bleeding in the pulp.

As regards the gums, these also often possessed a somewhat greenish-grey tinge. In 12—that is 18 %—of our 65 animals we noted that the gums were conspicuously hyperaemic and sometimes swollen. However this remark applies only to the gums on the front of the lower—in a few cases of the upper—incisors. Occasionally we found macroscopical haemorrhages under the mucous membrane of the gums. We have however never been able to detect ulcerations of the latter, nor could we see with the naked eye, any distinct traces of blood upon the surface of the mucous membrane. (As regards the microscopical observations, see the next section.)

Subjoined we give, in illustration of the observations just described, notes on four animals examined at different periods of our investigations.

1. Animal fed on *rye-bread* (baked with yeast) and water. Weight 1st day, 442 gms., died the 34th day, weight 220 gms. Diffuse haemorrhages in the peritoneal covering of duodenum, with hyperaemia of its mucous membrane. Bloody contents in the whole colon. Diffuse haemorrhages in the muscles of both thighs—particularly in the right—with a corresponding subcutaneous oedema; haemorrhages in the upper part of the peroneal muscles on both sides. A subcutaneous haemorrhage, the size of a pea, on the back. The gums on the front of the lower incisors somewhat hyperaemic. When removed, the upper epiphyses of both tibiae separated from their shafts, and diffuse haemorrhages were discovered in the corresponding periosteum and in the surrounding muscles. Ribs, inside of lower jaw and molar teeth not examined. (Microscopically, the upper end of the shaft of the right tibia shows very extensive haemorrhagic alterations of the specific kind described in the next section. Other bones were not examined in this way.)

2. Animal fed on *wheat-bread* (baked with yeast) and water. Weight the 1st day, 480 gms., died the 25th day, weight 285 gms. Small haemorrhages in the peroneal muscles of both sides and in the muscles of both antibrachiae. Enteritis, with bloody contents throughout small intestines, as well as in colon; petechiae in the walls of the coecum. No alterations in the stomach and duodenum. All lower molars, especially the rear ones, were loose and exhibited a somewhat greenish discoloration; the same applied to the back molars on each side of the upper jaw. Diffuse haemorrhages in the periosteum at the inside and outside of the latter bone, the cortical substance of which was very thin but without distinct defects. Ribs not examined. (Microscopically the marrow of the upper end of the shaft of the right tibia and of the lower end of the shaft of the right femur showed slight specific alterations. These, however, could not be detected in the upper end of the right humerus. Other bones not examined microscopically.)

3. Animal fed on water, and *oat groats* boiled for 15 minutes in water at 100° C. Weight the 1st day, 395 gms.; died the 29th day, weight 190 gms. Subcutaneous

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and muscular haemorrhages in both legs; the lower jaw very fragile, fractured when removed; defects in its cortical substance corresponding to all the root-tips of the molar teeth. The latter, together with the incisors of both jaws all loose, and the bone somewhat discoloured. Haemorrhages between the periosteum and bone at the inside of both *rami horizontales* of the lower maxilla. Disseminated haemorrhages in the walls of the small intestines and coecum; the contents of the latter mixed with blood. Several small erosions with haemorrhages in the mucous membrane of the stomach. The lower epiphysis of one femur separated from the shaft when removed. Haemorrhages around some of the foremost ends of the ribs. (These were not examined with respect to separation from their cartilages, but showed microscopically pronounced specific alterations. So also did the upper ends of the shaft of the right tibia, and the lower end of the shaft of the right femur.)

4. Animal fed on *raw, unpeeled wheat and water*. Weight 1st day, 575 gms.; died the 26th day, weight 315 gms. Haemorrhages under the skin, in the muscles, and in the periosteum around the lower end of the left femur and the upper end of the left tibia. Diffuse subcutaneous haemorrhages on the left brachium. Small muscular haemorrhages disseminated around the lower end of the sternum. Haemorrhages in the tissue around the foremost ends of three of the right ribs; after removal of the periosteum two of them were found to be fractured and separated from their cartilages. All the lower molars on the right, and one of the back ones on the left side, were loose; so also was one back molar on each side of the upper jaw. The gums and all the teeth were somewhat greenishly discoloured. No distinct hyperaemia of the gums. On the right outside of the lower jaw and at the base of *antrum Highmori*, there were some defects of the cortical substance corresponding to the root-tips of some of the molars. Diffuse subperiosteal haemorrhages at the inside of both *rami horizontales* of the lower jaw. Diffuse hyperaemia of the small intestines and stomach, also of the duodenum, where there were also some petechiae in the peritoneal cover. (Microscopic examination of the two ribs mentioned above revealed very pronounced specific alterations. The 3rd rib gave no results. Apart from the usual atrophy of the osseous tissue the microscopical examination of the right tibia, femur and humerus gave a negative result.)

It will be seen therefore that the principal points of the observations described above were:

(1) *Haemorrhages.*

(2) *Loose teeth*, connected in several cases with a marked hyperaemia of the gums on the front of the incisors, and also in some instances with macroscopical haemorrhages under the mucous membrane of the gums.

(3) A certain *fragility of the bones*, sometimes connected with demonstrable *intra vitam* fractures at the ends of the shafts.

From these observations we were led to assume that the disease might possibly be *scurvy*. It is true that there are some differences between the latter, as usually described, and the malady of our guinea-pigs. For instance, we only noted a marked hyperaemia of the gums

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in 18 % of our animals. Yet in cases of human scurvy we do not always find affected gums. During the siege of Paris, for example, Lasègue and Legroux[1] failed to discover affected gums in one-fifth of their cases. Moreover, they point out that these patients did not show carious teeth, which are also never to be found in guinea-pigs. We may, in addition, quote the observations of Berthenson[2] concerning an epidemic of 225 cases in St Petersburg. Of these more than one half did not show any affection of the gums. We may also draw attention to the observations of W. Samson v. Himmelstiern[3], who usually failed to find affected gums during the beginning of the epidemic. Also, considering the fact that our animals, on an average, died before the expiration of one month, it is of interest to observe that G. Samson v. Himmelstiern (Looser, *l.c.*) has noticed that patients suffering from scurvy did not get affections of the gums until a comparatively late stage of the malady. However, we shall see in the following section dealing with the microscopical alterations, that the gums were much oftener affected than appeared to be the case from the macroscopical examination.

With regard to the fragility of the bones, there is no essential difference between ordinary human scurvy and the disease we have described. Several of the older writers refer to this symptom. For instance, in *The disease of London or a new discovery of scurvy*, published in London, in 1675, we find that the author, Gideon Harvey, had seen scorbutic patients whose bones were so fragile that they were liable to fracture on quite slight injuries. Looser (*l.c.*), who has written an extremely interesting paper in proof of the identity of ordinary scurvy and Barlow's disease, also gives extracts from some of the earlier works on this subject. We subjoin, from this article, the following quotation from Hoffmann:

"In this disease (*i.e.* ordinary scurvy) all bones show a great fragility. It is astonishing to hear that patients suffering from scurvy have fractured an arm when lifting it in order to remove something, or a leg when walking, neither are observations wanting to show that such accidents have happened when the patients moved in their beds. Recently we observed, at Münster, a scorbutic patient who fractured his leg, by moving in his bed."

Looser also quotes some observations of the German anatomist Fries who found it extremely difficult to prepare the skeletons of

[1] *Archives générales de médecine*, 1871, II.

[2] *Deutsches Arch. f. klin. Medicin*, 1892, vol. XLIX.

[3] Quoted by Looser, in *Jahrbuch für Kinderheilkunde*, Dec. 1905.

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individuals who had died from scurvy on account of the fragility of their bones. We may mention, further, the often quoted remarks of Poupart[1] who found at post-mortems of all scorbutic patients below the age of 18, separations of the epiphyses from the shafts. In some cases he also found fractures of the ribs at their connection with the cartilages. The same fractures have been particularly mentioned subsequently by numerous authors, who at the same time found the fractures surrounded by haemorrhages (Looser). Finally we may point out that Uskov[2] examined, in cases of ordinary scurvy, the foremost ends of the ribs. Here he found a very marked microscopical rarefaction of the solid osseous substance.

As regards these alterations, therefore, there is a marked similarity between the disease of our animals and ordinary scurvy. In one respect, however, there is a distinct difference between the two maladies. This concerns the frequency of haemorrhages.

In the first place it may be objected that, apart from the petechiae on the muzzles and lips, we observed haemorrhages in 80 % only of our animals. This objection is however insignificant because in all epidemics of scurvy there occur cases in which the patients are said to suffer from a "taint of scurvy" but without visible haemorrhages. (As shown in the official medical reports from the North American war of rebellion these patients not infrequently die suddenly.)

In the second place the objection may be raised, that apart from the above-mentioned petechiae on the muzzles and lips only one of our animals showed some few haemorrhages in the skin itself. This obstacle is however removed by a comparison of the alterations seen in our animals with those, not of ordinary scurvy, but of *Barlow's disease*, that is to say, scurvy in young children. As demonstrated, first in the excellent paper of Barlow and afterwards by many other observers—for instance by the German pathologists quoted in the next section of this paper—this form of scurvy is accompanied by the same separations of shafts and epiphyses, and by the same fragility of the bones, as we have previously described. For instance, in this disease haemorrhages appear regularly around the foremost ends of the ribs, which after removal of the periosteum are found, to a large extent, to be separated from their cartilages. We may also observe that Barlow, and subsequently other observers, found a universal rarefaction of the bone substance. There are also affections of the gums relative to the

[1] Quoted by Lind, Looser, Netter (*Semaine médicale*, 1899) and others.

[2] *Centralbl. für die medic. Wissenschaften*, 1878, vol. xvi.

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stage of dentition, and there are periosteal, muscular and subcutaneous haemorrhages. Yet in the skin itself, haemorrhages are comparatively rare in this "infantile scurvy." It is true that they were observed in 182 out of 353 cases collected by the American Pediatric Society[1], but of the 31 cases which Barlow[2] had collected in 1883, only three showed such haemorrhages. (In two of these three cases they were limited to the eyelids.)

