3 of the animals received a third infusion directly into the portal vein by the angiostomy technic, and the volume of fluid necessary to make the animal vomit was recorded. Some of the animals received more than one test involving a single method of infusion.

Results and discussion. A comparison of the tolerance of animals to glutamic acid administered either intravenously or directly into the portal system is presented in Table I. More glutamic acid could be administered into the portal system without the animals vomiting than could be given into the peripheral venous circulation. In a single case (Dog 2) the glutamic acid solution was injected into an intestinal vein isolated under local anesthesia and a greater tolerance was found for the amino acid when given in this manner than when administered into one of the leg veins.

Since there was no constant difference in either the blood amino acid nitrogen or the urea plus ammonia nitrogen dependent on the route of administration these data will not be presented. Also there was no level of blood amino acid nitrogen following the glutamic acid infusion which was uniformly associated with vomiting.

This work was initiated on the assumption that free glutamic acid could be partially destroyed or removed by passage through the liver. Thus if an infusion of this amino acid were permitted to pass first into the liver it should be better tolerated than if it were given into a peripheral vein. The present study supports this view. The vomiting which followed the intraportal infusions may signify that the capacity of the liver to remove this substance is exceeded. Friedberg and Greenberg[5] have reported the partition of amino acid nitrogen among the various tissues of the rat 15 minutes after the intravenous administration of glutamic acid. They found that the amino acid is slowly cleared from the plasma and at the same time the concentration of the amino acid nitrogen in the liver approached a control value. This could be interpreted as showing that free glutamic acid is rapidly being destroyed or conjugated in the liver.

Summary and conclusions. A method is presented by which the spleen may be readily transplanted subcutaneously in dogs and used for intraportal infusions.

Dogs could tolerate more glutamic acid solution without vomiting when it was given either intrasplenically or directly into the portal vein by using the angiostomy technic, as compared to the peripheral venous administration.

The increased tolerance to glutamic acid solution when given intraportally is attributed to the direct passage of these amino acids to the liver where they may be removed from the circulation.

[5] Friedberg, F., and Greenberg, D. M., *J. Biol. Chem.*, 1947, **168**, 411.

16830

Effect of Atmospheric Carbon Dioxide on Adrenal Cortical Hyperplasia and Associated Changes Due to Stress.

CLAUDE FORTIER.* (Introduced by H. Selye.)
From the Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal, Canada.

By submitting animals to anoxia, under a high carbon dioxide partial pressure, Langley,[1] Hailman,[2] and their co-workers succeeded in preventing the activation of the adrenal

* This work was done during the tenure of a Life Insurance Medical Research Fellowship.

[1] Langley, L. L., Nims, L. F., Harvey, T. S., and Clarke, R. W., National Res. Counc. Div. Med. Sc., 1943, Rep. 108.

[2] Hailman, H. F., *Endocrinology*, 1944, **34**, 187.

TABLE I.
Effect on Organ Weights* of Exposure to Stress Under a 15% Partial Pressure of Carbon Dioxide.

Group	Treatment	Adrenals (mg)	Spleen (mg)	Thymus (mg)	Lymph nodes (mg)
I	None	9.3 ± 1.1	731.6 ± 41.9	167.6 ± 14	9.1 ± 1.1
II	Spinal cord transection + 15% CO_2	17.9 ± 2.5	472.9 ± 72.9	160.4 ± 9.6	5.7 ± 0.7
III	Immobilization + 15% CO_2	13.9 ± 1.7	274.6 ± 48.4	136.1 ± 8.9	6.4 ± 1.6
IV	Spinal cord transection + normal CO_2	11.6 ± 1.0	539.1 ± 102.8	127.5 ± 16.1	8.9 ± 1.6
V	Immobilization + normal CO_2	15.4 ± 2.9	414.0 ± 42.9	95.3 ± 13.8	7.2 ± 0.4
VI	15% CO_2 without other form of stress	16.1 ± 1.1	645.1 ± 250	149.0 ± 32.4	10.1 ± 1.1

* The mean organ weights are expressed per 100 g of final body weight.

cortex previously observed to follow acute or chronic exposure to decreased barometric pressure alone.[3-18] These investigators accordingly suggest that the stimulus responsible for the adrenal response during anoxia, is the alkaline shift of the acid-base balance which results from hyperventilation and the following acapnia.[19] The object of this study was to examine whether this mechanism, *i.e.* alkalosis, represents a necessary factor to the initiation of the alarm-reaction[20] or whether it is to be considered as but one form of non-specific stress.

Experimental. Forty-eight male albino rats of the Wistar strain weighing between 120 and 140 g at the onset of the experiment were subdivided into 6 groups of 8 animals. All experimental groups were fasted for the duration of the exposure. Group I received no treatment and served as a normal control group. Groups II and III were submitted respectively, under a 15% partial pressure of carbon dioxide, to 2 different forms of stress: spinal cord transection for Group II and immobilization on a board for Group III, both usually giving a well marked response within 24 hours.[21-23] Groups IV and V, which served as experimental controls, were exposed to the same types of stress under normal atmospheric conditions, while the animals of Group VI were subjected, without any additional alarming agent, to the elevated (15%) carbon dioxide tension.

