THE MORPHOLOGICAL CHANGES IN THE TISSUES OF THE RABBIT AS A RESULT OF REDUCED OXIDATION.

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The experiments which are described in this paper were undertaken with the idea of determining the morphological changes which might be found in the tissues of animals subjected to the change of a single factor in their chemical environment. For this purpose two series of experiments have been carried out. In one, a decrease in oxygen of the respired air has been the sole factor of change. In the other, the change has been an increase in the carbon dioxide of the air with other factors kept as a constant.

In considering the results of the two series it would seem reasonable to assume that we are dealing with results, direct or indirect, in one case of a reduced oxygen supply to the cells of the body, and in the other of an increased carbon dioxide content of the fluids and tissues of the body. The assumption, however, that the morphological changes found could be produced in no other way is not made. Death of a cell may, for example, be produced by anemia, or by bacterial toxins. A finer analysis might, however, show that in both instances a reduction of vital oxidation was the cause of the lesion; on the one hand through oxygen starvation, on the other through failure to utilize oxygen by interference with the cellular oxidases by the toxin. It is our opinion, then, that oxygen deficiency should at least receive consideration as a cause, in interpreting lesions similar to those we shall describe in the animals subjected to low oxygen tension.

EXPERIMENTAL.

In carrying out the experiments we have used the respiration chamber described by Kolls and Loevenhart.[1]

[1] Kolls, A. C., and Loevenhart, A. S., *Am. J. Physiol.*, 1915–16, xxxix, 67.

In the first set of experiments ten rabbits varying from young to full grown were used (Table I). The duration of the experiments, in which the animals were exposed to low oxygen tensions, was 7, 10, and 4 days respectively. The animals were removed from the cham-

TABLE I.

Oxygen Rabbits.

Animal No.	Weight.			O_2		CO_2	
	Before experiment.	After experiment.	Loss.	Minimum.	Average.	Maximum.	Average.
	gm.	*gm.*	*gm.*	*per cent*	*per cent*	*per cent*	*per cent*
1	2,100	1,820	280	4.78	7.74	0.80	0.25
4	950	820	130	4.78	7.74	0.80	0.25
9	1,900	1,380	520	3.58	7.21	0.30	0.23
10	940	720	220	3.58	7.21	0.30	0.23
11	1,320	1,000	320	3.58	7.21	0.30	0.23
12	2,080	1,700	380	3.58	7.21	0.30	0.23
13	1,300	987	313	5.47	7.33	0.20	0.20
14	1,660	1,419	241	5.47	7.33	0.20	0.20
15	760	Died.		5.47	7.98	0.20	0.20
16	1,680	"		5.47	7.98	0.20	0.20

Animal No.	Length of exposure to different O_2 tensions.*					Duration of experiment.
	12–10 % O_2.	10–8% O_2.	8–6% O_2.	Under 6% O_2.	Total.	
	hrs.	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*1915*
1	19.0	37.5	64.5	35.0	156.0	Oct. 18–25
4	19.0	37.5	64.5	35.0	156.0	" 18–25
9	11.50	86.25	73.0	60.50	231.25	Nov. 8–18
10	11.50	86.25	73.0	60.50	231.25	" 8–18
11	11.50	86.25	73.0	60.50	231.25	" 8–18
12	11.50	86.25	73.0	60.50	231.25	" 8–18
13		18.00	70.5	8.00	96.50	" 23–26
14		18.00	70.5	8.00	96.50	" 23–26
15		1.00	9.00	2.00	12.00	" 23
16		1.00	8.50	2.00	11.50	" 23

* Only O_2 tensions under 12 per cent are considered.

ber not more than once during the progress of the experiment and then only during the time the chamber was being cleaned (about an hour). The number of hours during which the rabbits were subjected to different tensions of oxygen and carbon dioxide together with the

average tensions of the gases is recorded in Tables I and II. The carbon dioxide determinations were made with Haldane's portable apparatus for the analysis of mine gases. The oxygen determinations were made with a Hempel phosphorus pipette. At the termination of the experiments the animals were killed and immediately autopsied. The tissues were preserved in formalin, Zenker's solution, and 95 per cent alcohol. All the rabbits were weighed before they were put into the chamber and immediately before they were killed. A portion of the record of an experiment is given here.

