THE EFFECT OF PROGESTERONE ON THE RESPIRATION OF PATIENTS WITH EMPHYSEMA AND HYPERCAPNIA *

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The possibility that progesterone could influence breathing was first suggested by studies investigating the respiration of pregnant women. In 1912 Leimdörfer, Novak and Porges (1) found that the alveolar concentration of CO_2 was lower in pregnant women than it was in the same individuals when they were not pregnant. These observations were amplified and confirmed in 1915 by Hasselbalch and Gammeltoft (2). Beginning in 1947, Döring, Heerhaber and co-workers (3–5) investigated the effect of pregnancy in lowering the alveolar CO_2 tension and later extended the studies to measurements of CO_2 tension made during the normal menstrual cycle. They were able to show that the alveolar CO_2 tension was depressed in the luteal phase of the cycle and that if pregnancy occurred this depression continued throughout gestation, rising shortly after delivery. This suggested to them that progesterone might play a role in the genesis of the decrease in alveolar CO_2 tension and they were able to show that 50 mg. of progesterone given intramuscularly to normal men caused a stimulus to breathing which reached its maximum about 12 hours after injection.

Persistent hypercapnia is a frequent finding in the terminal stages of chronic pulmonary disease. Present long-term methods for lowering this hypercapnia are not satisfactory. Since Döring and Heerhaber's studies were limited to single injections of progesterone, and because the effect of progesterone on respiration in the presence of hypercapnia was not known, the following studies were done to investigate the effect of repeated injections of progesterone on the respiration of patients with chronic pulmonary disease and elevated levels of arterial pCO_2. In an attempt to evaluate the relation of chemical structure to function, some analogues of progesterone have also been investigated.

METHODS

Patients were selected whose diagnosis of emphysema was established on the basis of the typical history, physical and radiological signs of chronic obstructive disease of the lungs, plus changes of an elevated arterial CO_2 tension. All patients continued to have significant respiratory symptoms in spite of intensive bronchodilator therapy. They had been in the hospital at least three weeks before the first control values were obtained and during this period had reached their maximum response to ordinary therapeutic measures as judged by the stability of their clinical condition and by measurements of timed vital capacity and maximum breathing capacity. Thus they were in a stable enough condition to allow demonstration of the hormonal effects on the respiration without the necessity of other changes in their therapy.

The subjects were studied when they were lying in the supine position, approximately two hours after a light breakfast. No special attempt was made to have them completely basal, but they were all thoroughly familiar with the procedure and it is believed that anxiety was minimal. An arterial needle was introduced into a brachial artery, after which a five minute rest period was allowed for the patients to become stable. Their expired gas was then collected over a three minute period and, during the second minute, arterial blood samples were taken. The arterial pH was determined immediately in a Cambridge Model R pH meter with a constant temperature electrode set at 37° C. Simultaneous samples agreed within 0.02 pH unit. Whole blood CO_2 content was determined according to the method of Van Slyke and Neill (6) and the pCO_2 was determined by the nomograph of Singer and Hastings (7). The expired gas was analyzed for oxygen and carbon dioxide with the Scholander microanalyzer. Duplicates agreed within 0.04 per cent. The Bohr equation was used to calculate the physiological dead space, and the alveolar ventilation was estimated by the equation $V_A = f\ (V_T - V_D)$.[1] Estimates of total vital capacity with one and two second fractions were carried out with a Collins respirometer, using standard methods.

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[1] V_A = alveolar ventilation per minute, f = respiratory frequency, V_T = tidal volume and V_D = physiological dead space volume.

In some instances, arterial pCO_2 was determined by the rebreathing method of Hackney, Sears and Collier (8). In 22 simultaneous measurements (range 40 to 78 mm. Hg) the mean difference between the directly measured arterial pCO_2 and the rebreathed value was -0.4 ± 0.4 (± 1 standard error).