A well ventilated decompression chamber

3 Armstrong, H. G., and Heim, J. W., *J. Aviat. Med.*, 1938, **9**, 92.

4 Dohan, F. C., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 404.

5 Evans, G., *Am. J. Physiol.*, 1934, **110**, 273.

6 Evans, G., *Am. J. Physiol.*, 1935, **114**, 297.

7 Fitzgerald, O., *Arch. F. O. Ges. Physiol.*, 1939, **241**, 741.

8 Giragossintz, G., and Sundstroem, E. S., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 432.

9 Langley, L. L., Conference on factors producing hypertrophy of the adrenal cortex, Macy Foundation, 1942.

10 Langley, L. L., *Fed. Proc.* 1943, **2**, 1.

11 Langley, L. L., and Clarke, R. W., *Yale J. Biol. and Med.*, 1942, **14**, 529.

12 Lewis, R. A., Thorn, G. W., Koepf, G. F., and Dorrance, S. S., *J. Clin. Invest.*, 1942, **21**, 33. Medical Res. Council, London, Haemoglobin Committee. Spec. Rep. No. 72, 1923.

13 Nims, L. F., Conference on factors producing hypertrophy of the adrenal cortex, Macy Foundation, 1942.

14 Reynolds, O. E., and Phillips, N. E., *Am. J. Physiol.*, 1947, **151**, 147.

15 Sundstroem, E. S., and Michaels, G., *Memoirs of the University of California*, 1942, **12**, 1.

16 Tepperman, J. H., Engel, F. L., and Long, C. N. H., *Endocrinology*, 1943, **32**, 373.

17 Tepperman, J. H., Tepperman, M., and Patton, B. W., *Endocrinology*, 1947, **41**, 356.

18 Thorn, G. W., Jones, B. F., Lewis, R. A., Mitchell, E. R., and Koepf, G. F., *Am. J. Physiol.*, 1942, **137**, 606.

19 Van Slyke, D. D., *J. Biol. Chem.*, 1921, **48**, 153.

20 Selye, Hans, *Canad. Med. Assn. J.*, 1936, **34**, 706.

21 Frank, J. D., *Endocrinology*, 1940, **27**, 447.

22 Selye, Hans, *Brit. J. Exp. Pathol.*, 1936, **17**, 234.

23 Selye, Hans, *Endocrinology*, 1937, **21**, 169.

TABLE II.
Probability That the Difference Between Mean Organ Weights Shown in Table I Might Have Occurred by Chance (P).*

Group	II-I	II-IV	III-I	III-V	IV-I	V-I	VI-I
Adrenals	<.01	<.05	<.02	>.20†	>.10†	<.05	<.01
Spleen	<.01	>.20†	<.01	>.20†	>.10†	<.01	<.01
Thymus	>.20†	>.10†	<.01	<.05	<.05	<.05	<.03
Lymph Nodes	<.01	>.10†	<.02	<.05	<.02	>.10†	>.20†

* From Fisher's table of T values.
† Difference not statistically significant.

of the R.C.A.F. standard model was used for maintaining a constant composition of the atmosphere, namely, CO_2, 15%; O_2, 19%; N_2, 66% at a pressure of 760 mm HG. and under normal hygrometric conditions. Samples of the gaseous mixture were analyzed at intervals by the Haldane method. The animals were killed after 38 hours by exposure and the adrenals, spleen, thymus and pelvic lymph nodes were weighed in the fresh state and histologically examined.

Results. The results are summarized in Table I. The probability of a chance occurrence of the differences in the means of the experimental groups (II, III and VI) from those of the normal control group (I) and the experimental control groups (IV and V), is indicated in Table II, in which we have taken as significant those differences for which the probability of occurrence by chance is not greater than 0.05. An increase in the weight of the adrenal glands is evident in both experimental and experimental control groups. In all but Group IV, this increase represents a significant deviation from the untreated control group. Conversely, the spleen, thymus and pelvic lymph nodes show in most groups, a significant decrease in weight which roughly parallels the increase in adrenal weight. The organ weights of Groups II and III, which were exposed to stress under a 15% pressure of carbon dioxide, are not significantly different from those of Groups IV and V which were submitted to the same damaging agents under normal atmospheric conditions. The adrenal hypertrophy and the splenic and thymic involution of Group VI which was exposed to 15% carbon dioxide without additional damaging agent, are significant. The histological examination of the organs revealed in all but Group I various degrees of lipid depletion in the cortex of the adrenals and of nuclear pyknosis in the lymphatic organs. These changes have been repeatedly described in connection with exposure to any non-specific damaging agent.[24]

Conclusion. Our results disprove the possibility that an alkaline shift of the acid-base balance is the necessary prerequisite for the development of the alarm-reaction, as the response of the organs (adrenals, spleen, thymus and lymph nodes) was of the same order in animals submitted to high and normal carbon dioxide tensions. The adrenal cortical hyperplasia as well as lymphatic tissue involution of the animals exposed, without other change in their environment, to a high carbon dioxide atmospheric tension, imply that this factor is in itself an alarming stimulus, perhaps through its action on the acid-base balance of the blood.[25]

This work was subsidized by a grant from the Commonwealth Fund of New York. The author is also indebted to Drs. L. Brouha, L. P. Dugal and A. Desmarais of the Institut d'Hygiène et de Biologie humaine, Université Laval, for the use of their decompression chamber.

[24] Selye, Hans, *J. Clin. Endocrinol.*, 1946, **6**, 117.
[25] Waud, R. A., *Tr. Roy. Soc. Canada*, Sect. V, Biol. Sc., 1944, **38**, 103.