Blood Destruction in the Polycythemia Induced by Hypoxia

By Kurt R. Reissmann, M.D., William L. Burkhardt, M.D. and Bernard Hoelscher, M.D.

It has been demonstrated that in steady states of blood balance red cell destruction is not a random process, but that the red cells disintegrate and are removed from circulation after they have reached a certain age. The factors leading to the aging of the cell are not exactly known, yet for the problem under investigation it is irrelevant whether one considers the longevity of the corpuscle as being determined by inherent metabolic factors of the cell or by the continuous trauma of the wear and tear, or by a combination of both. The main point is that under physiologic conditions only a “passive” mechanism of blood destruction has been demonstrated, i.e., that blood cell destruction depends on properties of the cell and is under these conditions apparently neither accelerated nor delayed by factors acting upon the cell.

Little information is available on the rate of blood destruction in unsteady states of blood balance, especially when the cell level is temporarily increased above normal. The question arises whether the normal organism has the capacity at all to destroy normal red cells at an increased rate and regardless of their age and other properties. If such an “active” mechanism of blood destruction exists, it should be demonstrable during transient polycythemia.

Indications of such an active blood destruction were found by earlier investigators after inducing a polycythemia by infusion of red cells. But recently, Birkhill, Maloney and Levenson reported that the normalization of a transfusion polycythemia is brought about by a “passive” mechanism, i.e., by a throttling of erythropoiesis while the cell destruction proceeds at a normal rate. These authors found an almost linear mortality curve of the infused donor cells and no significant increase in fecal urobilinogen excretion. The depression of erythropoiesis was reflected by very marked changes in the myeloid-erythropoietic ratio of the bone marrow cells.

The production of a marked transfusion polycythemia necessarily introduces unphysiologic factors. We therefore studied the blood destruction after inducing a polycythemia by exposure to reduced barometric pressure. Within a few weeks of exposure to a simulated altitude of 20,000 feet, the total circulating red cell mass increases to about 170 per cent of the ground level value and returns to normal within six to eight weeks after discontinuation of the exposure; yet these very marked fluctuations of hemoglobin can still be considered as physiologic responses to the new environment.

Our experiments were designed to provide information on: (1) whether the return of an altitude polycythemia to normal after termination of the altitude....

From the Departments of Physiology and Internal Medicine, USAF School of Aviation Medicine, Randolph Field, Texas
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exposure, henceforth called "normalization," is a passive process achieved by a throttling of blood formation, or whether an increased blood destruction can be demonstrated by which the cells not needed in the new environment are rapidly removed from circulation; (2) how the bile pigment excretion reflects the rapid formation of large amounts of red cells during the first weeks of altitude exposure.

METHODS

Internal-type bile fistulas (Kapsinow, Engle and Harvey) were established in mongrel dogs previously freed of intestinal parasites. Under ether anesthesia the common duct was ligated and severed, the gall bladder in part isolated from the liver bed, and sewed into the pelvis of the right kidney. In some cases a diffuse hemorrhage from the gall bladder wall caused obstruction of the fistula by blood clots. Only such animals were used in the experiments that had never shown any signs of icterus during the postoperative observation period of two months. The dogs were kept in metabolism cages, and the urine was collected every 24 hours. Every morning the dogs received 300 ml. water through a stomach tube to cause the dogs to void before the daily sample of urine was collected. The animals were fed a constant diet of raw horse meat and Purina dog chow. A supplement of 0.6 Gm. sodium taurocholate in gelatine capsules and 1 Gm. of yeast were given daily, and 5 ml. cod liver oil per os and 2 mg. menadione sodium bisulfite (vitamin K) intramuscularly twice a week. The stool of the animals was always well formed; no steatorrhea was observed. The animals were weighed at least once a week, and those with abnormal weight loss discarded.