Experiment 1. Reduced Oxygen.—Nov. 8, 1915.
Rabbit 9, white, male; weight 1,900 gm.
Rabbit 10, black, female; weight 940 gm.
Rabbit 11, speckled, male; weight 1,320 gm.
Rabbit 12, brown, male; weight 2,080 gm.
2.55 p.m. Experiment started. Burned hydrogen flame in the box to reduce oxygen rapidly, and started pump. All the animals were eating and seemed normal.
3.25 p.m. Rabbits becoming drowsy and slightly dyspneic.
3.30 p.m. O_2 = 9.61 per cent.
3.37 p.m. H turned off and O_2 turned on.
3.45 p.m. O_2 = 9.06 per cent. Animals becoming more dyspneic and drowsy. No. 10 seems to be most affected. Nos. 11 and 12 eating again.
4.15 p.m. O_2 = 9.11 per cent. Readjusted control for O_2 intake. Turned O_2 cup down slightly.
5.00 p.m. CO_2 = 0.25 per cent.
5.15 p.m. O_2 = 9.01 per cent.
7.15 p.m. O_2 = 8.47 per cent. Animals seem to be sleeping.
8.05 p.m. O_2 = 8.26 per cent. Readjusted O_2 intake.
10.40 p.m. O_2 = 8.65 per cent.
Nov. 9, 8.30 a.m. O_2 = 9.28 per cent. Readjusted O_2 intake. CO_2 = 0.30 per cent. Animals seem to be in good condition. Changed belt on motor.
8.50 a.m. Relative humidity 58 per cent.
9.00 a.m. O_2 off. The animals have been eating.
9.30 a.m. O_2 = 8.3 per cent.
11.50 a.m. O_2 = 6.16 per cent. Animals becoming very dyspneic.
1.05 p.m. O_2 on.
4.00 p.m. O_2 = 5.46 per cent. Readjusted O_2 intake.
4.05 p.m. CO_2 = 0.20 per cent.
4.15 p.m. Relative humidity 48 per cent. Drew off sulfuric acid.
7.00 p.m. O_2 = 7.12 per cent.
7.30 p.m. CO_2 = 0.25 per cent.
8.45 p.m. O_2 = 7.93 per cent.

The general data of the experiments are given in Tables I and II.

The symptoms manifested by the animals under different low oxygen tensions were constant in each series of experiments. When the oxygen was reduced to between 10 and 12 per cent, the rabbits became drowsy and slightly dyspneic. As the oxygen tension was reduced further, the dyspnea became more pronounced and was often accompanied by a swaying of the animal from side to side. When the tension was reduced below 7 per cent, the animals refused to eat or drink. Below 6 per cent oxygen, peculiar chewing movements were noticed. The movements of the rabbits became uncertain and it was difficult for them to retain the normal sitting posture. Inability to use the hind legs was noted in nearly all the rabbits. A characteristic symptom was the position of the head, which was thrown far back, possibly in an effort to make the act of breathing easier. One rabbit became paralyzed and appeared about to develop convulsions, when it was removed from the chamber. It recovered completely after a few minutes in normal atmosphere, but when put back into the chamber, the symptoms returned and the animal was discarded.

It is evident that three factors must be taken into account in interpreting the lesions: the low oxygen tension, the increased cardiorespiratory activity, and the lessened intake of food. The consistent loss of weight by all the animals indicates clearly that although the animals are not active in the cage, the intake of food is not sufficient for their vital demands. The general behavior of the animals indicates further that the compensatory effects, by the cardiorespiratory and hematopoietic systems, are not adequate to meet the severe demand made by the low percentage of oxygen which was maintained throughout the series of experiments.

The lesions of the animals at postmortem examination show the slight degree of change found in the various tissues. While the animals vary in the susceptibility of the different organs to oxygen deficiency there is a striking uniformity in the general picture. A single postmortem protocol may therefore suffice.

Rabbit 1.—Male; weight 1,820 gm. Killed Oct. 25, 1915.

Subcutaneous, mesenteric, and retroperitoneal tissues practically free from fat. Serous cavities free from excess of fluid.

