paragine were determined by the procedure of Vickery *et al.*[12] Total soluble N was determined on 3 per cent. trichloroacetic acid filtrates. Van Slyke α-amino N was determined on the deproteinized filtrates after the amides were hydrolyzed for 2 hours with 2N HCl at 100° C. followed by the liberation of the ammonia on the steam bath at pH 7.5.[13] The α-amino N associated with the amides was subtracted from this value to give the α-amino N reported in Table 1.

Since the data from the roots are similar, they will not be given here, except to note that the roots gained only 10 per cent. in dry weight during the experimental period, whereas the tops gained over 60 per cent. during the same period. This experiment has been repeated in the spring season with substantially similar results.

Discussion

The data of Table 1 indicate that the plants absorbed large quantities of ammonium N and made substantial growth. There was no significant trend in "true protein" N, but the nitrogen absorbed in excess of the plant's requirements went into the formation of glutamine, asparagine and one or more amino acids. There was also a great increase of undetermined forms of soluble N. Ammonia does not accumulate in the neutral sap until the amides and other soluble nitrogen constituents have reached a relatively high level. The factor or factors preventing further utilization of this absorbed ammonia are not known, but carbohydrate would not appear to be the limiting factor. It is appropriate to recall Prianischnikow's[14] speculation that ammonia may not always be the toxic agent, but the accumulation of some product arising from the utilization of the ammonia.

That the increase in α-amino N observed here is a net increase and does not come from the degradation of protein is inferred from the stable values for "true protein" N. This role of amino nitrogen has apparently not been appreciated in the past, since in the usual type of experiment with etiolated seedlings or excised leaves the amino acids arise from protein hydrolysis and, hence, their role in metabolizing ammonia can not be appraised. This function of amino N may not be universal, however; for Vickery, Pucher and Clark[15] found that all the ammonia absorbed by the beet was transformed into glutamine.

This rapid synthesis of one or perhaps more α-amino acids offers the possibility of a new approach to the study of amino acid synthesis and protein regulation in the plant.

Summary

When corn seedlings, previously depleted in soluble nitrogen constituents, are forced to absorb large quantities of ammonium nitrogen, soluble compounds accumulate in the sap. Asparagine, glutamine, one or more amino acids and undetermined compounds are synthesized. Ammonia does not accumulate until these constituents have reached a relatively high level.

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[12] H. B. Vickery, G. W. Pucher, H. E. Clark, A. C. Chibnall and R. G. Westall, *Biochem. Jour.*, 39: 2710, 1935.

[13] Personal communication from T. C. Broyer and D. R. Hoagland, University of California.

[14] D. Prianischnikow, *Z. Pflanzenernahr. Dungung*, 4A: 242, 1925; *ibid., Jour. Russian Botan. Congress*, 1: 65, 1921. (Abstracted in *Chem. Abs.*, 19: 3288, 1925.)

[15] H. B. Vickery, G. W. Pucher and H. E. Clark, *Plant Physiol.*, 11: 413, 1936.

THE EFFECT OF TRANSFUSIONS OF RED BLOOD CELLS ON THE HYPOXIA TOLERANCE OF NORMAL MEN[1, 2]

ONE of the most striking physiologic changes during acclimatization to high altitudes is the development of polycythemia.[3, 4] An artificial polycythemia has been produced in experimental animals by means of cobalt administration and has apparently increased their tolerance to hypoxia.[5] It appeared of interest to learn whether polycythemia induced in normal men by the transfusion of red blood cells would increase their tolerance to altitude hypoxia.

Experimental Procedure

A group of ten normal young men was divided into two groups of five each so that the mean ages and body weights were comparable. During the first two weeks of the experiment, control observations were made on both groups. These consisted of determinations of oxygen capacity of the blood; arterial oxygen (using arterialized venous blood[6]) and carbon dioxide content and pH of the serum at sea level and at a simulated altitude of 15,500 feet in a low pressure chamber; oxygen and carbon dioxide content of alveolar air; total urinary pigments; reticulocyte per-

[1] From the Naval Medical Research Institute, National Naval Medical Center, Bethesda 14, Maryland.

[2] The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

[3] D. B. Dill, "Life, Heat and Altitude." Cambridge: Harvard University Press, 1938.

[4] A. Hurtado, C. Merino and E. Delgado, *Arch. Int. Med.*, 75: 284, 1945.

[5] S. S. Dorrance, G. W. Thorn, M. Clinton, H. W. Edmonds and S. Farber, *Am. Jour. Physiol.*, 139: 399, 1943.

[6] S. Goldschmidt and A. B. Light, *Jour. Biol. Chem.*, 64: 53, 1925.

centages; blood volume by the carbon monoxide technic; and pulse rate, respiratory rate and respiratory minute volume responses to exercise, breathing air and various low oxygen mixtures.

