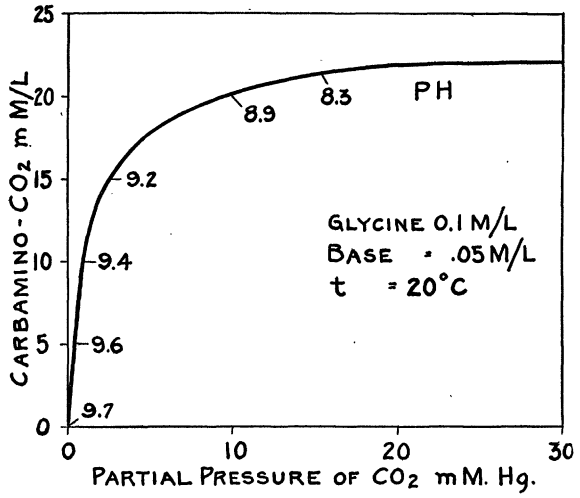

FIG. 1. Case 1. Equilibrium curve of 0.1 M glycine (with 0.05 M of base) and CO_2 showing the concentration of carbamino-CO_2 as a function of the partial pressure of CO_2. Equilibrium is assumed to exclude the formation of H_2CO_3 or its ions. t = 20° C.

action constant of the amino-acid-carbamino-CO_2 equilibrium.

Case 2: In Fig. 2 the curve of carbamino concentration for the same solution has been calculated from

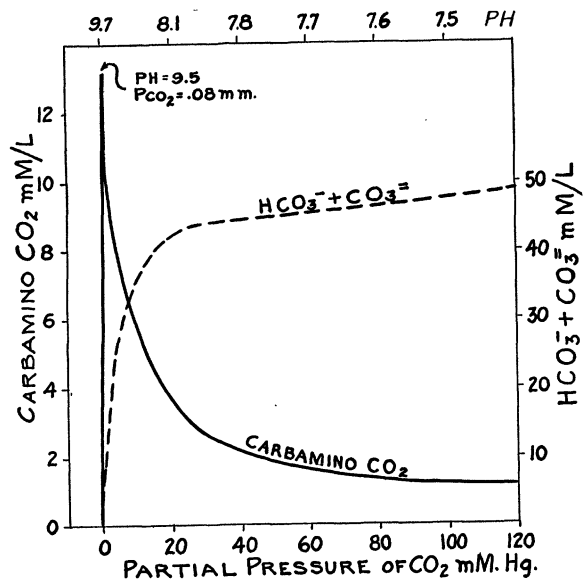

FIG. 2. Case 2. Complete equilibrium of 0.1 M glycine (0.05 M of base) and CO_2 showing (carbamino-CO_2) concentration as a function of P_{CO_2} calculated from the amino-acid carbamino-CO_2 mass action constant. H_2CO_3 and its ions are included.

this constant at 20° C., *but in this case the equilibrium includes H_2CO_3 and its ions.* The two cases, both in complete agreement with our experiments, are easily seen to be totally unlike. Fig. 1 shows that the total carbamino concentration approaches half of the base concentration as a limit at high P_{CO_2} and that at intermediate values of P_{CO_2} the carbamino concentration is high and *increases* appreciably per mm (Hg) change of P_{CO_2}. Whence by analogy one would conclude that carbamino hemoglobin, if it behaved in a similar way, would be an important carrier of CO_2 in the blood.

Fig. 2, however, shows that when total rather than partial equilibrium is considered the maximum of carbamino concentration is reached at P_{CO_2} 0.1 mm Hg and at a very alkaline pH. Moreover, it is only 13 per cent. of the base concentration. At higher P_{CO_2} the curve falls off sharply and at P_{CO_2} 50 mm Hg the carbamino concentration is low and *decreases,* but only by a trifling amount, as the P_{CO_2} is increased. Moreover, it can be easily shown that at pH < 8 the carbamino-CO_2 is only a small part (< 3 per cent.) of the total CO_2.

It is this total equilibrium state which corresponds to that of the blood under physiological conditions. If hemoglobin behaves similarly to amino-acids, the rôle of carbamino-hemoglobin as a carrier of CO_2 appears to be relatively insignificant.

In addition it must be remembered that carbonic anhydrase, a specific enzyme, enormously accelerates reaction 2 as has been shown by Meldrum and Roughton[6] and by Stadie and O'Brien.[7] Thus the discrepancy between the velocities of the two reactions is wiped out and the possibility of the occurrence of an equilibrium of the first type vanishes. This again emphasizes the necessity of considering only equilibrium 2 as being significant in the problem of the CO_2 transport by the blood.

WILLIAM C. STADIE

REFRACTORINESS TO OVARIAN STIMULATION IN THE RHESUS MONKEY

IN a series of publications Cole and Hart[1,2,3] and their collaborators have described the presence, quantity and biological activity of a gonadotropic substance in the blood serum of pregnant mares. Evans, Gustus and Simpson[4] have published a method for the purification and concentration of this gonadotropic substance and have also described its effects on the gonads of male and female rats.

[6] N. U. Meldrum and F. J. W. Roughton, *Jour. Physiol.*, 80: 113, 1933.

[7] W. C. Stadie and H. O'Brien, *Jour. Biol. Chem.*, 1933, 100: lxxxviii, 1933; *Jour. Biol. Chem.*, 103: 521, 1933.