The blood cell destruction in these animals was studied by measuring the total circulating hemoglobin and the daily excretion of bile pigment during the development and disappearance of polycythemia induced by exposure to hypoxia. After obtaining baseline values at ground level over sufficiently long periods, the animals were exposed in a decompression chamber to 16,000 feet simulated altitude. During one week the altitude was gradually increased to 20,000 feet. One group of 3 dogs was kept at this altitude for six weeks, then returned to ground level and observed for twenty weeks. The second group of 3 dogs was exposed to 20,000 feet for over twenty-two weeks and then returned to ground level. The third group was repeatedly exposed for various periods and at intervals.

After termination of the experiments an autopsy was performed on each animal and special attention was given to the complete separation of the bile ducts from the duodenum. To this end approximately 30 ml. of dye were injected into the gall bladder after a clamp had been placed on the right ureter, and the dye was massaged towards the duodenum. In no instance was any dye found in the duodenum, which demonstrates that the separation had been complete and that no recanalization or secondary ducts had developed.

The bile pigments in the 24 hour volume of urine were determined by a method similar to that of Whipple and associates. The calcium-bile pigment precipitate was dissolved in 100 ml. acid alcohol and divided into aliquots of 20 ml. to which increasing amounts of yellow nitric acid were added. The densities of the samples were measured in the spectral region of 640 m\(\mu\) every 30 seconds, and the highest value obtained was used, provided no turbidity was detectable. Calibration curves were obtained with purified bilirubin standards. The plasma bilirubin was measured by the method of Malloy and Evelyn. The absence of urobilinogen in the stool was checked during certain control periods with Watson's method.

The total circulating hemoglobin was obtained from the blood volume and the hemoglobin concentration. The latter was determined as oxyhemoglobin in the Beckman spectrophotometer at a wave length of 541 m\(\mu\) and 565 m\(\mu\). The blood volume was estimated from the plasma volume and the corrected haemocrit. The plasma volume was determined weekly with the dye method (brilliant vital red). Although the blue dye T-1824 has distinct spectrophotometric advantages, it could not be used because it is in part excreted in the bile, and, the spectral absorption being similar to that of biliverdin, interferes with the determination of the bile pigments. The dye concentration in the plasma withdrawn 15, 30, 45 and 60 minutes after injection was measured with the Beckman spectrophotometer.
and corrected for hemolysis according to the Vierordt principle. The densities were plotted semilogarithmically and extrapolated towards the time of injection. Details are given elsewhere. The amount of plasma remaining trapped between the cells in the hematocrit determinations (Chapin and Rose) was determined for the centrifuge used and found to be 6.5 per cent. A correction factor of 0.935 was therefore applied to all hematocrit values.

The liver function was tested by injecting 5 mg. bromsulfalein per Kg. body weight. The concentration of bromsulfalein in the plasma withdrawn 30 minutes after injection was compared in the Evelyn colorimeter with bromsulfalein standards in plasma, which were chosen in such a way that normal dogs gave retention values below 20 per cent. The ability of the liver to remove circulating hemoglobin was tested by intravenous injections of 2 Gm. hemoglobin, similar to the procedure used by Whipple.

**Comments on the Procedure**

Aside from the recent findings of London that part of the bilirubin is not derived from broken-down erythrocytes, the accuracy of the bile-fistula method in the quantitative measurement of the hemoglobin catabolism is affected by methodical errors inherent in the determination of the bile pigments in the urine-bile mixture, and by the liver damage found in bile-fistula dogs. The bile pigments in the urine-bile mixture represent a mixture of bilirubin, biliverdin and, to some extent, even higher oxidized derivatives. A reduction of these substances is not possible; their estimation therefore has to be carried out after oxidation of the bilirubin to biliverdin and after separation of the bile pigments from other urinary pigments. The conversion of bilirubin to biliverdin, however, does not lead to a steady end-point, but eventually to colorless substances. The efficiency of the oxidation depends on the amount of yellow nitric acid and the concentration of the bile pigments; the time course of the reaction is unpredictable. We tried to minimize analytical losses by a stepwise oxidation as described above.