RESULTS

The vital capacity and the one and two second fractions obtained on each patient are shown in Table I. The values for ventilation, pCO_2 and gas exchange during the study periods in the nine patients are given in Table II. The mean changes from pretreatment, and post-treatment controls brought about by progesterone,[2] 50 mg. daily, intramuscularly, are shown in Table III. The mean values were calculated by averaging the values from each period—pretreatment control, treatment, or post-treatment control—to obtain a value representative of this period for each patient. These mean values were then averaged to give the mean for all the subjects. The mean arterial carbon dioxide tension (Pa_{CO_2}) declined by 8.4 mm. Hg during treatment, followed by a rise of 5.9 mm. Hg when the drug was discontinued. Associated with the decrease in pCO_2 there was a rise in minute ventilation and alveolar ventilation of 1.78 and 0.75 L. per minute, respectively. The post-treatment control showed a 1.32 L. per minute fall in minute ventilation and a fall of 0.79 L. per minute in alveolar ventilation. Mean pH rose by 0.024 unit with progesterone and declined by 0.024 unit when the drug was discontinued. All these changes are statistically significant. The values obtained in Subject 1 are shown in Figure 1. Measurements during the first two days of treatment showed an effect by the thirtieth hour, but this was not maximal, for the Pa_{CO_2} fell 6 more mm. Hg during the next six days of treatment.

Anhydrohydroxyprogesterone[3] was given to Subjects 2 and 8. Complete studies were carried out in Subject 2 and there was no significant rise in ventilation, or fall in pCO_2. The findings in Patient 8 are shown in Figure 2. Complete studies could not be carried out in this individual because of the severity of his illness, but during the administration of anhydrohydroxyprogesterone, his arterial pCO_2 steadily rose as his clinical condition deteriorated; when progesterone was substituted he had a prompt fall in pCO_2 from 63 to 44 mm. Hg, and this was maintained with 50 mg. of progesterone given intramuscularly every third day. No other change in therapy was made during the period of study. This patient was confused and had a coarse tremor during the period of marked Pa_{CO_2} elevation. These findings disappeared when the hypercapnia was lowered by progesterone. He subsequently expired and extensive emphysema was found on postmortem examination.

Subject 3, as shown in Figure 3, had a fall in Pa_{CO_2} of 10 mm. Hg on progesterone, and when 1.8 Gm. aspirin daily was added to this, a further rise in minute ventilation and alveolar ventilation was produced. However, pCO_2 declined only 2 mm. Hg and oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) rose significantly. This patient was also given oral Progesterone Linguets®, 50 mg. per day. There was no effect on ventilation. Subsequent administration of intramuscular progesterone produced a fall in pCO_2.

Subjects 4 and 7 received a placebo intramuscularly during the control period. This produced no change in ventilation and both patients subsequently responded to intramuscular progesterone.

In Subject 9, 19 nor-ethinyl-testosterone produced no change in ventilation or pCO_2. This patient subsequently responded to progesterone.

1,2-Dehydroprogesterone was given to Patients 4 and 7, and in both instances it failed to produce

TABLE I

Timed vital capacity measurements

Patient no.	Total vital capacity	% Predicted normal values	1 Second vital capacity	2 Second vital capacity
	L.		*L.*	*L.*
1	1.22	46	0.50	0.77
2	1.79	58	0.54	0.81
3	1.82	48	0.50	0.77
4	3.28	88	1.21	1.93
5	2.06	54	0.76	1.16
6	2.16	65	0.58	0.81
7	0.98	37	0.49	0.80
8	1.75	46	0.45	0.72
9	2.46	62	0.67	1.07

[2] All steroid compounds and placebo kindly supplied by Dr. Henderson of the Schering Corp., Bloomfield, N. J.

[3] 17 Ethinyl-testosterone.