Heart.—Large and pale. Left ventricle 5 mm. thick; right ventricle 1.5 mm. Muscle is uniformily pale on section.

Lungs.—Left: Pale and air-containing throughout and exudes a small amount of frothy serum from the lower lobe upon pressure. There are several punctate hemorrhages in the lower lobe. The border of the lung is slightly emphysematous. Right: Similar to left and also shows two small hemorrhages.

Spleen.—Measures 57 by 13 by 5 mm.; is of a deep purplish color and has a pitted and wrinkled surface. On section, the Malpighian corpuscles are of normal size. The pulp is increased in amount and is quite firm.

Liver.—Weight 59 gm. The capsular and cut surface are uniformly and finely mottled, due apparently to a dark appearance of the center and a light opaque appearance of the periphery of the lobule. The gall bladder is filled with dark green bile.

Kidneys.—Left: Measures 35 by 21 by 15 mm. Capsule is not adherent. The surface of the kidney has a uniform grayish pink color, which also characterizes the cortex on section. The medulla is paler. The cortex measures 4 mm. in thickness and has a regular striation. Right: Measures 34 by 22 by 12 mm. and resembles the left in every detail.

Adrenals.—Left: Measures 9 by 7 by 2 mm. On section, cortex measures 1 mm. in thickness. Medulla is linear and about 0.5 mm. in width. Right: Measures 10 by 7 by 2 mm. and is similar to left on section.

Pancreas.—Appears normal.

Aorta.—Intima is slightly opaque and appears thickened.

Thyroid.—Small and pale. External parathyroids small.

Bone Marrow.—From center of femur is of a deep opaque grayish red color, fairly firm, and gives no gross evidence of adipose tissue.

Brain and Cord.—No abnormality evident.

The tissues were fixed in Zenker's fluid, in 10 per cent formalin, and in alcohol.

Microscopic Examination.—

Heart.—Blood and lymph vessels throughout the section are distended and there is some edema of the tissues. The muscle fibers throughout are swollen, granular, and vacuolated, but the lesion becomes extreme only in the inner third of the heart wall. Here the fibers on cross-section appear to have but a single peripheral row of sarcostyles about a vacuole which contains a granular precipitate and in some cases is crossed by delicate fibrils. On longitudinal section the fibers are extremely thin but show the cross-striation. Many of the fibers show hyaline masses which extend usually across the width of the fiber but in some cases appear spherical and of a diameter less than that of the fiber itself. These hyaline masses occur both at the ends of the cells and at intervening points. The nuclei of the fibers stain sharply but appear somewhat shrunken. No fat is shown by osmic acid staining.

Lung.—The vessels are congested. The subpleural air spaces are excessively dilated and their walls appear thin. There are scattered minute alveolar hemorrhages, of antemortem occurrence as shown by the presence of occasional phagocytes containing red blood cells. There is slight edema. The lymphoid tissue is hyperplastic.

Spleen.—There is some hyperplasia of Malpighian corpuscles and of pulp cells as shown by mitotic figures. Both the pulp and its sinuses are distended with cells, chiefly red blood cells, although numerous polymorphonuclear leukocytes are found in the pulp. There are scattered nucleated red cells in the pulp, and in the sinuses are numerous groups of nucleated red cells of all sizes from megaloblast to normoblast, resembling the erythrogenic groups of the marrow.

Liver.—There is a general congestion of the vessels. The liver cells are most normal in the peripheral zone and next to the portal spaces. Here the cells are swollen and granular, with a tendency to a separation of the granules by ill defined clear spaces. Practically every cell has two nuclei. As one approaches the central vein, there is a tendency for the swollen cell to appear paler, to show a greater clear area crossed by an irregular protoplasmic reticulum, with scattered granules. In some parts of the liver clear-cut small fat vacuoles are found in the cells of the middle zone. In most of the sections the central zone shows necrosis of the liver cells and invasion by polymorphonuclear leukocytes. These areas of necrosis extend from central vein to central vein, about the periphery of the secretory lobule.