Drill and associates described abnormalities in liver function tests on bile-fistula dogs some of which however were apparently icteric. We can confirm these observations. In our bile-fistula dogs, whose icteric indexes were perfectly normal, we found retentions of bromsulfalein ranging from 30 to 76 per cent, while the retention in normal dogs determined with identical technic was less than 20 per cent. No correlation was found between the degree of retention and the time lapse after the establishment of the bile fistula or the duration of the experiment.

The histologic examination of the liver at the end of the experiments revealed no damage of the liver parenchyma. The outlines of the lobules were well preserved and no signs of cellular disintegration or proliferation of the portal connective tissue were found.

The liver damage, as detected with the bromsulfalein test, did not impair grossly the ability of the animals to remove, metabolite and excrete intravenously injected hemoglobin. Intravenous injections of 2 Gm. hemoglobin in saline were given in small doses over periods of five consecutive days during the ground level period, during altitude exposure, and during the postexposure period, respectively. These five day periods were chosen at times when the animal showed a uniform daily bilirubin excretion. The elevation of bile output on the days of hemoglobin injection over the pre- and postinjection levels was assumed to be due to the injected hemoglobin. As 36 mg. bilirubin are chemically equivalent to 1 Gm. hemoglobin, the recovery of the injected hemoglobin could be calculated and was found to be 70 to 86 per cent. Much smaller recoveries were made when the 2 Gm. hemoglobin were injected in one single dose. Apparently, the plasma hemoglobin level exceeded in this case the glomerular threshold (Yuile Ottenberg), and part of the injected hemoglobin was excreted via the kidneys. To exclude a similar loss of pigment during the altitude experiments, especially in the period after return to ground level when large amounts of hemoglobin disappear from circulation, the urine of the dogs was examined for hemoglobin.

In the turbid urine-bile mixture neither spectrophotometric methods nor Bing's quantitative benzidine reaction, nor the pyridine hemechrome method of Flink and Watson was found to be applicable for the hemoglobin determination. Therefore, iron determinations were carried out with the modified Kennedy method, and the difference in the iron content of the samples with and without previous precipitation with trichloracetic acid was used...
as an estimate of the hemoglobin content. These investigations will be reported in detail elsewhere; it is sufficient to state here that the hemoglobin found in the daily urine samples never exceeded 150 mg. and was usually much less. This small amount of pigment can be neglected in the problem under investigation.

The determination of the blood volume from the plasma volume, as measured by the dye method, is open to criticism because the venous hematocrit does not represent the average body hematocrit. The direct determination of the cell volume with labeled red cells was infeasible because the repeated infusion of tagged red cells would have interfered with the investigation of the hemoglobin catabolism. The total circulating hemoglobin values

![Graph](image)

**Fig. 1.**—Bilirubin excretion, total circulating hemoglobin and hemoglobin concentration in a bile-fistula dog in the course of a seven week exposure to 20,000 feet altitude. Each column represents the daily bile pigment output averaged per week.

are therefore probably too high, and the calculations of the blood balance based on these figures do not claim a high degree of accuracy.

**Results**

The data are presented graphically in figures 1, 2, 3 and 4. The changes in total circulating hemoglobin and hemoglobin concentration during exposure to hypoxia do not need an interpretation. The daily determined bile pigment excretions were averaged for each week. A fairly uniform bile output was observed during the first period at ground level, the average daily bilirubin excretion varying between 3.9 and 5.1 mg. per Kg. body weight in the individual animals.

During the first weeks of exposure to hypoxia a definite increase in bile pig-
ment excretion was found in most of the experiments. This increase varied with the individual animal; e.g., it amounted to 50 per cent in the dog demonstrated in figure 1 and was much less in other animals. No significant correlation was found between the increase in bile pigment output and the magnitude of the hematopoietic response to hypoxia. The pigment excretion reached a maximum in the second and third weeks and returned to baseline values after six to eight weeks of exposure.