TABLE II

Changes in ventilation and gas exchange produced by hormone treatment

Patient no.	Age	Sex		$\dot{V}_E$*	Pa_{CO_2}	$\dot{V}_A$	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R*	pH
			Date	*L./min.*	*mm. Hg*	*L./min.*	*cc./min.*	*cc./min.*		
1	59	M	1/1	4.28	61	1.56	145	112	0.77	7.34
			1/18	4.54	61	1.82	157	130	0.83	7.38
				Progesterone 50 mg. I. M.						
		(24 hr.)	1/19	6.12	59	2.39	191	164	0.86	7.35
		(30 hr.)		6.34	57	2.53	207	170	0.82	7.37
			1/23	6.98			199	182	0.91	
			1/26	6.96	51	2.99	189	176	0.93	7.41
				Progesterone discontinued						
			1/31	6.22	61	2.42	189	171	0.90	7.36
				Progesterone 50 mg. I. M.						
			2/7	5.74	54	2.47	167	157	0.94	7.38
2	79	M	6/1	10.14	58	3.10	286	255	0.90	7.38
			6/6	10.21	59	3.58	276	243	0.88	7.37
				Anhydrohydroxyprogesterone 50 mg. q. i. d.						
			6/20	10.48	55	3.45	250	218	0.87	7.38
				Progesterone 50 mg. I. M.						
			6/29	11.85	51	4.15	277	249	0.90	7.37
				Progesterone discontinued						
			7/5	8.02	59	2.64	219	182	0.83	7.35
3	59	M	4/18	7.74	54	3.94	295	248	0.84	7.38
			4/23	9.56	54	3.83	248	243	0.98	7.35
			4/26	8.94	54	3.40	222	211	0.95	7.38
				Progesterone 50 mg. I. M.						
			5/2	10.4	44	4.06	224	208	0.93	7.40
			5/7	8.74	44	4.02	219	207	0.95	7.39
				Progesterone 50 mg. I. M. and aspirin 1.8 Gm.						
			5/11	12.11	42	5.21	257	253	0.98	7.35
				Progesterone and aspirin discontinued						
			5/16	8.83	51	3.44	226	207	0.92	7.34
				Oral progesterone 10 mg. 5 times daily sublingually						
			5/23	7.53	61	2.94	227	209	0.95	7.35
			5/31	8.03	51	3.13	218	193	0.89	7.37
4	62	M	9/11	10.52	55	4.21	317	276	0.87	7.32
			9/16	11.00	53	4.92	352	305	0.86	7.34
				Progesterone 50 mg. I. M. (9/17 to 10/1)						
			10/1	16.20	49	6.97	384	394	1.03	7.33
				Placebo 10/3 to 10/10						
			10/8	15.17	54	5.62	370	356	0.96	7.31
				1,2 Dehydroprogesterone 25 mg. I. M. daily (10/10 to 10/16)						
			10/16	14.14	50	4.89	314	274	0.87	7.36
			10/24	16.40	51	5.58	325	331	1.01	7.36
5	59	M	3/1	8.52	46	3.07	206	163	0.79	7.39
			3/5	11.0	45	4.07	254	216	0.85	7.39
				Progesterone 50 mg. I. M.						
			3/12	11.9	41	4.76	260	223	0.86	7.41

TABLE II (*Continued*)

Patient no.	Age	Sex		$\dot{V}_E$*	Pa_{CO_2}	V_A	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R*	pH
			Date	*L./min.*	*mm. Hg*	*L./min.*	*cc./min.*	*cc./min.*		
			Progesterone discontinued							
			4/5	10.65	46	3.72	248	201	0.81	7.39
			4/11	10.80	45	3.88	253	247	0.98	7.39
6	74	M	2/29	8.93	55	2.05	202	161	0.80	7.35
			3/2	7.82	55	2.27	198	149	0.75	7.36
			Progesterone, 50 mg. I. M.							
			3/8	8.70	42	3.04	183	150	0.82	7.43
			Progesterone discontinued							
			3/23	8.01	49	2.57	175	148	0.85	7.41
7	63	F	12/19	9.39	52	3.48	257	208	0.81	7.39
			12/31	9.72	53†	3.69	197	214	1.09	
			3/4	5.95	53	2.21	206	137	0.67	7.40
			Placebo 3/5 to 3/18							
			3/11		52†					
			3/18	8.36	51	2.93	210	172	0.82	7.40
			Dehydroprogesterone 25 mg. I. M. (3/18 to 3/24)							
			3/24	9.41	52	2.08	230	181	0.79	7.39
			Progesterone 50 mg. I. M. (3/24 to 4/2)							
			3/31	10.09	47	3.53	234	195	0.83	7.37
			4/9	8.99	47	3.43	213	178	0.84	7.39
8	60	M	12/31		51					7.43
			1/2		51					7.43
			1/3		Anhydrohydroxyprogesterone 50 mg. q. i. d. to 1/11					
			1/8		55					7.42
			1/11		59					7.44
			1/16		63					7.40
			1/19		Progesterone 50 mg. I. M. daily					
			1/22		45					7.45
			1/25		Progesterone 50 mg. I. M. every other day					
			1/29		46					7.48
			2/5		45					7.42
			2/6		43					7.50
			2/8		Progesterone 50 mg. I. M. every third day					
			2/13		42					7.48
9	49	M	4/2	12.04	50	3.98	263	233	0.89	7.37
			4/3	10.72	52	3.11	226	187	0.83	7.36
			19 Nor-ethinyl-testosterone 10 mg. orally t. i. d.							
			4/5	11.07	54	3.40	236	204	0.86	7.37
			Progesterone 50 mg. I. M. daily							
			4/9	12.26	47	3.94	227	218	0.96	7.39