(2) *On histological changes in guinea-pigs fed on unpeeled grains, groats, bread and milk.*

We have examined the nerves of many of the 65 animals mentioned in the foregoing section of this article and have repeatedly found many degenerated fibres in some of the finer muscular or diaphragmatic ramifications. In contrast to the experiments on pigeons which one of us has described in the foregoing article, we have, however, been able to detect a pronounced polyneuritis in two animals only. (One of them had been fed on wheat-bread baked with yeast; the other animal had been fed on barley groats, boiled ½ hour at 100° C.) These observations may possibly correspond to the doubtful cases of neuritis, which, under the name of "acrodynie," have been described as occurring in some cases of human scurvy[3]. They may also possibly correspond to the neuritis occurring in some cases of ship-beri-beri[4].

We have further, in very many cases, examined the *muscles* of the limbs. The fibres of these were to a large extent more slender than usual and many of them showed some fatty degeneration; at the same time a larger or smaller number of them were often dissolved into rows of irregular hyaline clots which did not always stain in the same way as the unaltered fibres. Between these clots there could be seen here

[1] *Medical Record*, 2nd July, 1898.

[2] *Medico-Chirurgical Transactions*, vol. XLVI., London, 1883.

[3] See the remarks concerning the epidemic of scurvy during the Crimean War in the foregoing article on polyneuritis in poultry. Such cases occurred also in the epidemic of scurvy in the siege of Paris, 1871. (Charpentier, *Étude sur le scorbut en générale, l'épidémie de* 1871 *en particulier*. Paris, Adrien Delahaye, 1871, pp. 59—62.)

[4] We may add, that very many of our animals showed, when examined microscopically, an extensive degeneration of the *axis-cylinders* of the nerves without any degeneration of the myeline sheaths. This latter phenomenon proves, that the degeneration of the axis-cylinders has occurred only a short time before death. The same degeneration also occurred frequently in the animals, which, as will be shown in the next section of this article, were fed on cabbage or fresh potatoes only. This degeneration, therefore, has no particular connection with scurvy.

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and there small accumulations of the multiplied sarcolemma-cells; but otherwise no multiplication or immigration of cells could be discovered.

There was further in several, but not in all cases, a marked *fatty degeneration of the heart* as well as of the epithelium of the mucous membrane and the glands of the stomach and intestines.

In particular we have submitted *the osseous system* of our animals to an extensive microscopical examination, because numerous microscopical examinations have proved that *infantile scurvy* presents absolutely specific alterations of the bones. Before turning to speak of our own investigations on this subject we shall briefly sum up the results of these latter researches.

Thomas Barlow[1] in his classic treatise on infantile scurvy observes: "The periosteum of the femur vascular and thickened, but without cellular infiltration; extensive haemorrhage in the deeper portions and also between the periosteum and bone; considerable absorption of the trabecular structure with large spaces showing in places slightly eroded margins."

In 1890, Thomas Fischer[2] described a case in which he found that the bone-marrow at the ends of the shafts of the long bones directly beneath the intermediary cartilage had assumed an appearance like that of gelatinous tissue and contained abundant extravasations of blood. In these localities of the long bones there also was a pronounced absorption of the bone trabeculae. He also found similar changes, but even more pronounced, in the ribs.

Afterwards there appeared a series of communications from German pathologists on microscopic examinations of the osseous system in cases of infantile scurvy. For instance, Nägeli[3], Jacobsthal[4] and Hoffmann[5], published casuistic articles on this subject, to which Schödel and Nauwerck[6], Schmorl[7] and Eugen Fränkel[8] drew attention by their

[1] *Medico-Chirurg. Transact.*, London, 1883, p. 187.

[2] *Münchner medic. Wochenschr.*, 1890, No. 36.

[3] *Centralbl. für allgem. Pathol. und pathol. Anatomie*, 1897, vol. VIII. p. 687.

[4] *Ziegler's Beiträge zur pathol. Anat.*, vol. XXVII. p. 173.

[5] *Ibid., Supplement (Festschr. für Professor Jul. Arnold)*, 1905. Other isolated cases are described by Stoos and Butzke.

[6] *Untersuch. über die Möller-Barlow'sche Krankheit.* Jena, 1900.

[7] *Centralbl. f. allgem. Pathol.* etc., 1899, vol. x. p. 834; *Ziegler's Beiträge*, 1901, vol. xxx.; *Jahrbuch für Kinderheilkunde*, January, 1907.

[8] *Fortschritte auf dem Gebiete der Röntgenstrahlen*, 1904, vol. VII. Nos. 5 & 6, 1906, vol. x. No. 1.

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searching investigations on an extended scale. The number of published cases amounted recently to a total of not quite 30.

These investigations have given the uniform result—a result that constitutes a law—that infantile scurvy is accompanied by the following alterations:

(1) The *bone-marrow* loses, in quite definite localities, its lymphoid cells. These are replaced by a reticular or fibrillated, sometimes also a homogeneous, tissue containing only a few or no osteoblasts and marrow cells; instead of the latter there appear spindle-shaped or stellated cells. As regards the blood-vessels, their number, too, is considerably reduced. In this tissue there appear often, but not always, fresh haemorrhages or blood-pigment. Because this marrow is poor in cells it does not, for instance with haematoxylin-alum, stain as well as the normal one. In stained sections it can therefore often be distinguished from the normal marrow by its palish colour ("Helles Mark" of the Germans).

This reticular, fibrillated, or homogeneous tissue is considered by the German pathologists as the remaining unchanged or somewhat altered reticular ground or "supporting" substance of the original lymphoid marrow; they therefore often call it "frame-work" or "supporting marrow" ("Gerüst-" or "Stütz-Mark"; Schödel and Nauwerck).

These alterations appear in more or less numerous tubular bones or ribs, being limited, as mentioned above, to quite definite localities of the bones; for they are limited to the zones of the *endochondral ossification*, that is to the *ossification nuclei* of *the epiphyses*, but especially to the *ends of the diaphyses*. Here the "Gerüst-Mark" is intercalated as a layer of varying thickness between the intermediate cartilages or—as regards the ribs—between the cartilages of the latter and the normal marrow of the bone. Going downwards from the upper epiphysis of a tibia, we meet first the intermediary cartilage. Next follows a layer, "Helles Mark," which often may be 1—1·5 cm. thick. Beneath the latter the marrow is again normal throughout the whole length of the bone until possibly a new layer, "Helles Mark," may appear above the lower intermediary cartilage. (See Plate XVII.)

Finally it may be mentioned that the same diseased marrow is often to be found in the Haversian canals.

(2) There appears *a defective new formation of bone with a defective apposition on that already formed, which atrophies* and is absorbed. These alterations, too, appear principally though not exclusively, in the zones of ossifications, particularly in the ends of the shafts of the tubular bones and in the foremost ends of the ribs.

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This atrophy of the bone-substance results in a pronounced rarefaction of the osseous trabeculae, while the remaining ones become slender or irregular, or appear, in microscopical sections, as isolated islets without any connection with the intermediate or—in the ribs—with the rib cartilages. With respect to the cortical substance, this too, becomes, in the same situation of the shafts, markedly reduced. Apart from macroscopical fractures, this reduction results occasionally in microscopical ones or in infractions; in places there is no cortical substance to be seen at all. Finally it may be added that the cortical substance in the ends of the shafts is often found perforated by comparatively numerous canals containing fibrillated tissue.

As the result of these alterations the bones become fragile, which fragility chiefly affects the ends of the shafts of the long bones just beneath the intermediate cartilages or—in the ribs—at their foremost ends. This is the reason why the so-called "separations of the epiphyses," that is fractures of the shafts at their epiphyseal ends, so often occur in cases of infantile scurvy.

The above-mentioned alterations have already been shortly summed up in the first of the above-mentioned articles of Schmorl. He says, that the alterations of the bones are, in infantile scurvy, characterised by an affection consisting of a defective apposition and an increased absorption. That further the marrow in the ends of the shafts of the long bones and in the ossification nuclei in the epiphyses is deprived of its lymphoid cells, which are replaced by a fibrillated tissue, which is poor in cells, blood-vessels and osteoblasts. The correctness of these observations with the supplements described above have afterwards been confirmed from all quarters. At the same time, these affections are never to be found in any other diseases of children. It follows, "that infantile scurvy is an absolutely specific disease, a disease *sui generis*" (E. Fränkel).

(3) *Alterations of the intermediate cartilages and the cartilages of the ribs.* With respect to these, the authors have found the rows of the cartilaginous cells irregularly arranged and a pronounced persistence of the zone of calcification in form of a network of trabeculae of calcified cartilage.

The alterations mentioned above apply to infantile scurvy properly speaking. With respect to older scorbutic patients, there have, hitherto, only been published very few corresponding investigations. One of

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them has been briefly described by Looser (*l.c.*). He examined the bones of a boy of 14 years, who died of sporadic scurvy, and succeeded in finding just the same alterations as those mentioned above. Another case has been very minutely described by E. Fränkel[1]. His examinations apply to a boy of 7 years, who also died of sporadic scurvy and who had been, for several months, fed almost solely on rice.

In the bones from this case, Fränkel found alterations which were absolutely identical with the affections of the osseous system in infantile scurvy; he therefore has no hesitation in declaring both diseases identical.

Being under the impression that perhaps Russian medical literature might contain publications bearing upon this subject we wrote to Professor Moissejew in St Petersburg and asked if he could give us some particulars.