The different durations of the exposures to hypoxia, as indicated in the graphs, were chosen because in evaluating the bile pigment output in the course of altitude polycythemia, due consideration must be given to the fact that within the

![Graph showing bilirubin excretion, total circulating hemoglobin and hemoglobin concentration in a bile-fistula dog in the course of two exposure periods to 20,000 feet altitude. Each column represents the daily bile pigment output averaged per week.](image)

first two or three weeks of altitude exposure a large number of red cells is formed and that, therefore, the age distribution of the red cell population is not uniform. Assuming a life span of the red cell of approximately one hundred days, the first group of dogs was exposed to 20,000 feet altitude over a period of six weeks, which is relatively short, though sufficient to produce marked polycythemia; thereafter they were returned to ground level. In this case, it could be expected that the normalization of altitude polycythemia took place before the life span of the red cells formed in the first week of the exposure was exhausted. The results of one of these experiments are presented in figure 1. In the first two weeks after termination of altitude exposure, a definite increase in bilirubin excretion was observed; yet, in the following weeks the bilirubin output was similar to that found during the baseline period. A second peak of bile pigment output occurred
in the twenty-seventh and twenty-eighth weeks of the experiment. This peak was very likely caused by the destruction of those red cells which had been rapidly formed in relatively large amounts during the second and third weeks of exposure. The time interval between this rapid rise of hemoglobin and the peak of bile pigment output was found to be about 115 days, and represents the life span of the red cells formed during altitude exposure. It is of the same order of magnitude as that found in dogs with other methods.\textsuperscript{19-21}

![Graph](image_url)

Fig. 3.—Bilirubin excretion, total circulating hemoglobin and hemoglobin concentration in a bile-fistula dog in the course of a twenty-two week exposure to 20,000 feet altitude. Each column represents the daily bile pigment output averaged per week.

In the experiment demonstrated in figure 1, the total hemoglobin at the end of altitude exposure amounted to 210 Gm. and returned to 150 Gm. within 50 days after return to ground level. Hence, 60 Gm. hemoglobin disappeared from the circulation within this time; this amount includes the 18 Gm. which were withdrawn during this time for the various determinations. Thus, the amount of hemoglobin that actually disappeared from the circulation in the organism was 42 Gm. This decrease in total hemoglobin can be caused by (1) decreased erythropoiesis while the blood destruction proceeds at a normal rate, in which case the bile pigment excretion would be similar to the values found during the baseline period; (2) by an increased blood destruction which would be reflected by an increased bile pigment excretion; (3) by a combination of both.
The bilirubin output in excess of the baseline value during these 50 days amounted to 232 mg. Assuming that only 70 per cent of the actually excreted bilirubin was detected (this value was obtained in recovery experiments after injection of a known amount of hemoglobin as described above), the value of 232 mg. has to be corrected to 320 mg. bilirubin, which are equivalent to 9 Gm. hemoglobin. Therefore, of the 42 Gm. hemoglobin removed by the organism during 50 days after termination of altitude exposure, only 9 Gm. were removed by an increased blood destruction. The decrease in circulating hemoglobin by the remaining 33 Gm. must have been brought about by a throttling of erythropoiesis provided there was no conservation of the pyrrole nucleus nor a formation of end products other than bile pigments in the hemoglobin catabolism. The degree of this depression of erythropoiesis can be estimated if one assumes that of the 135 Gm. of circulating hemoglobin measured during the baseline period, 0.8 per cent were destroyed and newly formed every 24 hours under normal conditions, as is indicated by the daily bilirubin output of 34 mg. found in this animal during the baseline period. The normal blood production in this animal therefore amounted to 1.1 Gm. hemoglobin per 24 hours, and to 50 X 1.1 Gm. or 55 Gm. of hemoglobin over a 50 day period. If the hemoglobin that had to be eliminated, namely 33 Gm., is subtracted from this value, the resulting 22 Gm. constitute the amount of hemoglobin actually produced during the 50 day period after return to ground level; i.e., the erythropoiesis during this period was only 42 per cent of the normal.