* $\dot{V}_E$ = volume of gas expired per minute; R = respiratory exchange ratio.
† Rebreathed method for Pa_{CO_2}.

an increase in ventilation, but in Patient 4 there was a 4 mm. fall in pCO_2. However, in this case the post-treatment control period failed to show a rise.

DISCUSSION

It is apparent from the data that progesterone is capable of lowering the arterial pCO_2 in patients with emphysema and hypercapnia. That this hormone lowers the alveolar pCO_2 in normal subjects has been demonstrated by several observers in the past. Döring, Loeschcke and Ochwadt (5) gave 50 mg. of progesterone intramuscularly to five normal subjects and tested its effect on the CO_2 stimulus to respiration. Twenty-four hours after injection there was a drop of

TABLE III

Mean changes from control values produced by progesterone

	Progesterone 50 mg. I.M. daily					
	Change from control period during treatment		No. of observations	Change during after-control period		No. of observations
Pa_{CO_2} (*mm. Hg*)	−8.4 ± 1.4 (± 1 S.E.)	$p < 0.01$	10	+5.9 ± 1.3	$p < 0.01$	7
$\dot{V}_E$ (*L./min.*)	+1.78 ± 0.56	$p < 0.02$	9	−1.32 ± 0.42	$p < 0.02$	7
$\dot{V}_A$ (*L./min.*)	+0.76 ± 0.24	$p < 0.02$	9	−0.79 ± 0.19	$p < 0.01$	7
pH	+0.024 ± 0.0096	$p < 0.05$	10	−0.024 ± 0.0097	$p < 0.05$	7

2.18 mm. pCO_2 from control values, both measurements being made at the point in the CO_2 stimulus curve when the patient was breathing 12 L. of the CO_2 mixture per minute. Estradiol did not cause a lowering of the resting pCO_2. Progesterone caused a small rise in body temperature, but a greater increase in temperature induced by a pyrogen did not alter the pCO_2. Their conclusion was that progesterone produced a primary stimulus to respiration and did not cause the hyperventilation by bringing about a metabolic acidosis. Essentially the same results were found by Goodland, Reynolds, Pommerenke and McCoord (9, 10).

If one assumes that the action of progesterone causes a small but definite degree of hyperventilation, then it is of interest that this increase in ventilation is sufficient to cause a fall in Pa_{CO_2} in patients with severe obstructive disease and hypercapnia. It has been shown by Wilson, Borden,