From the fourteenth day of the experiment to the seventeenth day inclusive, a total of 2,000 ml of a 50 per cent. suspension in dextrose and saline of red cells prepared from blood drawn less than 24 hours previously was injected intravenously in each of the men in the first group (hereinafter known as the transfused group or T.G.) and a total of 2,000 ml of the dextrose and saline diluent alone was injected intravenously in each of the men in the second group (hereinafter known as the control group or C.G.). Arrangements were made so that no man knew whether he was receiving red cells or dextrose and saline. The above physiological and biochemical observations were then resumed on both groups and continued for two months.

RESULTS

The transfusions of red cells were accomplished without any untoward sequelae other than urticaria in one man. There was neither hemoglobinuria nor increase in total urinary pigments. Both the oxygen capacity and the arterial oxygen content of the transfused group at sea level and at 15,500 feet increased significantly as a result of the transfusions (Fig. 1).

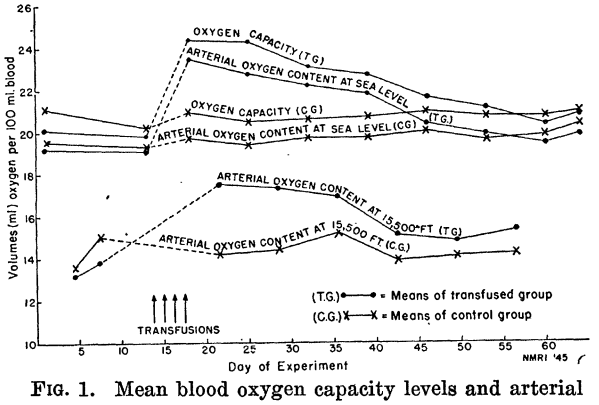

FIG. 1. Mean blood oxygen capacity levels and arterial oxygen contents at sea level and at 15,500 feet of ten men, five of whom were transfused with 2,000 ml of a 50 per cent. red cell suspension over a period of four days (transfused group) and the remaining five transfused with an identical volume of dextrose in saline solution (control group) over the same period.

One of the most striking observations was that the oxygen saturation of the arterial blood both at sea level and at altitude was unchanged by the transfusions. In other words, the hemoglobin of the transfused red cells as well as of the original cells was being effectively oxygenated. During the polycythemic period the pulse rate following exercise when breathing low oxygen mixtures was significantly lower than control measurements (Fig. 2). The pulse rate

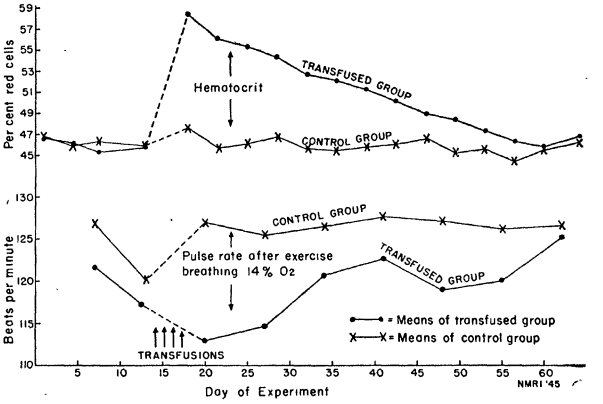

FIG. 2. Mean blood hematocrit levels and pulse rates after exercise when breathing 14 per cent. oxygen of ten men, five of whom were transfused with 2,000 ml of a 50 per cent. red cell suspension over a period of four days (transfusd group) and the remaining five transfused with an identical volume of dextrose in saline solution (control group) over the same period.

following exercise at simulated altitude appears to be an objective method of determining hypoxia tolerance in groups of subjects. The polycythemia persisted approximately six weeks (Figs. 1 and 2). There was no significant difference in the reticulocyte percentages of the two groups. The detailed results of all the various determinations will be presented in a forthcoming paper.

COMMENT

It is believed that this procedure of red cell transfusion in normal men reproduces to a large extent the physiological pattern of acclimatization to altitude. There were both subjective and objective indications that the transfused group tolerated hypoxia significantly better than the control group. The fact that the red cells persisted six weeks is of considerable interest. This period is longer than might have been anticipated from homeostatic considerations and yet shorter than what is said to be the life of the human red cell following transfusion,[7,8] namely, about three months. Thus, either the transfused cells were destroyed at a slightly increased rate or the polycythemia resulted in a reduction of the stimulus to normal erythropoiesis. Neither the urinary pigment excretion nor the reticulocyte counts of the transfused group, however, differed significantly from that of the control group.

The use of "arterialized" venous blood[6] for arterial

[7] W. Ashby, *Jour. Exp. Med.*, 29: 267, 1919.
[8] A. S. Wiener and G. Schaefer, *Med. Clin. N. Amer.*, 24: 705, 1940.

blood chemistry has been validated in this laboratory by comparison with blood obtained by arterial puncture in both normal and polycythemic (induced by red cell transfusion) men at various degrees of oxygen saturation.