He was kind enough to reply that Dr Krivoucha in St Petersburg had examined, in 1888, the bones from six cases of scurvy in adults, in which he had found: in the marrow of the tubular bones a network of fibres, the meshes of which were filled with lymphatic cells and red blood-corpuscles; in the ribs a reticular tissue, between the fibres of which there was shown lymphatic elements, red corpuscles and pigment-cells. Further he found absorption of the compact and spongy bone-substance. Though it does not appear whether these alterations were found exactly in the ends of the shafts and the ribs, their correspondence with those mentioned above is very conspicuous indeed. When we add the researches of Uskov (*l.c.*) referred to in the foregoing section, who also found, by microscopical examination of cases of ordinary scurvy, a marked absorption of the bone-substance, we therefore assume scurvy in children and adults to be accompanied by the same alterations of the osseous system.

Turning to speak of our own researches we shall briefly premise the following:

From the guinea-pigs examined we usually removed, from each animal, one or sometimes both tibiae, femora and humeri; we have also usually removed some ribs and one or both jaws with their gums. Sometimes we also examined the fibulae and scapulae. In several cases in the beginning of our examinations we only removed one tibia; or we only removed one tibia and one femur.

These bones were either completely decalcified by nitric acid or—

[1] *Fortschritte auf dem Gebiete der Röntgenstrahlen*, vol. x. 1906, No. 1.

https://doi.org/10.1017/S0022172400033623 Published online by Cambridge University Press

usually—by trichloracetic acid; or they were partly decalcified by Müller's fluid (Pommer's method). This latter process has extensively been used by the German pathologists; chiefly because there has been, to begin with, some doubt as regards a connection between infantile scurvy and rickets, the osteoid substance of which is stained, when decalcified by Müller's fluid, by means of carmine. This doubt has, however, been dissipated, rickets being proved sometimes, but by no means always, to accompany infantile scurvy. For our purpose Pommer's method has been of comparatively little use, because our animals but very rarely showed any microscopical alterations which might suggest any formation of osteoid substance. The only advantage of the method was, that it permitted a closer study of alterations in the cartilages. On the other hand, this decalcification takes a very long time: in spite of the bones of guinea-pigs being small, they as a rule could not be cut before several months.

Of the bones so prepared we have made sections, which we have stained by means of Delafield's haematoxylin or haemalum and eosin; when prepared by Pommer's method, we also used the first named stains in conjunction with carmine.

The alterations which we have found in the so prepared bones recurred with small modifications in nearly all the 45 animals which we have examined in this direction. We therefore limit ourselves to a summary of the alterations which were, for instance, to be found in a longitudinal section of the upper end of a tibia from the diseased animals.

The shaft presents a normal marrow and a nearly normal cortical substance except in the vicinity of the intermediary cartilage. Here the compact substance becomes thin and atrophied or it is often traversed by larger or smaller irregular channels filled with a fibrillar tissue which may show haemorrhages. So far may this rarefaction of the corticalis go that it here and there may be completely wanting or there remain only some few fragments of bone substance or spiculae surrounded by fibrillar tissue and haemorrhages.

It is evident that the result of this atrophy must be that the bone becomes fragile just below the intermediary cartilage. That this is so, is also proved by the fact that there often appear small microscopical fractures with extravasations of blood. Or there appear *microscopical fissures* proceeding horizontally beneath the intermediary cartilage into the spongy substance of the bone.

As a rule, however, these latter fissures are only seen in the *spongy*

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substance, being due to an atrophy of the bone trabeculae. As regards the latter, some of them are extant though to some extent atrophied and irregular. To a large extent, however, they appear as thin or irregular fragments or islets without connection with the intermediary cartilage. Finally it happens rather often that there are only few trabeculae to be seen in a comparatively great part of the section.

As regards the apposition of new-formed bone this does not seem to exist. We have, however, sometimes, but not often, seen a little new formation of osteoid substance being stained red by means of carmine in bones prepared by Pommer's method.

It is evident that this alteration, too, must contribute, to a large extent, to the result, that the bone becomes fragile just beneath the intermediary cartilage.

As regards the *marrow*, it is, in the middle of the bone, quite normal. But proceeding upwards in the section the lymphoid cells disappear or get markedly scarcer at a varying distance from the intermediary cartilage; this alteration occurs either at once or little by little. The cells are replaced either by more reticular or more fibrillated tissue containing only few or no osteoblasts and consisting of spindle-shaped or stellated cells, in the meshes of which may be seen some few remaining marrow cells and a few blood-vessels.

This tissue fills up all the cavities between the irregular bone trabeculae in the end of the shaft and may enter into the intermediary cartilage. In some cases it only appears in some sections, but not in others. Or we found it only beneath some but not beneath all portions of the intermediary cartilage. When this happened, we have repeatedly been surprised to see that the atrophy of the bone trabeculae did not always correspond to the degeneration of the marrow. Very atrophied trabeculae might appear in a normal marrow and *vice versa*; a very pronouncedly degenerated marrow might include apparently well-formed trabeculae.

However, in general, this degenerated marrow appears as a continual layer beneath the whole cartilage. As a rule, it extends 1—2 mm. downwards from the latter, differing, not only in stained sections, from the normal marrow by its palish colour.

In this tissue there usually appear multiple haemorrhages, which may be comparatively large. But we must expressly draw attention to the fact that these characteristic alterations of the marrow also occur without any extravasations of blood. In many animals we have seen, in this tissue, smaller or larger accumulations of a hyaline substance.

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In the cases in which we have found fractures between the shaft and the epiphysis (separations of the epiphyses), the line of fracture has gone through this zone and consequently also through the corresponding atrophied part of the cortical substance.

As regards *the epiphyses*, they do not contain, in animals of the weight used in our experiments, any ossification nuclei. Being, on the whole, very strictly limited to the ossification zones, the above-mentioned alterations of the bone-marrow did not appear in the epiphyses except in one single animal fed on rye-bread; in this case there was a narrow, but marked strip on the upper side of the intermediary cartilage, where the normal marrow was replaced by a reticular tissue containing a considerably reduced number of lymphoid cells. Otherwise the compact as well as the trabecular bone-substance is, in the epiphyses too, somewhat, but not much, reduced.

There remains to be mentioned the essential alterations of the *intermediary cartilage.* This is as a rule markedly narrow. Its cells are of an unequal size and are to a large extent irregularly heaped up instead of being arranged in regular rows; where these latter exist, they very often may be seen diverging against the periphery of the cartilage. The zone of calcification is preserved, but we have often found the network of calcified trabeculae irregularly arranged or in some places wanting. In some cases the primary marrow cavities, containing fibrillar tissue, enter into the cartilage separating the rows of its cells from one another.

Finally we may observe that the periosteum surrounding the upper part of the shaft is, as a rule, thickened both in the outer fibrous and in the inner osteogenetic layer; in both layers there may be seen large extravasations of blood which may communicate through the corticalis with haemorrhages in the marrow.

. *Consequently these alterations are, in all essentials, wholly identical with those found in human scurvy.* We must especially draw attention to the fact, that the bone-marrow is affected, in guinea-pigs, in quite the same way and in quite the same localities as in the latter disease. That is: there is intercalated a more or less broad or narrow layer of the "Helles" or "Gerüst-Mark" of the Germans between the intermediate cartilage and the normal marrow of the shaft.

We have, as an example of the usual affections of our animals, described the alterations of the upper ends of the *tibiae.* Here they are nearly always very prominent indeed. If possible, they are still more pronounced in the ribs, which are, like the tibia, affected just at

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the connection with their cartilages, that is in their epiphyseal ends. Also here we meet exactly the same alterations of the cartilages and of the periosteum as well as the same reduction of the compact and trabecular bone-substance in connection with a reticular or fibrillated tissue, which may contain haemorrhages or not, and which may form a more or less narrow or broad layer between the cartilage and the normal marrow. Usually the most affected ribs are those surrounded by macroscopic haemorrhages. But this is not always so, some ribs being altered without the latter and *vice versa*: some ribs are surrounded by extravasations of blood without distinct alterations of the marrow. The reasons seem to be, that the surrounding haemorrhages of the periosteum and muscular tissue are due to small fractures of the compact substance which may occur before the alterations of the marrow have become manifest; and *vice versa*: the alterations of the marrow may be comparatively far advanced without the compact substance being correspondingly reduced.

Before leaving the ribs, we may add, that their cartilages are, on microscopical examination, often found to be to some extent driven into the marrow substance, while the adjacent cortical substance has become somewhat convex outwardly. Probably it is the act of respiration, which, in some way, wedges the rigid cartilage into the softened bone.

The same alterations which are to be seen in sections of the upper ends of the tibiae, occur also to a large extent in the lower ends of the shafts of the femora as well as in the upper ends of the shafts of the humeri. Also in these localities there appear the above-mentioned alterations of the solid bone-substance, of the periosteum, and the intermediary cartilages; and at the same time there appear, between the latter and the normal marrow of the shafts, more or less narrow or broad layers of a reticular or fibrillar tissue, which tissue may or may not contain haemorrhages. In these bones, however, the alterations are not so extensive and not so constant as in the ribs or tibiae.

How often these alterations occur, will appear from Table II.

This table shows, that the microscopical examination of the bone-marrow from only three of our 44 animals gave a wholly negative result. (Two of these guinea-pigs were fed on rye-bread baked with yeast or baking-powder. They belonged to the first period of our researches; in each case we only examined one tibia. However, with respect to the third animal, fed on oaten groats, the negative results applied to two ribs, one tibia, one femur, and one humerus.) On the other hand, the

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TABLE II.

Summary of the typical scorbutic changes of the bone-marrow comprehending all 44 examined animals.