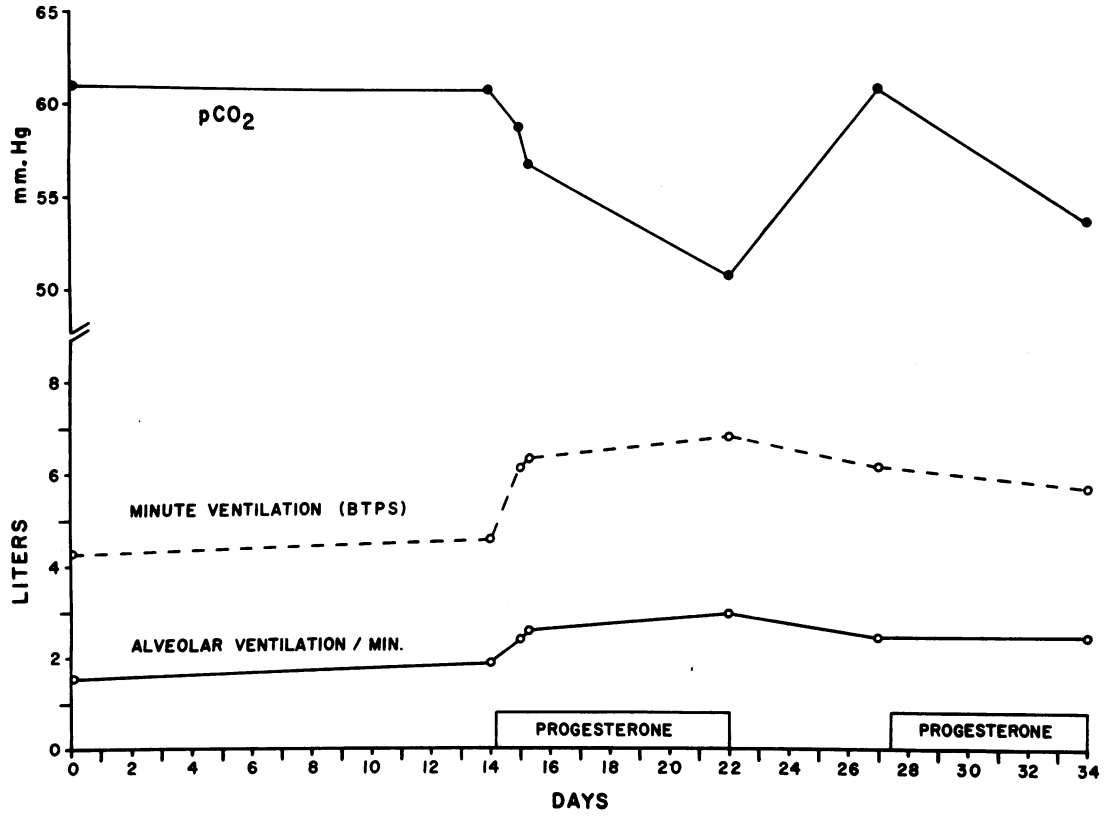

FIG. 1. VALUES FOR ARTERIAL CO_2 TENSION, MINUTE VENTILATION AND ALVEOLAR VENTILATION DURING THE STUDY PERIOD IN PATIENT 1

Progesterone, 50 mg. per day, was given intramuscularly during the indicated periods.