Kidney.—The vessels are congested. The cells of the cortical tubules are, in general, swollen until the tubular lumen is practically obliterated. The cells are granular but paler than normally. The granules appear to be separated from one another by serum. The lesion varies in the different cells from this condition to one in which the entire cell appears to consist of a nucleus and a vacuole surrounded by a cell membrane. In some cells the vacuole shows an irregular reticulum of protein material. The lesion appears most marked in the subcapsular region. Some of the tubules show a granular precipitate in the lumen and here and there a hyaline droplet is seen. There is no definite cast formation.

Bone Marrow.—The blood vessels are widely dilated and engorged with red cells. The marrow spaces are practically free from adipose tissue cells. The spaces are occupied by regular groups of nucleated red blood cells and by groups of myelocytes and leukocytes. The erythrocyte-producing centers predominate.

Aorta.—The muscle cells of the media are swollen and show a poorly defined vacuole about the nucleus.

Thyroid.—The alveoli of the thyroid are relatively small. The larger are filled with colloid, but there are many smaller alveoli devoid of colloid and practically without lumen.

Testicle.—There are few mature spermatozoa in the lumina. The germ cells appear to be vacuolated and in some places have pyknotic nuclei.

To summarize, the lesions found in the rabbit are: marked hyperplasia of the bone marrow; extramedullary (splenic) production of red cells; degenerative lesions of parenchymatous cells of the nature of a diminution of cell protoplasm with increase of serum (hydropic or vacuolar degeneration or serous imbibition); necrosis of parenchymat-

ous elements in some organs, especially the liver; hyaline degeneration and necrosis; congestion and edema of organs.

Rabbit 4, cage-mate of the animal described, showed practically the same lesions with two exceptions. The liver was less affected and showed no central necrosis, but instead well marked serous imbibition involving the whole lobule with the exception of an occasional cell close to the portal space. The kidney, on the other hand, gave evidence of a previous injury, in the presence of connective tissue scars, and appeared to be more injured by the oxygen deficiency. The serous imbibition was more marked, and some disintegration of cells and necrosis existed.

Rabbits 2 and 3 of this 7 day period were discarded as they were found to be pregnant when examined post mortem, although their lesions agreed with those described.

In studying the tissues of the rabbits of the 4 day and 10 day periods, similar lesions were found throughout, with but slight individual variations. In the hearts of animals of the 4 day period fatty infiltration was a prominent feature, and in fact was more marked than the vacuolar change. In the 10 day animals visible fat was lacking and the serous imbibition was the prominent lesion. In none of the four animals, however, was it as marked as in those of the 7 day period. This was interpreted as indicating a more complete though still insufficient compensation on the part of the blood and respiratory systems.

A tendency to emphysema of the borders of the lungs was noted in practically all the animals, though it was very slight in Rabbit 11. Minute hemorrhages and slight edema were constant. Hyperplasia of the lymphoid tissue in the lungs was also constant. In addition, in all the animals that were in the cages over 24 hours a mononuclear cell invasion of the lung framework of varying degree was present.

The livers uniformly showed hydropic degeneration of the cells of the mid-zone and central zone. In addition, Rabbits 12 and 14 showed a well marked central necrosis, while Rabbit 11 showed a fatty degeneration in the mid-zone and a serous imbibition in the central zone.

The kidneys of the series uniformly showed parenchymatous and hydropic degeneration. Hydropic degeneration was, however, very slight in Rabbit 14, which showed a well marked fatty degeneration.

The spleens showed, in general, hyperplasia of the Malpighian corpuscles and congestion of the pulp. Groups of erythroblasts were noted in the pulp sinuses in Rabbits 9 and 11. Rabbit 13 showed an excessive amount of hemosiderin in the pulp cells, a condition not found in the others of the series.

The aortæ of the animals generally showed a serous vacuolation of the smooth muscle fibers.

The bone marrow showed a marked hyperplasia in all the animals of the 7 and 10 day periods and less marked in those of the 4 day period. The erythroblastic centers were especially hyperplastic, although there was an increase also in the leukogenetic centers.

There was also a general hyperplastic condition of the thyroid gland in all the animals, with some variation in degree.