The results of experiments of this type were fairly reproducible as shown in figure 2. This dog was exposed twice to 20,000 feet altitude, the first time over a

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Fig. 4.—Bilirubin excretion, total circulating hemoglobin and hemoglobin concentration in a bile-fistula dog in the course of two exposure periods to 20,000 feet altitude. Each column represents the daily bile pigment output averaged per week.
period of ten weeks and, after an interval of fifteen weeks at ground level, a second time for a period of seven weeks. The bile pigment output in this animal was followed throughout fifty-four weeks. In the first part of the experiment the life span of the red cells, as determined by the time interval between the abrupt rise in hemoglobin during the second week of altitude exposure and the peak of bilirubin output, was found to be fifteen weeks, and in the second part of the experiment sixteen weeks. During six weeks following the first exposure to hypoxia, 40 Gm. hemoglobin were removed from the circulation by the organism, and 41.5 Gm. during the same time after the second exposure. Of these amounts the equivalent of 14 Gm. hemoglobin was recovered as excess bile pigment output after the first exposure, and 16.5 Gm. after the second. Erythropoiesis was throttled to 31 per cent of the normal in the six weeks after the first exposure, and to 33 per cent after the second.

The results of the experiment presented in figure 4 are of particular interest. This dog was exposed to hypoxia twice, and the bile pigment output was followed over a period of sixty-one weeks. The first exposure to altitude was extended to five weeks; after an interval at ground level, the second exposure was arranged in such a way that the breakdown of the relatively great amount of corpuscles rapidly formed in the first three weeks of altitude exposure, occurred in the period when the dog was returned to ground level. In the six week ground level period following the first exposure, 90 Gm. hemoglobin disappeared from circulation, 38 per cent of which were removed as excess in bilirubin output and had, thus, been removed by an increased blood destruction. The remaining normalization was brought about by a depression of erythropoiesis, and the blood formation during the six week period was estimated at 25 per cent of the animal's normal erythropoiesis. An entirely different result was obtained after the second exposure. Within eight weeks, the total hemoglobin returned to ground level values, and 105 Gm. hemoglobin disappeared from circulation, 25 Gm. of which had been withdrawn by blood sampling. The net amount removed by the organism was, therefore, 80 Gm. hemoglobin, which are equivalent to 2,880 mg. bilirubin. The excess in bile pigment output during this period was found to be 2,434 mg.; with the same allowance being made for undetected bilirubin as in other experiments, this figure has to be corrected to 3,480 mg. The bilirubin output in this experiment was much greater than in all others, and was due to the fact that the life span of the cells rapidly formed during the first three weeks of altitude exposure had expired, and that these cells were rapidly destroyed. This destruction already began in the two weeks before the animal was returned to ground level, as indicated by the rise in bilirubin excretion. Under these conditions the excess in bile pigment output even exceeded the amount of hemoglobin which apparently disappeared from circulation. It can therefore be concluded that erythropoiesis was not depressed as usual, but must have increased during the first weeks after return to sea level.