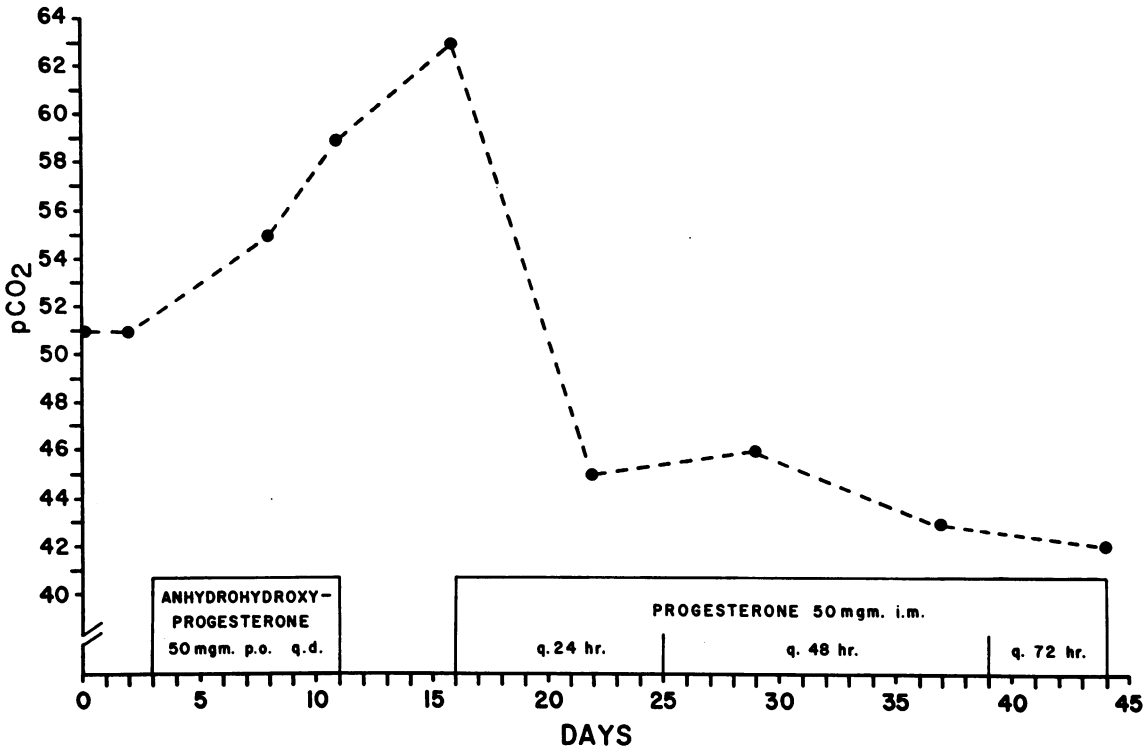

FIG. 2. THE EFFECT OF PROGESTERONE ON INCREASING HYPERCAPNIA IN PATIENT 8

Without other change in therapy, progesterone produced a lowering in arterial CO_2 tension; anhydrohydroxyprogesterone was ineffective.

Ebert and Wells (11) that voluntary hyperventilation is incapable of lowering the Pa_{CO_2} in patients with emphysema and hypercapnia.

On the basis of a theoretical analysis, Otis (12) has related the alveolar CO_2 tension to the work of breathing and the minute ventilation. As the ventilation increases, a point is reached when it is no longer effective in lowering the alveolar CO_2 tension because the increased volume of CO_2 produced by the increased work of breathing cannot be eliminated by the ventilation. With the increased work of breathing that exists in emphysema, this point at which ventilation ceases to be effective in lowering CO_2 tension is shifted to lower values than in the normal subject. Presumably this point would vary with the degree of emphysema. Since, in the present study, the arterial CO_2 tension fell and the arterial pH increased, progesterone caused an increase in effective ventilation.

Aspirin added to progesterone in Patient 3, as shown in Figure 3, caused a marked further augmentation in ventilation over and above the increase in resting level produced by the hormone alone, but brought about only a 2 mm. Hg fall in Pa_{CO_2}. However, aspirin caused a sharp rise in CO_2 production and this may have canceled the effect of hyperventilation in so far as lowering the arterial CO_2 tension was concerned. The ability of aspirin to lower the Pa_{CO_2} in hypercapnia has been claimed by some (13) and disputed by others (14). It is of interest that in another study in this laboratory, on individuals without heart or lung disease, progesterone produced approximately the same decline in alveolar CO_2 tension as did aspirin, 2 Gm. every six hours (15).

Riley (16) has reviewed the problem of hypercapnia and the increased work of breathing, and has concluded that the hypercapnia may be a desirable adjustment in that it enables the patient to eliminate carbon dioxide at a lower minute ventilation and, therefore, at a smaller work of breathing than would be possible if the ventilation were driven at a high enough level to main-