	Died after	The Ribs			Tibia			Femur			Humerus		
		Examined bones	Typical changes in	Normal marrow in	Examined bones	Typical changes in	Normal marrow in	Examined bones	Typical changes in	Normal marrow in	Examined bones	Typical changes in	Normal marrow in
Oats	22 days	5	5		2	2		2	2		2	2	
	25 ,,	5	5		2	2		2	2		1	1	
	28 ,,	3	3		1	1		1		1	1		1
	28 ,,	3	3		2	2		2		2	1	1	
Rye	25 ,,	4	4		1		1	1		1			
	28 ,,	3	3		2		2	1		1	1		1
	25 ,,	2	2		1	1		1	1		1	1	
	24 ,,	2	2		1	1		1	1				
Wheat	27 ,,	1	1		1	1		1	1		1	1	
	26 ,,	3	2	1	1		1	1		1			
	29 ,,	3	3		1	1		1	1		1	1	
	25 ,,	2	1	1?	1	1		1	1		1	1	
Barley	26 ,,	3	3		1	1		1	1		1	1	
	27 ,,				1	1					1	1	
	26 ,,	4	3	1									
Oaten groats ...	29 ,,	2	2		1	1		1	1				
	31 ,,	2	2		1	1		1	1				
	29 ,,	2	2		1	1		1	1				
	33 ,,				1	1		1	1				
	29 ,,	2	2		1	1		1	1				
	28 ,,	2	2		1	1		1	?				
	31 ,,	2	2		1	1		1	1				
	29 ,,	2		2	1	1		1	1				
	24 ,,	2		2	1		1	1		1	1		1
Barley groats ...	29 ,,				1	1					1	1	
	29 ,,				1		1				1	1	
Rye-bread baked with yeast	21 ,,				1	1		1	1				
	31 ,,				1	1		1	1		1		1
	31 ,,	2	2		1	1		1	1				
	34 ,,				1	1							
	34 ,,				1	1							
	46 ,,				1		1						
	31 ,,	1	1		1		1	1		1	1		1
	33 ,,	2	2		1	1		1		1			
	15 ,,	6	3	3	1	1		1		1	1		1
Do. baked with baking-powder	34 ,,				1	1							
	37 ,,				1	1							
	33 ,,				1		1						
Wheat-bread baked with yeast	31 ,,	2	2		1		1	1		1			
	32 ,,	2	2		1		1	1		1			
	25 ,,				1	1		1	1				
	23 ,,				1	1		1		1	1		1
Rye-bread and oats ...	29 ,,	3	3		1	1		1	1				
	27 ,,	4	4		1	1		1		1	1		1

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examination of the remaining 41 animals gave a positive result. Still it must be admitted that the specific alterations of the marrow did by no means always appear in all examined bones; for instance, they sometimes were only demonstrated in the ribs. The ribs were examined in 29 of the 41 cases, in 28 cases with a positive result. Tibia, femur and humerus were examined in 40, 33 and 18 cases respectively; in 33, 20 and 11 cases respectively the result was positive.

There remain some remarks concerning the microscopical examination of the *gums*. We have examined sections of the gums from 11 animals, fed, on all sorts of the nutriments mentioned above, and have always found haemorrhages in the mucous membrane between some of the molar teeth. We have further, by microscopical examination, repeatedly observed blood in the *free spaces* between the molars; in some cases this blood could be seen to have percolated from the periosteum of the alveolar cavity. Very commonly there also existed more or less extensive haemorrhages in the periosteum and bone-substance at the walls and base of the alveoli. In connection with the atrophy of the osseous walls of the latter, these haemorrhages may be of some importance as regards the loosening of the teeth.

As already mentioned in the foregoing section, we have also, in some cases, found large haemorrhages in the pulp cavities of the teeth.

Finally we must draw attention to the interesting researches of Bartenstein[1], who fed quite young guinea-pigs on both uncooked and boiled milk and produced, in both cases, a malady, which he considers as identical with infantile scurvy.

We are in some doubt as to the existence of this identity. It is true, his animals showed fractures of the tubular bones with surrounding haemorrhages; at the same time, there appeared an atrophy of the solid bone-substance which was apparently even more pronounced than in our animals. However, it may be objected, that the fractures are not expressly said to have been localised at the ends of the shafts; and apart from the surroundings of the fractures there did not appear any haemorrhages. At the same time, the communication of Bartenstein leaves some doubt with respect to the localisation and nature of the alterations of the bone-marrow, that he, too, was able to demonstrate. Finally we may add, that he did not examine the teeth.

We have therefore, to a rather large extent, repeated these interesting researches, and we have closely followed the *modus operandi* described by Bartenstein. As for our results, we limit ourselves meanwhile to the following general remarks:

Whether our animals received fresh or boiled milk, they showed, to a large extent, fractures; but these were often localised at the centres of the shafts. Further they were, in several cases, connected with a very pronounced formation of

[1] *Jahrbuch für Kinderheilkunde*, Vol. LXI. 1905, p. 6.

https://doi.org/10.1017/S0022172400033623 Published online by Cambridge University Press

callus. Though it must be admitted that we also have seen veritable "separations" of the epiphyses, the first named fractures are not analogous either with those of the animals mentioned above or with those of human scurvy. Nor did we observe haemorrhages apart from the fractures; this applies also to the ribs. With respect to the *teeth*, we have only seen a slight indication of looseness in one case. Finally it must be admitted, that the bone-marrow in the ends of the shafts and ribs was, in our animals, too, markedly altered, being poor in cells and often infiltrated by blood. However, this alteration was often accompanied by a diffuse degeneration of the lymphoid cells, which also appeared in the centres of the shafts, where the lymphoid cells, in cases of scurvy as well as in the guinea-pigs mentioned above, appear normal. This *diffuse* alteration manifests itself by the fact that the nuclei of the lymphoid cells cannot be stained distinctly.

We may add, that the altered tissue in the ends of the shafts and ribs had not the same distinct fibrillated or reticular character as the corresponding marrow in the guinea-pigs mentioned above. On the whole, it seems probable that this interesting disease of Bartenstein must, for the present, be placed in a class by itself.

(3) *On the alterations seen in guinea-pigs which die of starvation or of the effects of feeding on cabbage, on fresh or dried potatoes, or on hay.*

We have seen in the foregoing section that guinea-pigs fed on different sorts of unpeeled grains, groats or bread also get the same microscopical alterations of the bones which are found, by numerous German pathologists, to be the essential alteration in Barlow's disease and which do not, according to the same authors, occur in any other malady of children. We have also seen that these alterations have been demonstrated in the few cases of scurvy in individuals of a more advanced age who have been more closely examined in this direction.

In the present section of our article we shall deal with experiments regarding the question whether these alterations are due to the injurious effect of some special nutriments or not.

In the first place we have tried to ascertain whether the malady described instead of being due to a direct effect of the food is caused simply by *starvation*. Because, as mentioned above, the animals, at their death, are found to have lost about 40 % of their original weight, and because they do not eat much for about the last week of their life. Therefore, as a control, we gave two animals water only, while three others received daily 40—60 gms. of cabbage each (otherwise they eat, when fed on cabbage only, between 100 and 200 gms. a day).

The first-named animals died after a few days, the last ones after

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10—12 days. At the microscopical examination the lymphoid cells of the marrow of the tubular bones were partially normal. In other bones, however, their number had greatly and equally decreased not only in the ends of the shafts but also and to the same degree in their central parts as well as in the epiphyses, that is in the localities which are, as we have seen in the foregoing section, not affected either in Barlow's disease or in the guinea-pigs described above. In "starvation-marrow," which we will, for the sake of brevity, call this affection, the remaining groups of lymphoid cells are separated by a mucous tissue without any haemorrhages and without fibres or reticular tissue. This affection corresponds with the "gelatinous" marrow which is so often found in human cases where death is due to wasting diseases.

As regards other symptoms, there were also in these animals some petechiae in the follicles of the vibrissae of the muzzle and lips. But otherwise there were no haemorrhages at all; at the same time, not a single tooth was found loose. Finally all animals showed a pronounced universal anasarca.

These alterations might have been anticipated. In the first place, the same "starvation-marrow" has already been described in starved animals by Neumann. In the second place, there does not appear any symptom of scurvy in *human* diseases causing an ordinary starvation. For instance, a cancer of the oesophagus or stomach does not give rise to any scurvy; on the other hand, such cases often show marked oedema.

We may add that a "starvation-marrow" without any haemorrhages was also often demonstrable in the young and other animals which we have seen, in the first section, to die within a couple of weeks when fed on unground grains, groats or bread. These animals very often were seen to eat very little or nearly nothing. The same applies to three of the six animals which we have fed on ordinary rice-groats. These animals died within 8—12 days. However, in the three remaining cases we found the same alterations of the marrow that are characteristic of scurvy. With respect to one of these animals, living for eight days, we found these alterations in two ribs and in the upper end of the right tibia and the lower end of the corresponding femur. In the two remaining cases, living for 8 and 22 days respectively, in which we only examined the right tibia, the result was positive. (We may add that the longest living animal showed loose molar teeth. But in no case were there macroscopical haemorrhages.)

We see, therefore, that *rice produces the same effects as the other kinds of grain* used in the foregoing experiments.

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In the *second place*, we have successively fed 11 animals on *cabbage* only, eight of them died after 2—6 months, with a loss of weight corresponding to about 30—40 % of the original one. Also in these cases there appeared petechiae on the muzzles and lips. But otherwise there were no haemorrhages at all; at the same time the teeth were never loose and always shining and white. The marrow of the ribs was usually normal: to some extent, however, it also showed a slight indication of a starvation-marrow without any of the qualities described in the foregoing section. A starvation-marrow without any of these qualities was also generally to be found in the tibia, femur and humerus. In addition, there was some atrophy of the osseous substance of the bones which was probably due to the general under-feeding. Also in all these eight animals there was a marked subcutaneous oedema all over the body.

In the *third place*, we have fed 11 animals on *boiled fresh potatoes* only. All these guinea-pigs died after 2—5 months with the usual petechiae in the follicles of the vibrissae; as in the foregoing animals, there were no haemorrhages anywhere else, and all teeth were tight and shining white. The marrow of the ribs was usually normal. The same applied in some cases to the humerus, femur and tibia, while these bones, in some cases also some ribs, showed a more or less pronounced starvation-marrow without any trace of the ordinary scorbutic alterations. Sometimes there was a slight subcutaneous oedema; in other cases no oedema could be discovered.