The lesions that we found then, in animals subjected to low oxygen atmospheres, may be summarized briefly as: (1) Hyperplastic changes in the bone marrow and in the thyroid. (2) Degenerative changes, with ultimate necrosis, in the elements of the heart and glandular organs. These changes are parenchymatous (albuminous), fatty, and serous (hydropic) degeneration, with some hyaline degeneration, and are most marked in the organs at points which are at the greatest distance from the blood supply; *i.e.*, the central zone of the liver, the inner part of the heart wall.

Before discussing the interpretation of the changes, it seems best to describe the experiments with animals kept at normal oxygen pressure and increased carbon dioxide. In this part of the work we have used only four rabbits, as the results were highly uniform. We find that there are certain similarities and differences as compared with the changes in animals subjected to diminished oxygen supply. Identical precautions were observed in this experiment with those in the series of reduced oxidation experiments in that normal atmospheric pressure, humidity, and temperature were maintained. The number of hours during which the animals were subjected to different carbon dioxide tensions is given in Table II.

The symptoms manifested by the animals in the atmosphere of high carbon dioxide were not so severe as those shown by the animals in the low oxygen atmospheres. The dyspnea was less marked, but the respirations had a peculiar short and jerky character. Through-

out the period, the animals ate and drank normally and showed no loss of muscular power, a condition contrasted to the first group described.

In examining these animals post mortem so little deviation from the normal was found, grossly at least, that it seems unnecessary to transcribe the protocols in detail. In fact, it would seem to suffice

TABLE II.

Carbon Dioxide Rabbits.

Animal No.	Weight.			O_2		CO_2	
	Before experiment.	After experiment.	Loss.	Minimum.	Average.	Maximum.	Average.
	gm.	*gm.*	*gm.*	*per cent*	*per cent*	*per cent*	*per cent*
5	2,250	1,860	390	15.50	22.38	19.64	7.44
6	1,700	1,500	200	15.50	22.38	19.64	7.44
7	1,360	1,240	120	15.50	22.38	19.64	7.44
8	2,250	2,020	230	15.50	22.38	19.64	7.44

Animal No.	Length of exposure to different CO_2 tensions.										
	Under 1%	1-4%	4-6%	6-8%	8-10%	10-12%	12-14%	14-16%	16-18%	18-20%	Total.
	hrs.	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*	*hrs.*
5	4.0	46.5	25.0	25.0	8.0	10.0	2.0	27.5	5.5	7.0	160.5
6	4.0	46.5	25.0	25.0	8.0	10.0	2.0	27.5	5.5	7.0	160.5
7	4.0	46.5	25.0	25.0	8.0	10.0	2.0	27.5	5.5	7.0	160.5
8	4.0	46.5	25.0	25.0	8.0	10.0	2.0	27.5	5.5	7.0	160.5

The duration of experiment on each of the rabbits was from Oct. 28 to Nov. 4, 1915.

to point out how they differ from those of the reduced oxygen series.

Like the latter, the carbon dioxide animals lost weight and were found to have a minimum of body fat at the time of the postmortem. This occurred even though during the course of the experiment they appeared to eat normally.

The hearts showed no abnormality but the blood in the chambers was dark.

The lungs of the animals showed less emphysema of the free borders

than in the oxygen rabbits. Slight emphysema was noted in Nos. 7 and 8, none in Nos. 5 and 6.

The spleens of the animals showed a reduced amount of pulp which was also pale in contrast to the congested dark red pulp of the animals of the oxygen series.

The livers were of uniform color upon section and showed none of the fine mottling characteristic of the animals of the previous series, with the exception of Rabbit 7, which showed lobules with dark center and light periphery.

The kidneys were similar in appearance to those of the oxygen rabbits. Rabbit 5 showed many depressed cortical scars.

The most striking difference in postmortem findings was in the bone marrow taken from the center of the femur. The hyperplastic marrow of the reduced oxygen series was lacking. The marrow instead was soft, pale, and fatty. The absence of hyperplasia was fully confirmed by microscopic study. The bone marrows showed the presence of many adipose tissue cells and but a few peripheral groups of blood-producing elements.

The microscopic examination of the tissues of this series of animals showed a striking uniformity of lesions which were very slight in all cases and much less pronounced than those in the animals of the reduced oxygen experiments. The lesions were chiefly of a degenerative character and of the nature of the hydropic change noted in the other series.