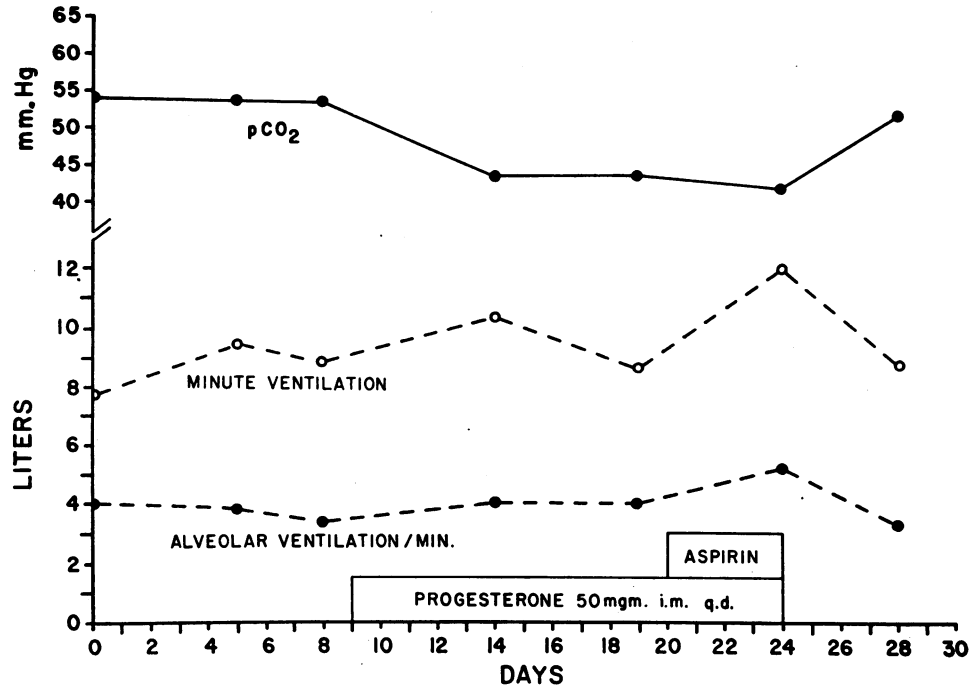

FIG. 3. THE EFFECT OF PROGESTERONE, WITH AND WITHOUT ADDED ASPIRIN, ON THE VENTILATION AND ARTERIAL CO_2 TENSION

When 1.8 Gm. aspirin per day was added, there was a marked increase in ventilation but only a small decrease in CO_2 tension.

tain the CO_2 tension in the normal range. This adjustment to hypercapnia reduces the oxygen consumption necessary for ventilation and leaves more for nonventilatory work. Riley thus stresses the value of reducing the work of breathing to lower the hypercapnia associated with emphysema. However, this is an adjustment which the patient makes at some detriment to his overall condition because of the well known cerebral depressant effects caused by an elevated arterial CO_2 tension.

On the basis of preliminary studies it would appear that the effect of progesterone on ventilation is not solely the result of progestational activity, because anhydrohydroxyprogesterone and 19 nor-ethinyl-testosterone, both of which were employed in doses known to have marked progestational activity, were ineffective. The structural formulas of the hormonal compounds employed are given in Figure 4. Apparently the ethinyl group inactivates the respiratory effects seen with progesterone itself. Also, it appears that alterations of the molecular structure at other sites can abolish the effect; *e.g.*, substituting a double bond in the 1, 2 position. However, more subjects should be studied with these three compounds before a definite statement can be made as to their activity.

Conclusions on the exact mode of action of progesterone are not possible from this study. Robin, Travis and Crump (17) have found that, in five normal subjects, progesterone lowered the arterial pCO_2 without altering the ventilatory response to carbon dioxide, and inspection of the CO_2 stimulus curves of Döring, Loeschcke and Ochwadt (5) failed to show an increase in responsiveness with progesterone. It is felt that other areas of the brain, possibly the hypothalamus, may represent the site of action.

It appears that progesterone is effective in lowering the Pa_{CO_2} in patients with emphysema and hypercapnia. In one patient the effect was striking. However, this study does not establish its clinical usefulness in individuals with severe elevations of pCO_2.