It is thus evident that scurvy *cannot* be caused in guinea-pigs either by simple starvation or by diets of *any* kind; *on the contrary, the disease originates in these animals as well as in man as a result only of certain special diet.*

The correctness of this view is further supported by the fact, that dried potatoes produce scurvy. We have seen, in the foregoing article, that the experiments on *pigeons* did not show any convincing difference between fresh and dried potatoes. Not so as regards guinea-pigs. We fed ten animals on the latter. The potatoes, bought from a ship-chandler, were first soaked, and afterwards boiled for half an hour at 100° C. Six of the guinea-pigs died within a fortnight without particular alterations. The remaining four animals died after 15, 20, 22 and 26 days, the first one without, the three latter with loose molar teeth. At the same time, all four animals showed haemorrhages round some of the foremost ends of the ribs, which were shown microscopically

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to be affected in the usual scorbutic way. In the longest living animal there also appeared extensive haemorrhages in the muscles of the thighs and of the axillae: there also was some hyperaemia of the gums in front of the lower incisors. Though we did not find any specific alteration of the marrow of tibiae, femora or humeri, these results support the working hypothesis, discussed by one of us in the foregoing article, that dried potatoes may be of importance in respect of the etiology of ship-beri-beri.

Finally, we also fed seven animals on hay and water alone. They died after about one month after developing what may perhaps be termed pseudo-scurvy. The alterations were as follows. The animals showed the usual petechiae on the muzzles and lips. But further four of them had one or two molar teeth somewhat loose. Two of them had also a little reddish-blueness of the gums on the front of the incisors of the lower jaw; finally two of them had small subcutaneous haemorrhages on the fore-limbs, while one animal showed a haemorrhage of the area of about 1 centimeter in the muscles of the right thigh. Other haemorrhages could not be discovered. In spite of these results the marrow of all bones examined, the ribs included, did not show any indication of a scorbutic affection; on the contrary, it was, in all animals, the most pronounced starvation-marrow we have seen. Even in the marrow of the ribs, which was, in the "cabbage-" and "potato-animals" quite normal, the lymphoid cells often were reduced, all over the bones, to an astonishing minimum. It may be added, that all seven animals had a marked, some of them a very pronounced, universal subcutaneous oedema; in some cases there was also ascites.

(4) *On the effects of certain so-called antiscorbutic nutriments and of certain salts added to bread or oats.*

In order to obtain further evidence as to whether the disease described in the two first sections of this article is identical with human scurvy or not, we have tried to find our bearings as regards a possible preventive effect of some of the nutriments known as "anti-scorbutics" from human experience. For this purpose we fed several animals on oats, bread or rice mixed with fresh apples, fresh potatoes, fresh lemon-juice or cabbage. Finally, we also for reasons mentioned below, examined the effects of an addition of carbonate of lime, in some cases also of a mixture of this salt and neutral phosphate of lime.

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TABLE III.

(+ indicates a positive, − a negative result of the examination.)

Nutriment	Life-time in days	Loose molar teeth	Haemorrhages		
			Around the epiphyseal ends of the ribs	In the muscles, periosteum and fasciae of the limbs and trunk	In or under the skin
Rye-bread (prepared with yeast) and 30 gms. *fresh apples* per animal a day.	52	+ (faint indication)	−	−	−
	39	−	−	−	−
	...	Alive the 97th day	...	...	...
	51	+ (faint indication)	−	−	−
Do. 5 parts and *fresh boiled potatoes* 4 parts.	23	−	−	−	−
Do. and *fresh boiled potatoes* equal parts.	36	+ (faint indication)	−	−	−
	63	+ (faint indication)	+	−	+ (1 petechia in the skin of the right leg)
	48	−	+ (faint indication)	−	+ do.
Do. and juice of $\frac{1}{3}$, from the 29th day of $\frac{1}{4}$ *lemon* per animal a day.	34	−	−[1]	−	−
	34	+ (faint indication)	−	−	−
	30	+ (faint indication)	−	−	−
Unpeeled oats and *lemon-juice* as above.	30	+	−	+ (in the muscles of the right leg)	−
	28	+	−	−	+ (under the skin of both groins)
	48	+	+[2]	−	+ (in the skin of the right fore-limb)
Wheat-bread, prepared with yeast, and juice of $\frac{1}{3}$ *lemon* a day.	19	−	−	−	+ (several haemorrh. in the skin on the chest and abdomen)
Do. and juice of $\frac{1}{2}$ *lemon* a day.	43	+ (faint indication)	−	−	−
	29	−	−	−	−
Do. and 10 gms. *fresh cabbage* per animal a day.	85	−	−	−	−
	46	−	+	−	−
	113	−	−	−	−
	109	− (abscess)	−	−	−
Do. and 15 gms. do. per animal a day.	43	−	−	−	−
	8	− (pneumonia)	−	−	−
	33	−	−	−	−
Rice-groats and 10 gms. *fresh cabbage* per animal a day.	105	−	−	−	−
	72	−	−	−	−
	40	+	−	+	−
	28	+ (faint indication)	−	−	−
	61	−	−	−	−

[1] In spite of the missing haemorrhages around the ribs, the foremost end of one of the latter was very pale and found after removal of the periosteum to be separated from the cartilage. Microscopically, the marrow of this rib was typically affected.

[2] Haemorrhages around the foremost ends of 2 ribs; after removal of the periosteum both found to be separated from their cartilages.

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TABLE III (*continued*).

(+ indicates a positive, − a negative result of the examination.)

Subcutaneous oedema	Results of the microscopical examination of the bone-marrow in: The ribs (the figures indicate the number of examined ribs)	Tibia, femur, and humerus	Results of the macro- and microscopical alterations in guinea-pigs fed on the corresponding food without any addition of antiscorbutic nutriments. (See the 1st and 2nd sections of this Article and Table II.)
+	5+, 1−	There was examined from each animal 1 tibia, 1 femur and 1 humerus. In all cases the result was negative.	The 9 animals, which were only fed on rye-bread without any addition, died after 14, 21, 31, 31, 31, 33, 34, 34 and 44 days respectively. In 6 of these animals the molar teeth were examined and found pronouncedly loose. In one animal (dead after 33 days) there was not found any haemorrhage (not around the epiphyseal ends of the ribs either). In one animal there were only found haemorrhages around the epiphyseal ends of the ribs. In one animal there appeared haemorrhages around the latter and in the fasciae and periosteum around both knee-joints. In one animal there was found haemorrhages around the epiphyseal ends of the ribs and amongst other localities in the muscles of both legs and thighs. In the remaining 5 cases the ribs were not examined. 3 of them showed haemorrhages in the muscles, some also under the skin on both legs and thighs. One animal had subcutaneous haemorrhages on the abdomen and around the left elbow-joint. In the remaining case there was found subcutaneous haemorrhages on both thighs and on the abdomen. The bone-marrow of the ribs was examined microscopically in 4 cases; the result was always positive. The result of the corresponding examination of tibia was positive in 8 of 9, of femur in 3 of 5 cases. Humerus was only examined in 2 cases; both were negative.
+ (indications)	6−		
...	...		
?	2−		
−	3−		
+ (indications)	1+, 5−		
−	4−		
+ (slight)	1+, 3−		
+	1+, 3−		
+	2−		
+ (very extensive)	2−		
−	2−	The examined bones and the results were quite as in the foregoing cases.	The 4 animals which were exclusively fed on oats without any addition, died after 22, 23, 29 and 29 days respectively. In all cases there were haemorrhages around the epiphyseal ends of the ribs and in the muscles of the legs, in 1 case also around the upper end of one humerus. Microscopically all examined ribs gave, in all cases, positive results. The same applies to the tibiae from all 4, to femora from 2, and to humeri from 3 animals. All 4 animals showed pronouncedly loose molar teeth.
+	1+, 6−		
−	2+, 3−		
−	Not examined	The examined bones and the results were quite as in the foregoing cases except as regards the 3 animals marked with a star and the 1st lemon-animal. In the first-named animals only tibia and femur, in the latter animal no bones were examined.	
−	5−		
+ (slight)	1+, 5−		6 animals fed exclusively on wheat-bread prepared with yeast died after 23, 25, 31, 32, 33 and 36 days respectively. The molar teeth were examined in 4 cases and were always loose. 2 animals only showed haemorrhages around the foremost ends of the ribs. The latter were not examined in the remaining 4 guinea-pigs; these, however, showed all more or less extensive muscular, in some cases also subcutaneous haemorrhages on the limbs. The bone-marrow was examined microscopically in 4 cases. In 2 of them the ribs, but not tibia or femur, showed typical scorbutic affections. In the 2 remaining cases the examination of the ribs was forgotten; in one of these animals tibia and femur, in the other tibia, but not femur or humerus were typically affected.
+	8−		
?	1+, 5−		
+ (and ascites)	7−		
− (but indication of ascites)	9−		
+ (and ascites as above)	2+, 3−*		
−	2−*		
+ (and ascites as above)	2−*		
−	6−		
+	7−	The examined bones etc. as in the foregoing cases. However from the animal marked with a star we only examined tibia and femur.	6 animals fed exclusively on raw rice groats died after 8, 8, 8, 8, 12 and 22 days respectively. The latter showed loose molar teeth. In no case haemorrhages on the limbs, trunk, or around the ribs. One of the shortest living animals showed typical scorbutic alterations of the marrow of 2 ribs as well as in one femur. Another of the shortest, as well as the longest living animal, showed the same alterations in one tibia (ribs not examined). The bones of the remaining guinea-pigs showed to a large extent "starvation-marrow."
− (but a slight ascites)	4−		
+ (slight)	6−*		
+ (and a slight ascites)	6−		

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The results of the first named experiments may be seen from Table III. In connection with the latter we beg to remark as follows:

We have, hitherto, as a rule limited ourselves to comparatively large quantities of the antiscorbutic nutriments. We daily gave each guinea-pig juice from one-ninth to one-half lemon or 30 gms. of fresh apples in addition to oats or rye- and wheat-bread. (The weight of our lemons varied from about 120—150 gms., each giving about 35—45 c.c. juice. As for the apples, we used so-called "American" apples, each weighing about 100—120 gms.) A similar remark applies to a mixture of bread and fresh potatoes containing these nutriments in the proportion of 5 : 4 or 1 : 1. However with respect to the *cabbage*, we consider a daily quantity of 10—15 gms. as a very moderate quantity indeed.