The second group of dogs was exposed to 20,000 feet over a period of twenty-two weeks. It was expected that in this case the red cells rapidly formed during the first weeks of altitude exposure would be destroyed while the animals were still at altitude. Figure 3 shows one of these experiments. The time interval between the abrupt rise in hemoglobin and the peak of bile pigment excretion was
found to be about 110 days, indicating that no differences exist between the life span of red cells at ground level and that during exposure to hypoxia. In this experiment, the age distribution of the red cell population at the end of altitude exposure was more uniform than in the experiments described in figures 1 and 2, because the red cells formed during the ground level period were presumably no longer in circulation, and the cells rapidly formed in the first week of exposure were already broken down. However, the normalization of polycythemia after discontinuation of the altitude exposure was found to be similar to that described in the experiments above. In the experiment presented in figure 3, the net decrease in hemoglobin was 57 Gm. during the eight week period following the return to ground level. The bile pigment excretion in excess of the baseline value was equivalent to 28.3 Gm. hemoglobin. As the total drop in circulating hemoglobin was found to be 57 Gm., while only 28.3 Gm. can be accounted for by a stepped-up blood destruction, the remaining decrease in hemoglobin must have been brought about by a depression of erythropoiesis below the normal turnover. With a computation method similar to that described above, the erythropoiesis during the eight week period following return to ground level was found to be 50 per cent of the normal. This value is higher than those in the other experiments, probably because the destruction of the cells, which were rapidly formed in the first weeks of altitude exposure and whose life span expired in the twenty-fifth and twenty-sixth weeks of the experiment, was not quite completed when the animal was returned to ground level.

DISCUSSION

1. The Bile Pigment Excretion during the Development of Altitude Polycythemia

Bilirubinemia in man during a few weeks sojourn at high altitude has been reported by various investigators (Talbott and Dill, Monge, Hurtado, Merino, Verzár, Verzár and Vogtli) but only a few studies were carried out on the bile pigment excretion. Heilmeyer found in man a decrease in the fecal and total urobilinogen excretion and an increase in the urinary bile pigments during two weeks sojourn at 8,500 feet. However, in view of the moderate altitude, the significance of these findings is doubtful. Verzár and Vogtli found in man increases of 25 to 56 per cent in the fecal urobilinogen excretion during a few days sojourn at 11,300 feet (Jungfrau-Joch), and in rats a 10 per cent increase under the same conditions. (The rat, in our experience, is not a suitable animal for experiments involving urobilinogen determinations. In many instances we found that a complete reduction of the urobilin in the rat feces to urobilinogen could not be achieved, even by repeated reductions according to the Terwen-Watson method. Similar observations have been reported by Lemberg.) Merino found increases in fecal urobilinogen excretion in 5 of 6 test subjects during a sojourn at Morococha (14,900 feet). The highest values of fecal urobilinogen were found in subjects that showed the largest increases in circulating hemoglobin. However, in those studies the urobilinogen excretion was not measured continuously from day to day, but only during certain periods.

Our observations confirm the findings of Verzár and of Merino; we found a definite increase in bile pigment output during prolonged exposure to hypoxia.
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The maximum of this increase appears to occur during the development of altitude polycythemia.

This apparent waste of pyrrole nuclei during a time of very markedly increased erythropoiesis has aroused some speculation on the underlying mechanism; and especially Verzár and his school have placed much emphasis on this subject. They concluded that the increased bile pigment output during hypoxia in connection with bilirubinemia substantiates an increased blood destruction and suggests that the bilirubin liberated in the initial phase of altitude exposure acts as the stimulus in promoting the increased erythropoiesis. In generalization of this hypothesis it has been proposed that even under normal conditions the breakdown products of the heme molecule, notably bilirubin, serve as the physiologic stimulus of erythropoiesis. Such a “feed-back” mechanism would explain the self-regulation of the equilibrium between destruction and formation in a very attractive way. Verzár and associates claim an erythropoietic effect of bilirubins administered parenterally or even orally. Bomford found, after intravenous injection of 50 mg. bilirubin in anemic dogs, an increase in the rate of hemoglobin production and a prolonged reticulocyte response. Bomford does not believe, however, that the bilirubin acts as a hormone-like stimulus, and suggests that bilirubin improves in some way the absorption of iron. A reinvestigation of the erythropoietic effect of bilirubin and other breakdown products on a sound statistical basis appears necessary before Verzár’s theory can be discussed further.