The hearts uniformly showed, on section, muscle fibers which may be described as somewhat swollen, granular, and vacuolated (serous vacuolation). The vacuolation was never so extreme as in the earlier series. It showed, furthermore, a different distribution, being as well marked in the subpericardial layers of muscle fibers as in the deeper layers. Fatty infiltration was noted also in the hearts of Rabbits 5 and 8.

The lungs showed well marked congestion but no edema, very slight emphysema, and slight lymphoid hyperplasia.

The livers of the rabbits showed swollen, granular cells with a tendency to serous vacuolation. This was well marked in but one rabbit, No. 8, and in it was not of the degree seen in the oxygen deficiency rabbits. Moreover, in the four rabbits of the carbon dioxide series, the

change was more marked in the peripheral and mid-zone than in the central zone, the point of most marked change in the oxygen series.

The kidneys of the four rabbits showed a moderate swelling of the parenchymatous elements with increased granulation and some vacuolation. The last feature was well marked in Rabbits 6 and 8. The kidneys of Rabbits 5 and 8 showed old cortical scars and hyaline casts in the collecting tubules. Rabbit 7 also showed casts, and an albuminous precipitate in the glomerular capsular space.

The spleens showed well marked hyperplasia of the Malpighian corpuscles, and of pulp elements, with but moderate congestion. The spleen of Rabbit 5 showed an excess of hemosiderin in the pulp.

The thyroids showed a slight hyperplasia.

The aortæ showed slight fatty degeneration of the muscle fibers by a Sudan III stain, and serous imbibition was noted in the aorta of Rabbit 7.

The adrenals appeared normal.

The characteristic lesions in the rabbits exposed to a high carbon dioxide atmosphere may be summarized as very slight and of a degenerative character, affecting the parenchymatous cells of the heart and important glandular organs. This lesion which is of the nature of a serous imbibition, or vacuolar degeneration, is much less marked than in the animals exposed to an atmosphere deficient in oxygen and fails to show the same distribution, particularly in the heart and liver. Evidence of hyperplasia of the bone marrow is entirely lacking.

DISCUSSION.

In considering the results of these series of experiments, one finds in the oxygen deficiency series lesions of two types, those of a progressive or hyperplastic variety, and those of a retrogressive or degenerative character, while in the carbon dioxide series degenerative lesions alone are noted.

Another interesting contrast in the two sets of experiments is shown in the location of the degenerative lesions within certain of the affected organs. Thus in the oxygen deficiency experiments the lesion increases in intensity with increasing distance from the arterial blood supply. On the other hand, in the carbon dioxide experiments

the lesions are in general more marked the nearer the tissues are to the arterial supply. These facts are especially clearly brought out in the liver and in the heart muscle. The difference seems due to the fact that in one case we are dealing with a deficiency of a vital element in the arterial blood supply, whereas in the other we are dealing with a toxic agent reaching the tissues through the same medium.

The hyperplasia of the bone marrow, that is extension of the red marrow throughout the cavities of the long bones, found in the oxygen deficiency series is the most marked example of the progressive lesion. This finding is in accordance with the results obtained by Dallwig, Kolls, and Loevenhart[2] in animals subjected to the same experimental procedure as that employed here. This is a direct stimulation of the cells of the marrow to proliferation and differentiation by decrease in oxygen fixation of these cells and forms with the more prompt response of the respiratory center a good example of an adaptive mechanism of the body. The occurrence of degenerative processes in these animals would indicate, however, that the compensation was not adequate for the extremely low oxygen percentage maintained in the experiments.

Whether the hyperplasia of the thyroid may be looked on as the result of a deficiency in oxygen or as the result of some uncontrolled factor in the maintenance of the animals before or during the experiment must, perhaps, remain unanswered. Slight hyperplasia was noted in the thyroids of animals subjected to an increased carbon dioxide pressure, though not nearly so marked as in the oxygen deficiency series. If the theory that the thyroid is the gland controlling internal oxidation is maintained, such a hyperplasia would be expected in oxygen deficiency. Conversely, the finding of hyperplasia of the thyroid under these conditions may be urged as evidence in favor of the theory. It is to be noted further that this hyperplasia as a result of oxygen deficiency is in agreement with the marked hyperplastic state of the human thyroid which may be found in pernicious anemia where there is also a marked oxygen deficiency. Since it is well known that increased thyroid activity increases oxidation in the body it may be assumed, we believe, that in this

[2] Dallwig, H. C., Kolls, A. C., and Loevenhart, A. S., *Am. J. Physiol.*, 1915–16, xxxix, 77.

hyperplasia of the thyroid we have another adaptation to oxygen want.