In spite of these quantities it will be seen that an addition of *lemon-juice* did *not* prolong the life of the nine animals[1] fed on oats, rye- or wheat-bread. The same applies to three of the four animals fed on fresh apples and rye-bread and to three of the four animals fed on fresh potatoes and rye-bread. However, one animal of each of the two latter experimental series lived markedly longer than usual; and with respect to the quantities of fresh cabbage, mentioned above, their addition to wheat-bread or rice saved the lives of several of the 12 animals, that were fed on these nutriments, for a comparatively very long time.

Far more pronounced was the effect of the antiscorbutic nutriments on the specific scorbutic affections. This effect was very conspicuous indeed. For the table shows, that some of the animals did not present any indication of scurvy; in fact the macroscopical indications of this disease were so slight, that the examination had to be made very closely in order to detect them.

To begin with the teeth, they were not pronouncedly loose except in the three animals fed on oats and limejuice. They were, apart from the animals fed on oats, always shining white.

The table further shows that haemorrhages around the foremost ends of the ribs, so common after feeding on bread or oats, appeared in four only of 25 animals that got the same food with an addition of antiscorbutic nutriments. Haemorrhages in the muscles of the limbs and trunk did not appear except in two cases. And though it may be admitted, that haemorrhages in or under the skin were somewhat more frequent, *the bone-marrow of the great majority of the ribs examined and of all tubular bones examined was wholly normal.*

[1] Six other animals, fed on the same quantities of lemon-juice in addition to the same nutriments, died within 8 to 14 days.

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Otherwise it appears from the table that several of the animals presented a more or less pronounced subcutaneous oedema, sometimes also an indication of ascites. In some cases, we found ascites only. Having comparatively seldom observed oedema or ascites in animals fed on oats, bread, etc., without any addition, we have imagined *the abortive scurvy* of guinea-pigs to be analogous to ship-beri-beri. This opinion perhaps scarcely agrees, however, with the following experiments made in order to ascertain *the effects of strong heating on the anti-scorbutic power of cabbage.*

These experiments concern nine guinea-pigs, all fed on the same wheat-bread, baked with yeast. Each of three of them received daily an addition of 30 gms. of cabbage, boiled for half an hour at 110° C.; each of three others received the same quantity of cabbage, boiled for half an hour at 100° C., whereas each of the three remaining animals obtained 30 gms. of the same cabbage unboiled. (The quantities of cabbage were always weighed in fresh state.)

The details of these experiments were as follows:

1. *Wheat-bread and* 30 *gms. of cabbage boiled for half an hour at* 110° C. 1*st animal.* The weight on the 1st day was 415 gms. and kept nearly unaltered until the 25th day (400 gms.), when it began to decrease. (Died the 47th day (260 gms.)) A slight subcutaneous and considerable muscular oedema in the limbs and a slight subcutaneous oedema of the lower jaw were found. No haemorrhages; but the ribs were not examined. Some hyperaemia of the small intestines; all teeth tight. Microscopically the marrow of two ribs and of the right tibia and femur showed typical scorbutic alterations.—2*nd animal.* The weight being the 1st day 325 gms., increased slowly to 480 gms. (the 83rd day); thereupon it decreased slowly until the *death the* 105*th day* (325 gms.). Slight muscular oedema. Subcutaneous haemorrhages in the left popliteal and on the left knee. Haemorrhages round the foremost ends of several ribs. Hyperaemia without haemorrhages of the small intestines. The molar teeth loose. Urine very alkaline. *Microscopically* several ribs and the right tibia showed *typical scorbutic alterations.*—3*rd animal.* Weight at the start 440 gms.; increased slowly until the 94th day (525 gms.); thereupon it decreased little by little until *death the* 125*th day* (355 gms.). No oedema. Extensive haemorrhages under the skin, in the fascia and muscles of both hind limbs and round the foremost ends of several ribs. Molar teeth loose. Defects in the cortical substance on the outside of the lower jaw. Hyperaemia with haemorrhages of duodenum. Urine slightly acid. Microscopically *typical scorbutic alterations of the marrow* of several ribs, and of the right femur and tibia were found.

2. *Wheat-bread and* 30 *gms. cabbage boiled for half an hour at* 100° C. The three animals weighed at the start 300, 400 and 440 gms. respectively. They were killed the 153rd day weighing 440, 700 and 550 gms. respectively. They were macro- as well as microscopically *quite normal*[1].

[1] We always examined several ribs as well as one tibia and femur.

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3. *Wheat-bread and* 30 *gms. of fresh cabbage.* The three animals weighed at the start 350, 350 and 345 gms. respectively. *The* 1*st animal* increased slowly in weight until the 268th day (690 gms.); it is still living, weighing the 299th day 565 gms.—The 2*nd animal* was killed the 153rd day weighing 540 gms. It was macro- as well as microscopically quite normal[1].—*The* 3*rd animal* was killed the 105th day as a control for the 1st 110 degrees animal; its weight was 330 gms. We found some subcutaneous and muscular oedema of the hind limbs. But otherwise all was normal; no haemorrhages; all teeth tight; microscopically the marrow of two ribs and of the right tibia, femur and humerus was normal.

Though we did not, in these experiments, observe the extensive oedema that we anticipated, the results present a new proof of the correctness of the view discussed in the paper on polyneuritis in poultry: *that there may exist a connection between strongly heated nutriments and scurvy.* However, at the same time, it must be pointed out that the preventive power of the cabbage had by no means been wholly destroyed by the strong heating. For two of the animals, fed on cabbage heated to 110 degrees, lived for a comparatively very long time; and with respect to the third animal, it died with tight teeth. That is, in spite of the strong heating of the cabbage, the animals were far better situated than was the case when they received no cabbage at all.

There remain to be considered some experiments regarding the question whether possibly the malady described in the first sections of this paper may be due to some injurious effect of the *acid salts* which are contained in grains, groats and flour.

The German author Weiske[2] has found that *rabbits* decrease in weight and die with rarefactions of the osseous substance when fed on *oats* only. He is of the opinion that this effect is due to the acid salts in connection with a want of lime. For an addition of carbonate of lime wholly neutralises the effects of the oats, while neutral phosphate of lime, though advantageous, has a less pronounced effect. Still less pronounced, though advantageous, is an addition of carbonate of magnesia.

These experiments have been repeated by Stoelzner[3], who found the same alterations microscopically. If he fed rabbits on oats only, he found a pronounced rarefaction of the bone-substance with a defective or wholly wanting apposition of new-formed bone. If, however, he fed them on oats with *carbonate of lime*, the apposition was very pronounced; finally, if he replaced the latter salt by carbonate of

[1] We always examined several ribs as well as one tibia and femur.

[2] *Zeitschr. f. Biol.* 1895, Vol. XXXI.

[3] *Virchow's Archiv.* Vol. CXLVII. p. 430.

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sodium, the result was somewhat less pronounced than when the animals received oats only.

We have attached the more importance to these experiments because not only oats but also the other one-sided diets on which we have fed our scorbutic animals are also poor in lime.

We have also taken into consideration the opinion of A. E. Wright[1], who basing on the fact that grains, flour and some other nutriments contain acid salts, theoretically drew the conclusion that the rarefaction of the osseous tissue and the other symptoms connected with human scurvy are due to an intoxication by acids. He further ascertained a diminution of the alkalinity of the blood in seven cases of scurvy.

Though these latter results disagree with the researches made by Lamb[2] in 11 cases of scurvy, we have given 28 guinea-pigs liberal quantities of carbonate of lime in addition to the various sorts of grains, bread, etc., that were used in the experiments mentioned in the first and second sections of this article. This salt was used because it gave, in Weiske's as well as in Stoelzner's experiments, the best results. Each animal received some grams daily. However, the result was wholly *negative*. Nor were the animals protected by a mixture of carbonate and phosphate of lime.

At the post-mortem, we also examined, in 17 of the 28 animals, the reaction of the urine. In seven cases it was alkaline, sometimes strongly alkaline; in five cases it was neutral, and only in five acid. Though these results did not seem to agree with the hypothesis of an intoxication by acids; and though we further have found that the ashes of *dried potatoes*—which nutriment, too, produces scurvy in guinea-pigs—have a strongly *alkaline* reaction; we shall not, at present, draw any definite conclusion concerning the value of the acid-theory.

(5) *On etiological analogies between the scurvy of guinea-pigs and human scurvy.*

It remains for us to examine whether human scurvy can be caused by food similar to that which we have mentioned in the foregoing experiments.

Before entering on this question it may be useful to consider the present theories on the etiology of scurvy in general.

Of these theories there are three. The first one supposes the malady to be of an infectious nature. This idea, as shown in the work of Lind,

[1] *Lancet*, 1900, II. [2] *Ibid.* 1902, I.