The increased bile pigment output during the development of altitude polycythemia has gained new aspects by recent investigations on the metabolic origin of the bile pigments. In extending the fundamental work of London, West, Shemin, and Rittenberg, Gray and co-workers discriminate, on the basis of tracer experiments with \( \text{N}^{18} \) labeled glycine, three different metabolic fractions of the bile pigment: fraction 1 (about 70 per cent of the total bile pigment) originates from the breakdown of circulating hemoglobin; fraction 2 (about 10 to 15 per cent) originates from the breakdown of porphyrins other than hemoglobin (cytochrome, catalase, myoglobin); and fraction 3 (about 15 to 20 per cent), which causes an initial peak of the \( \text{N}^{18} \) concentration in the bile pigments, is believed to be associated with the red cell formation. It is conceivable that the increased bile pigment output during the development of altitude polycythemia is, at least in part, related to this third fraction. Details on the origin of this fraction of the bile pigments are still hypothetical.

2. The Bile Pigment Excretion during the Normalization of Altitude Polycythemia

An active blood destruction during the disappearance of altitude polycythemia was suggested by various investigators who described a bilirubinemia in man during the de-acclimatization period, and by studies on the urobilinogen excretion. Heilmeyer, Verzár and Merino reported increases in the fecal urobilinogen during the first weeks after return to sea level of humans who had spent several weeks at altitude.

Recently, J. H. Lawrence and his group reported studies made in Peru on the effect of altitude on hematopoietic activity. As to the normalization of altitude polycythemia, these authors conclude, on the basis of measurements of the iron turnover, that after return to sea level of an acclimatized subject about
half of the decrease in the red cell mass is due to a decreased cell production, and the other half presumably to an increased blood destruction.

Our results, obtained through an entirely different approach, are in good agreement with the findings of Lawrence and his associates, and indicate that the normalization of the altitude polycythemia after return to sea level is achieved by the combined effect of a depressed erythropoiesis and of an increased blood destruction. The major effect is that of the greatly depressed erythropoiesis, which was 30 to 50 per cent of the normal cell production during six weeks following the termination of altitude exposure. The increased blood destruction, on the other hand, is indicated by the increased bile pigment output during the first two weeks after return to sea level.

It was further demonstrated that the cells which were in circulation at the time the animals were returned to ground level were undamaged and had a normal life expectancy. One must, therefore, accept the existence of an "active" mechanism of blood destruction through which the organism can destroy, under certain conditions, normal red blood cells before their life span is expired. The appropriate stimulus, the pathways, and other details of this mechanism are as yet unknown.

Summary

The hemoglobin catabolism during the development and during the disappearance of polycythemia induced by hypoxia was studied by measuring the total circulating hemoglobin and the daily bile pigment excretion in bile-fistula dogs before, during, and after prolonged periods of exposure to 20,000 feet simulated altitude.

1. The increased erythropoiesis during the first weeks of altitude exposure was accompanied by a significant increase in bile pigment output. The possible sources of this pigment excretion are discussed.

2. The life span of the red cells during altitude exposure was found to be about 115 days. No differences were observed in the longevity of the cells in animals at ground level and at altitude.

3. The normalization of the polycythemic blood levels took place within six to eight weeks after return to ground level, and was achieved by the combined effect of a depressed erythropoiesis and of an increased blood destruction. The increase in red cell destruction observed under these conditions demonstrates the existence of an "active" mechanism of blood destruction by which the organism is able to destroy normal blood cells before their life span is exhausted. This increased red cell destruction, however, accounted for only 21 to 39 per cent of the hemoglobin which disappeared from circulation after return to ground level. The major part of the normalization of altitude polycythemia was brought about by a temporary depression of erythropoiesis which was estimated to amount to 30 or 40 per cent of the normal cell production in the six weeks after the discontinuation of the altitude exposure.

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KURT R. REISSMANN, WILLIAM L. BURKHARDT and BERNARD HOELSCHER

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