The interpretation of the more general degenerative lesion in the rabbits of the oxygen series offers somewhat greater difficulty. The lesion is of the nature of an increase in the size of the cell with an increase in its fluid content and with apparently a decrease in the protoplasm, a lesion which has been termed hydropic degeneration, vacuolar degeneration, or serous imbibition. This lesion cannot be attributed to the inability of the experimenters to control the food intake in animals in the cages. The histological picture is entirely different from the simple atrophy found in young rabbits accidentally starved as a result of their having eaten sawdust or shavings, which accumulated in the stomach. Moreover, as pointed out, the lesion in the various organs is most marked at those points which are farthest from the blood supply, where in extreme cases anemic necrosis was found. The lesion appears then to be due definitely to a deficiency in oxygen.

Confirmation of this was offered by the tissues of a dog in the laboratory stock which had extreme stenosis of the trachea due to a marked goiter. A similar hydropic lesion was found throughout the parenchymatous organs.

It is of interest in connection with the theory of thyroid function, cited above, that the lesions found in these animals and attributed to oxygen deficiency are identical with the lesions described by Tatum[3] in animals which had been thyroidectomized early in life. Tatum notes that in this experimental cretinism "degenerative changes have been noted in practically every parenchymatous organ. Among these the most striking has been that of serous imbibition by the most active cells of these organs." Accepting the theory as to the function of the thyroid, Tatum's results confirm the interpretation we have given our results. Again, the converse is true. Our results, clearly due to changes in but a single factor, that of oxygen supply, explain Tatum's findings and support the contention that the thyroid is concerned in vital oxidation.

An attempt has been made by us to explain the morphological changes resulting from reduced oxidation upon the basis of physico-

[3] Tatum, A. L., *J. Exp. Med.*, 1913, xvii, 636.

chemical changes within cells. On this basis one might assume that as a result of reduced oxidation there occurs an increased osmotic pressure within the cell and a consequent increased flow of water into the cells. On the other hand, one might assume that as a result of suboxidation, an acid condition of the cell occurs which would in turn lead to acid imbibition by the colloids of the cells according to the theory of Fischer. It should be borne in mind that while decreased oxidation probably causes increased acidity, there is evidence that increased acidity leads to decreased oxidation. The experiments which we have performed do not enable us to determine whether the swelling of the cells was due to acid imbibition of the colloids or to the osmotic factor. The lesion itself as seen in the liver cell, for example, in the oxygen series is identical in appearance with that seen in the rabbit in moderate chloroform poisoning, in ether intoxication, and in extreme fatigue, as well as in the condition where the carbon dioxide content of the air is maintained at a high level. In the case of chloroform poisoning Graham[4] has drawn the conclusion that the pathological changes in the cell are due to the liberation of hydrochloric acid through the decomposition of chloroform, although he states in addition that chloroform is "a drug which is known to suppress oxidations." In carbon dioxide poisoning one must assume a cell retention of carbon dioxide with increased acidity, autolysis, and probably also suboxidation. In fatigue it is assumed that the edema of the cell is due to accumulation of acid waste products.

CONCLUSION.

Exposure of rabbits to an atmosphere of low oxygen content results in a stimulation of the cardiorespiratory systems, in an extension (hyperplasia) of red bone marrow and probably of a thyroid hyperplasia, with the further production of hydropic and hyaline degeneration in the cells of the parenchymatous organs. An atmosphere of high carbon dioxide and normal oxygen content produces, however, a stimulation of the cardiorespiratory systems, but no marrow extension and, in the concentrations used, but slight hydropic degeneration in the parenchyma of the glandular organs.

[4] Graham, E. A., *J. Exp. Med.*, 1912, xv, 307; 1915, xxi, 185, xxii, 48.