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was held by Boerhaave; in the 19th century it was supported by Villemin; and in our days it is accepted by many Russian physicians. As far as we have been able to see, this theory is only based on speculation. Indeed, we have only seen the following two observations quoted in favour of the theory. The first one concerns an epidemic of "mild scurvy," which broke out in the German prison of Möhringen and its neighbourhood and was described by Kühn[1]. The disease attacked 253 individuals and seems to have been contagious; only 10 of the patients, however, showed haemorrhages of the skin, while many others had an urticaria, erythema or herpes. At the same time, not only stomatitis but also angina and bronchitis; that is a *status catarrhalis*, as well as intermittent chills and rheumatism, were frequent symptoms. No doubt, this disease was not ordinary scurvy but a *peliosis rheumatica* or similar undefinable malady. The second observation was published by Tschudakoff[2]. During an epidemic of scurvy in a Russian famine-district he observed, in connection with another Russian physician, 12 cases of sore gums in individuals whose food is said to have been "satisfactory." He therefore believes them to have been contaminated by the surrounding scorbutic population. No importance can, however, be attached to these cases for the reason that the author does not mention the special nutriments of which the "satisfactory" food consisted.

The *second theory* supposes scurvy to be due to *damaged food*. This theory can be seen, in the work of Lind, to date back to the middle ages; and there are still many authors who are of this opinion. Above all, many writers consider *damaged* salt meat to have been, for instance on board ships on long voyages, the real cause of many epidemics of scurvy. As will be shown below, we do not wholly deny every importance of such sorts of food. We must, however, point out that their influence has not been proved by any convincing observation. In fact, the theory is based on experiences during famines, campaigns, sieges, or on board ships on long voyages. That is under circumstances where it must be admitted, that various articles of food often are damaged. On such occasions, however, the selection of nutriments will also be very limited; that is the diet will become one-sided. How easily this will happen may be seen when comparing the article on scurvy of

[1] Über leichte Scorbutformen. *Deutsches Archiv. für klin. Medicin*, Vol. xxv. 1880, p. 115.

[2] *Über das Auftreten des Scorbuts in Zusammenhange mit Hungersnot.* Inaugural Dissertation. Berlin, 1903, p. 27 *a* foll.

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Immermann[1] with that of Hirsch[2]. The first one quotes two epidemics of scurvy on board the "Columbia" and among some gold-diggers following on damaged food; the last one points out that there had also, in these same epidemics, been a complete lack of fresh vegetables. The same applies to an epidemic among the Circassian cavalry during the Crimean war, quoted by W. Koch[3]. He tells that the troopers got some damaged fat and biscuits, in some cases also a little damaged peas, beans or mutton; but beyond this their food only consisted of one or two handfuls of rice daily. He further mentions an epidemic of scurvy in a French prison, published by Beurmann[4]. Koch points out that the prisoners got damaged meat. In the original paper, however, prominence is given to the fact that, during the last two months before the appearance of the malady, the prisoners were deprived of fresh potatoes and that in addition to the meat, their food consisted only of dried beans, rice and similar nutriments.

Jackson and Harley[5] have supported the theory of damaged food by experiments on monkeys. When fed daily on tainted tinned meat together with some rice and Indian corn these animals got diarrhoea which was accompanied by bloody and mucous stools and spongy and easily bleeding gums. In some cases the gums showed also small ulcers. As far as we are able to see these experiments, however, only prove that tainted meat, when eaten daily, may provoke an intense inflammation[6] of the upper as well as of the lower part of the intestinal canal. If the experiments were also to throw light upon the etiology of scurvy, they ought also, at least in some animals, to have provoked haemorrhages in other organs than the alimentary canal; and even as regards the latter, the authors do not mention whether they found much or only very little blood.

Before leaving this theory we may, however, admit, that we do not deny all injurious effect from damaged meat or other damaged nutriments. In the first place such nutriments may, as shown in Jackson's and Harley's experiments, provoke an intense diarrhoea, which evil seems, for instance during the Crimean war, very often to have created

[1] Ziemssens, *Handbuch der spec. Path. und Therapie*, Vol. XIII. 1876, p. 560.

[2] *Handbuch der historisch-geogr. Pathol.* 1883, pp. 385—387.

[3] *Die Bluterkrankheit*, Stuttgart, 1889 (Billroth-Lückes Deutsche Chirurgie).

[4] *Archives générales de médecine*, 1887, I. p. 27.

[5] *Lancet*, 1900, I. p. 1184.

[6] Also six control monkeys got a fatal diarrhoea; but there did not appear blood or mucus in the stools; nor did the animals get spongy gums.

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a predisposition to scurvy. In the second place, many people do not like to eat damaged nutriments. For instance, if the salt meat gets damaged on board a ship it may be imagined to cause scurvy, not because the sailors eat it, but because they do *not* eat it or because they eat too little of it and prefer to stick to the other, *i.e.* mostly farinaceous nutriments.

The *third theory* supposes the disease to be caused by a one-sided diet, especially a diet which does not contain, or contains too little of fresh aliments. It seems to us that the facts by which Lind, Hirsch and many other writers have supported this theory, are in every respect convincing, and they agree with our own experiments as to the influence of fresh cabbage, apples, potatoes, and so on.

It lies beyond the plan of the present article to enter into the details of these epidemiological observations. We may, however, draw attention to the fact *that scurvy has repeatedly arisen where the food consisted of the same or about the same nutriments as we have used in our experiments on guinea-pigs.* To commence with *infantile scurvy*, Barlow[1] has pointed out that this disease seems often due to the injurious effect of farinaceous food. In this connection he quotes Cheadle, who has been aware of the same coincidence, and who has raised the question why nearly all of the children who principally live on *bread*, escape scurvy. This question Cheadle has replied to in the same way, as we have, ourselves, so often done in respect of large parts of the Norwegian population, living chiefly on "bread and coffee." The answer is: because they live, at the same time, on potatoes.

As regards older individuals, a German author[2] mentions two women who got scurvy having been for several weeks reduced by poverty to a diet of tea and bread without sugar and milk. (See also one of Bucquoy's cases below.) Furthermore the Danish author Adolph Meyer[3] mentions a boy of 10 years who got the disease after having lived chiefly on cocoa and wheat-bread; he never ate vegetables, eggs, milk, butter, or fat, and had "without doubt but seldom" got any meat. Meyer also quotes a boy of five years, observed by Evans, who got the disease after having chiefly lived on bread and butter [?] and "a small quantity" of milk, while he never ate vegetables, meat or soups. We may further mention that cases of scurvy, of which some were fatal, were observed in con-

[1] *Medico-Chirurg. Transact.* 1883.

[2] *Encyclopädisches Wörterbuch der medic. Wissensch.*, von Busch, Dieffenbach and others. Berlin 1843, Vol. xxxi. p. 382.

[3] *Barlow's disease*, Copenhagen, p. 1901, p. 122 a.f.

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nection with the so-called thirst-cures of Schroth, in fashion in Germany in the middle of the 19th century. In addition to a very small quantity of fluids, the food consisted, during these cures, of wheat-bread ("Semmel-Kur") and some porridge of rice and millet[1].

Again, we may recall the interesting observations of Curran[2] during the epidemic of scurvy, which broke out after the failure of the potato crop in Ireland 1846–47. Four-fifths of the numerous patients concerning whom he got information had lived only upon bread and coffee or tea. The food of the remaining one-fifth had consisted of cereals of various kinds or cereals and flesh or fish; but in no single instance could green vegetables or potatoes be discovered to have formed a part of their regular diet.

It seems to us that such observations are convincing. In famines, flour and bread are very often the only foods on which the population can fall back. In this connection we may also draw attention to the following cases observed in Finmarken, the most northern part of Norway, where the population is very poor, and sporadic cases of scurvy are not uncommon, especially during the failures of the potato-crop. These cases have been observed by Dr Wessel, Medical Officer of Health of Syd-Varanger, who has kindly permitted us to mention them.

1. A woman, 37 years old, came under observation 2/3/1907. Had been ill for five to six weeks; large haemorrhages of the skin of one leg; sore and bleeding gums. Had not got potatoes, fish or milk during the whole winter: no meat since the beginning of January. Had only lived on rye-bread, soup of oaten flour and coffee without sugar.

2. A man of 44 years and his three children of four, six and eight years, came under observation 2/3/1907. The man had only sore gums, the others also extensive purpura. Two of the children had been ill since Christmas, one for from two to three weeks. Since October no potatoes or milk; they had lived on coffee, bread and a soup made of flour; very seldom meat or fish.

3. During the same epidemic a woman got haemorrhages and sore gums, having lived, for the whole winter, on flour and groats. Besides she had very little meat and no potatoes or milk.

4. Finally Dr Wessel mentions a patient who got, in 1901, sore gums and haemorrhages of the skin all over the body after living for a long time, exclusively on dry bread and black coffee.

Finally we may take the opportunity of pointing out that *rice, which is so often supposed to be the cause of tropical beri-beri,*

[1] H. Salomon, *Über Durstkuren*, Berlin, Hirschwald, 1905, p. 2; Jürgensen, *Deutsches Arch. für klin. Med.* 1866, I.

[2] *Dublin Quarterly Journal of medic. Science*, August, 1877, p. 109.

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occasionally has provoked scurvy. For instance, Delpech[1] mentions, in his article on scurvy in Paris in 1870–71, a patient who got the disease who for four months had only eaten meat four times, besides this, he had had nothing but rice. During the same epidemic Bucquoy[2] observed two cases of the same kind. The first patient had for three or four months lived exclusively upon rice and water thrice a day. The second patient had, for the same time, lived *almost* only on rice; in addition he had two or three times got beans or potatoes. A third and a fourth patient had, for the same time, only eaten bread and rice; a fifth patient only bread, rice and some few times meat; a sixth patient had only eaten bread. Again, we may quote the above-mentioned 10th of Fränkel's[3] cases, a boy of seven years with all symptoms of an ordinary scurvy, whose bones showed the regular microscopical alterations of Barlow's disease which we have observed in our guinea-pigs. Because he could not endure any other food, he had for months lived on rice only. Finally we may refer to the interesting article in which Maitland[4] has replied to the above-mentioned experiments of Jackson and Harley. He instances as one of the causes originating scurvy among sepoys the following: a sepoy wishes to save money; he therefore only eats the rice and dhal from the military kitchen and refuses to have such extras as fresh vegetables, meat or milk, because he is obliged to pay for them out of his own pocket. Within from 2—3 months, says Maitland, this man will get scurvy and will recover after a short time as soon as he gets fresh potatoes or lemons in addition to his previous food.