CONCLUSION

The direct transfusion of erythrocytes into normal young men appears to be a safe procedure and when the volumes transfused are sufficiently great, the resultant polycythemia appears to afford increased tolerance to hypoxia. The polycythemia persists approximately six weeks.

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CYTOPLASMIC DISEASES AND CANCER

RECENT articles by Dixon,[1] Potter[2] and others prompt us to review various data obtained in certain fields and to interpret these in the light of a theory we have proposed that links three groups of diseases: namely, virus diseases, variegational diseases and cancer. The theory is based on the similarity of plants and animals at cellular and subcellular levels. Realization of this similarity has repeatedly shown the way to new approaches in research. We only have to mention a few cases: (a) the laws of heredity, proven for plants and applied to animals; (b) studies on enzyme and respiration processes in yeast and organs of higher plants, often elucidating similar processes in animals; (c) studies on plant viruses, indicating the way for isolation and purification of animal viruses; (d) studies on lower plant and animal forms, demonstrating the similarity of these forms on a cellular level.

That the ultimate agent of cancer may reside in the cytoplasm was suggested by Warren Lewis,[3] among others, in 1936. However, he did not specify what component of the cytoplasm might be involved. In recent years there has been an increasing tendency[2,3,4] to consider many cancers as cytoplasmic diseases and to regard the nuclear abnormalities associated with them of a secondary nature. Without doubt certain diseases of the tumor type are induced by viruses: *e.g.*, the Shope papilloma and Rous sarcoma. Oberling[4] has suggested that all cancers may ultimately be shown to be virus diseases. However, in the great majority of cases it has not been possible to demonstrate a causal virus. Moreover, the induction of cancer by specific carcinogenic agents such as methylcholanthrene, x-rays, etc., can be explained on the basis of the pure virus theory only when a series of rather involved assumptions are made. Granting that some cancers may be cytoplasmic diseases, that viruses are for the most part typically associated with the cytoplasm and that at least some cancers are virus-induced, what evidence do we have for a theory which reconciles both the virus and the so-called non-virus theories of cancers?

There have been numerous theoretical discussions on this subject, but in practically all instances definite experimental or observational evidence has been lacking. After Bensley and Hoerr[5] in 1934 separated mitochondria from liver tissue, Claude[6] in 1940 isolated from tumor tissue macromolecular complexes containing ribose nucleoprotein. He subsequently suggested that these fractions might be identical with mitochondria and that they might have an etiologic significance. However, considering the rate of cell division of neoplastic tissues, the mere presence of mitochondria in such tissues is not of itself significant, because mitochondria are always abundant in dividing tissue. Claude could not show that the fraction differed qualitatively from a similar fraction obtained from normal tissues nor did he point to any analogous case in which plant or animal mitochondria function as pathogenic entities.

As a result of studies on the interrelations of plastid chromoprotein, tobacco mosaic protein and cell metabolism, Woods and duBuy suggested in 1941[7] that a fundamental relationship might exist between mitochondria (or plastids, which are specialized mitochondria *sensu* Guilliermond) and virus proteins. Later, in 1943,[8,9] they were able to show that plant variegations are diseases often of virus-like nature, which are caused by abnormal cytoplasmic particulates of hereditary character: the plastids or mitochondria. That plastids can be modified by a nuclear factor, and that this modification is transmitted thereafter by cytoplasmic heredity, was shown in maize by Rhoades in 1943.[10] Other cases of plastid inheritance were reported by Anderson, Demerec, Imai, Renner and others.[11] Woods and duBuy were able to establish a "spectrum of variegation" ranging from

[1] T. F. Dixon, *Nature*, 155: 596, 1945.
[2] Van R. Potter, SCIENCE, 101: 609, 1945.
[3] Warren H. Lewis, SCIENCE, 81: 545, 1935.
[4] Ch. Oberling, "The Riddle of Cancer," Yale University Press, 1944.
[5] R. R. Bensley and N. L. Hoerr, *Anat. Rec.*, 60: 251, 1934.
[6] A. Claude, SCIENCE, 91: 77, 1940.
[7] M. W. Woods and H. G. duBuy, *Phytopath.*, 31: 978, 1941; *id.*, 32: 288, 1942.
[8] M. W. Woods and H. G. duBuy, *Phytopath.*, 33: 637, 1943.
[9] H. G. duBuy and M. W. Woods, *Phytopath.*, 33: 766, 1943.
[10] M. M. Rhoades, *Proc. Nat. Acad. Sci.*, 29: 327, 1943.
[11] E. G. Anderson, *Bot. Gaz.*, 76: 411, 1923; M. Demerec, *Bot. Gaz.*, 84: 139, 1927; Y. Imai, *Genetics*, 13: 544, 1928; O. Renner, *Flora*, 30: 218, 1936.