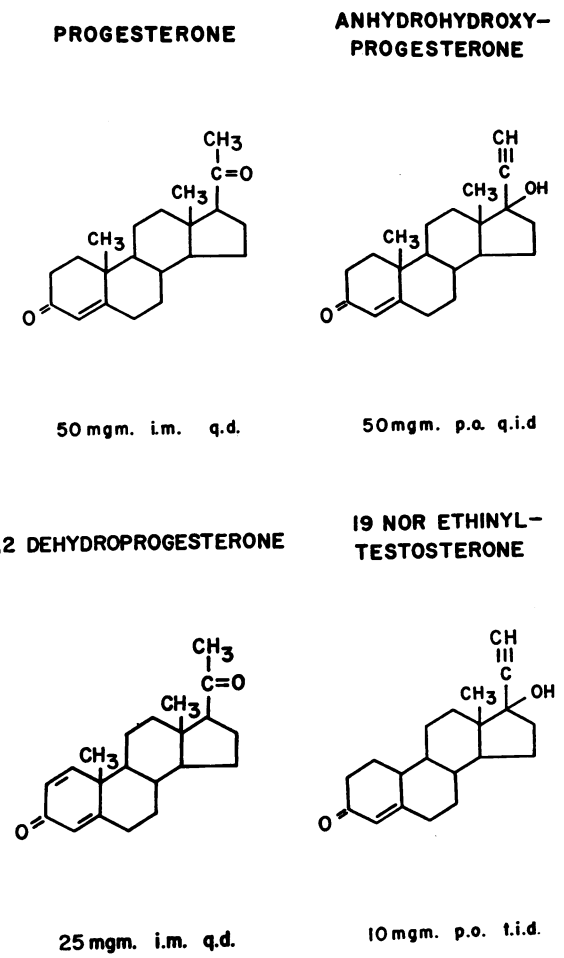

FIG. 4. THE STRUCTURAL FORMULAS OF THE COMPOUNDS EMPLOYED

SUMMARY

1. Progesterone produces hyperventilation and lowers the arterial pCO_2 in patients with emphysema and stabilized hypercapnia.

2. Limited studies with compounds other than progesterone suggest that this progestational property is not sufficient in itself to cause the hyperventilation effect.

REFERENCES

1. Leimdörfer, A., Novak, J., and Porges, O. Ueber die Kohlensäurespannung des Blutes in der Gravidität. Z. klin. Med. 1912, **75**, 301.
2. Hasselbalch, K. A., and Gammeltoft, S. A. Die Neutralitätsregulation des graviden Organismus. Biochem. Z. 1915, **68**, 206.
3. Döring, G. K., and Loeschcke, H. H. Atmung und Säure-Basengleichgewicht in der Schwangerschaft. Arch. ges. Physiol. 1947, **249**, 437.
4. Heerhaber, I., Loeschcke, H. H., and Westpahl, U. Eine Wirkung des Progesterons auf die Atmung. Arch. ges. Physiol. 1948, **250**, 42.
5. Döring, G. K., Loeschcke, H. H., and Ochwadt, B. Weitere Untersuchungen über die Wirkung der Sexualhormone auf die Atmung. Arch. ges. Physiol. 1950, **252**, 216.
6. Van Slyke, D. D., and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. biol. Chem. 1924, **61**, 523.
7. Singer, R. B., and Hastings, A. B. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine (Baltimore) 1948, **27**, 223.
8. Hackney, J. D., Sears, C. H., and Collier, C. R. Estimation of arterial CO_2 tension by rebreathing technique. J. appl. Physiol. 1958, **12**, 425.
9. Goodland, R. L., Reynolds, J. G., and Pommerenke, W. T. Alveolar carbon dioxide tension levels during pregnancy and early puerperium. J. clin. Endocr. 1954, **14**, 522.
10. Goodland, R. L., Reynolds, J. G., McCoord, A. B., and Pommerenke, W. T. Respiratory and electrolyte effects induced by estrogen and progesterone. Fertil. and Steril. 1953, **4**, 300.
11. Wilson, R. H., Borden, C. W., Ebert, R. V., and Wells, H. S. A comparison of the effect of voluntary hyperventilation in normal persons, patients with pulmonary emphysema, and patients with cardiac disease. J. Lab. clin. Med. 1950, **36**, 119.
12. Otis, A. B. The work of breathing. Physiol. Rev. 1954, **34**, 449.
13. Wégria, R., Capeci, N., Kiss, G., Glaviano, V. V., Keating, J. H., and Hilton, J. G. Effect of salicylate on the acid-base equilibrium of patients with chronic CO_2 retention due to pulmonary emphysema. Amer. J. Med. 1955, **19**, 509.
14. Samet, P., Rosenthal, A., and Bernstein, W. H. The effect of salicylates upon the ventilatory response to carbon dioxide in patients with pulmonary emphysema and hypercapnia. Amer. J. Med. 1958, **24**, 215.
15. Dresner, E., and Tyler, J. M. Unpublished observations.
16. Riley, R. L. The work of breathing and its relation to respiratory acidosis. Ann. intern. Med. 1954, **41**, 172.
17. Robin, E., Travis, D., and Crump, C. Unpublished observations.