It is true, in this case the food did not exclusively consist of one single kind of grain. On the whole, it must be admitted that this happens rather seldom, and that most cases of scurvy have occurred after a somewhat more varied food. But in these cases, too, the food can often be proved to have been very like the nutriments which cause the disease described in guinea-pigs. For instance, each prisoner of the Akershus prison in Christiania, from the beginning of 1845, received 2 oz. of pork and 6 oz. of meat a week; once a week the prisoners got butter. Besides this, the food consisted of potatoes, milk, bread, broth, porridge of barley groats and barley flour, ale and a soup made of ale. Owing to the failure of the potato-crop, however, no potatoes were distributed from the middle of 1846; from this time, also, the prisoners

[1] *Annales d'hygiène* publ. 1871, Vol. xxxv.

[2] *Union médicale*, September and October, 1871.

[3] *Fortschritte auf dem Gebiete der Röntgenstrahlen*, 1906, Vol. x. No 1.

[4] *Lancet*, 1900, II. p. 1164.

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only exceptionally got any milk. The result was, that after some months, there broke out a very extensive epidemic of scurvy[1]. This epidemic did not cease until, in 1847, fresh potatoes were again distributed.

We may further mention an epidemic in the Wartenburg prison in Germany[2], where the food consisted of a soup of flour, porridge, bread, and different sorts of beans. Only twice a year was meat distributed, and owing to failure of the crop neither potatoes nor other fresh vegetables could be procured. Finally the prisoners were provided with fresh vegetables and got in addition meat several times a week; thereupon the epidemic rapidly disappeared. Again, Delpech (*l.c.*) records a patient, who got scurvy after for two or three months living only on bread, rice, soup and sometimes boiled peas. Finally it may be mentioned that the epidemics of scurvy which prevailed, during the siege of Paris, in several prisons of the city, began some time after the potatoes and other fresh vegetables had been finished and the food had been reduced to rice, bread and dried peas and beans (haricots) in addition to some wine and coffee with sugar; the beans and peas were partly replaced by maccaroni or barley-groats, boiled with a little fat[3]. It may be added, that the prisoners are expressly said not to have got any fresh, salt or smoke-cured meat.

Thus also epidemiological facts speak in favour of the opinion that the described disease in guinea-pigs is identical with human scurvy.

Before leaving this subject, we may, however, shortly draw attention to one objection, that possibly may seem obvious. This refers to the fact, that prisoners when being punished with "bread and water" (with some salt) are not known to get scurvy. However, in Norway the prisoners are not confined to this diet for more than 20 days (in Finland up to 28 days). As will be seen from the observations mentioned above, it takes, however, months before a bread diet produces scurvy.

CONCLUSIONS.

We have seen in the foregoing sections of this article, that a one-sided diet consisting of various sorts of grain, groats and bread, produces

[1] *Forhandlinger i Kristiania medicinske selskab.* (*Transact. of the medic. Soc. of Christiania*), *Norsk Magazin for Laegevidenskaben* (*Norweg. Magaz. for medic. Science*), 1847, p. 523.

[2] Wald, *Vierteljahrschrift für gerichtliche Medicin*, 1857, Vol. XI. p. 45.

[3] See the articles of Delpech (*l.c.*) and of Lasègue and Legroux (*Archives générales de médecine*, 1871, II.).

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in guinea-pigs a disease that corresponds, macro- as well as microscopically, to human scurvy.

On the other hand, we have found that this disease does not occur after a one-sided diet consisting of fresh cabbage or fresh potatoes, whereas it again is produced by dried potatoes. That is, the disease originates in guinea-pigs as well as in man as a result of a diet confined to some special nutriments.

We have further observed that the disease is favourably influenced by different sorts of nutriments known, from human experience, as "antiscorbutics." We have, however, also found that at least one of these nutriments, that is cabbage, loses a deal but not all of its preventive power when boiled for half an hour at 110° C.

Finally we have quoted several examples showing that the same or similar one-sided diets that produce the disease in guinea-pigs, have repeatedly produced scurvy in man.

However, we have not, hitherto, been able to produce the disease that has been the proper aim of our experiments, that is the younger brother of scurvy or ship-beri-beri. It is true, we have repeatedly, in guinea-pigs, seen abortive cases of scurvy recalling the latter disease. This problem is, however, by no means clear. Nor have we, hitherto, been able to make experiments explaining, in an unmistakeable way, why the one-sided diets, mentioned above, produce scurvy.

Postscriptum. We had already finished the present paper when we examined two guinea-pigs that had been fed on wheat-bread and one that had been fed on rye-bread. In spite of their dying 29, 30 and 27 days after the beginning of the feeding, the microscopical examination of 2—4 ribs as well as of one tibia, femur and humerus from each animal did not show any scorbutic alteration. We are of the opinion, that this negative result may possibly have something to do with the fact, that the weight of the animals was 1140, 1085 and 995 gms. respectively; that is, the animals were comparatively very old. For we have pointed out, that the specific alterations of the bone-marrow are limited to the zones of ossification. In old animals, however, the ossification has, in all essentials, ceased. In one of the cases there were some muscular haemorrhages; all three animals showed discoloured and loose molar teeth.

On the other hand, we arrived at other results when examining a dog, concerning which we got the following information:

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Drawing showing a slightly enlarged section of the lower end of a femur from a guinea-pig which died after feeding on oaten groats. A pronounced layer of "palish marrow" between the intermediate cartilage and the normal marrow of the shaft. The bone trabeculae of the latter are very atrophied; the same applies to the corresponding part of the cortical substance. The section was stained with haematoxylin but is drawn with Chinese ink.

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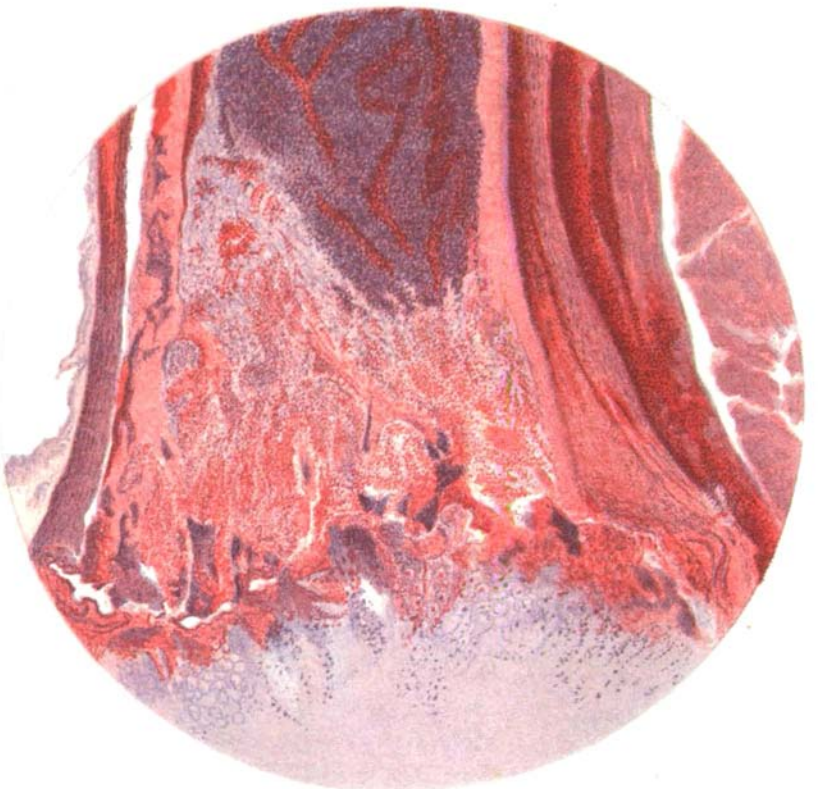

The figure shows a longitudinal section of a rib with the adjacent cartilage from a guinea-pig fed on rye-bread. Trichloracetic acid; haematoxylin, eosin. Only some of the cells of the cartilage are shown in the drawing. Small fissures between the cartilage and cortical substance as well as the bone-marrow. A broad layer of blood infiltrated "palish marrow" with few and irregular bone-trabeculae between the cartilage and the normal marrow. On the one side there are haemorrhages in the periosteum and also between the latter and the cortical substance. Leitz obj. 3; drawing-prisms.

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It was fed, for two months after birth, on its mother's milk; thereupon it got, for 3—4 months, a mixed diet. About 5—6 months after birth it was, in addition to a number of other dogs, placed in a kennel and fed on oaten-flour, boiled with water, on some days also on Indian corn; at the same time the animals received a certain amount of mesentery of an ox boiled with water, but without the fat.

Fed on these aliments, the dogs began little by little to become weaker until the owner after 2—3 months changed the food for dog-biscuits. As soon as this was done, the animals recovered very rapidly. However, a month afterwards the owner reverted to the oaten-flour, etc. Again the animals became weak. After some months they therefore again received dog-cakes and recovered rapidly, whereas one dog was killed because of an apparent paresis of the fore-limbs. We did not get any nerves for examination; nor do we know anything certain with respect to haemorrhages or looseness of the teeth. However, we examined four ribs and the upper end of the right tibia as well as the lower end of the corresponding femur. *In all these bones we found microscopically a thick layer of typical reticular or fibrillated tissue with or without haemorrhages between the intermediary cartilage or rib-cartilage and the normal marrow of the shaft or the rib.* As for the solid bone-substance, it did not look very much atrophied; considering the very reduced or wholly wanting osteoblasts, we may, however, conclude, that the solid substance, too, was somewhat abnormal.

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