[1] H. H. Cole and G. H. Hart, *Amer. Jour. Physiol.*, 93: 57, 1930.

[2] H. H. Cole and G. H. Hart, *Amer. Jour. Physiol.*, 94: 597, 1930.

[3] H. Goss and H. H. Cole, *Endocrinology*, 15: 214, 1931.

[4] H. M. Evans, E. L. Gustus and M. E. Simpson, *Jour. Exp. Med.*, 58: 569, 1933.

Since this substance manifests biological activity similar to extracts of the anterior pituitary gland containing gonadotropic hormones, it became of interest to determine its effect on the ovaries of immature rhesus monkeys.

Each of five immature monkeys weighing between 2,100 and 2,500 grams was injected daily with 5 r. u.[5] of the gonad-stimulating hormone purified by the method of Evans, Gustus and Simpson. The periods of injection varied from forty-five to seventy days. (Some of the monkeys are being injected as this report is being written.) Two of five monkeys were injected intravenously and the others subcutaneously. Reddening and swelling of the sexual skin (which occurred on the fourth to tenth day after the first injection) were the first indications that the hormone injected was stimulating the ovaries. The maximal development of the sexual skin was reached on the thirteenth to twentieth days of the injection period and had returned to interval or castrate type by the twenty-seventh to fortieth days.

The ovaries were examined and measured at intervals and it was found that very great follicular development had occurred as early as the ninth to twelfth days. The size of the ovaries at this time varied in different monkeys, but the average dimensions were of the order of $14 \times 12 \times 7$ mm. There was no evidence at any time that corpora lutea had been produced or that ovulation had taken place. Examination of the ovaries at the thirty-eighth to fortieth days of the injection period showed that they had decreased in size, and in two cases the regression was such that they were of infantile dimensions. Such ovaries were white, shrunken structures which did not show any evidence of the many large follicles which had been present earlier.

Vaginal lavages were taken daily and a study of these showed that there was an early increase in the number of epithelial and cornified cells with a decrease in the number of leucocytes. As the injections were continued, the leucocytes increased in number and the cornified cells gradually disappeared.

The decrease in the number of cornified cells and regression of the sexual skin were followed by menstruation in all the monkeys. The occurrence of this phenomenon varied between the fifteenth and thirty-second days of treatment. Menstruation was observed eighty-seven days after the last injection in one of two monkeys which had been injected for fifty-four days. The other monkey began to menstruate on the forty-eighth and again on the eighty-second day after the treatment had been stopped.

[5] A rat unit is defined as the total amount of hormone which, when administered in daily doses of one cc for three days to immature female rats, causes an increase of approximately 500 per cent. in weight of ovaries ninety-six hours after the first injection.

We conclude from these data that the ovaries of immature monkeys are first greatly stimulated by the gonadotropic hormone of pregnant mare's serum, but later and during the chronic administration of the hormone they regress to a relatively infantile condition.

Zondek[6] has reported that the ovaries of mice which have received chronic treatment with a gonadotropic extract of pregnancy urine first show a great increase in weight, but that after a certain time the weight was normal, although the administration of the extract had been continued. Collip and his co-workers[7] have reported the same results for rats which have received hypophyseal implants for many days or have been subjected to chronic treatment with placental extracts. They[8] have also demonstrated that the blood of rats injected with placental extracts for many weeks inhibits the ovary-stimulating effect of such extracts when tested in the immature female rat.

We have tested the serum of our monkeys for such an inhibitory effect against the gonad-stimulating hormone of pregnant mare's serum. If it is present at all in the serum of monkeys before injections were begun, it is there in relatively small amounts, since one cc of monkey serum does not inhibit the ovary-stimulating effect of the hormone when tested in immature female rats twenty-one to twenty-three days of age.[9] However, the blood serum acquired an inhibitory action as the injections of the hormone were continued. A definite inhibitory effect was obtained with one cc of serum as early as the twenty-seventh day of the injection period, and continued administration of the hormone caused the antagonistic effect to become greater. Thus after thirty-nine days of injections as little as 0.025 cc of monkey serum per day for five days was sufficient to completely prevent the gonad-stimulating effect of one rat unit of mare serum hormone. However, the usual amount required at this time was 0.05 to 0.10 cc per day.

A very definite inhibition of the action of the mare serum hormone has been obtained with serum obtained from a monkey sixty-seven days after the injections of the hormone had been stopped.

The antagonistic action of the monkey serum exhibits considerable specificity, as evidenced by the fact that the serum did not demonstrate an inhibitory

[6] Cited by J. B. Collip.[7]

[7] J. B. Collip, *Jour. Mt. Sinai Hospital*, 1: 28, 1934.

[8] H. Selye, C. Bachman, D. L. Thomson and J. B. Collip, *Proc. Soc. Exp. Biol. Med.*, 31: 1113, 1934.

[9] The method of testing for the antagonistic effect consists of injecting $\times$ cc of monkey serum per day for five days and one third of a rat unit of gonadotropic hormone per day for the last three of the five days that the monkey serum is being injected. The rats are killed 144 hours after the first injection of monkey serum and the ovarian weights compared with those of control animals which have received only one third of a rat unit of the gonadotropic hormone per day for three days.

effect toward the gonad-stimulating action of human pregnancy urine, whole sheep pituitary gland and whole human pituitary gland extracts, when tested in the immature female rat.

Thus an apparent refractory condition of the ovaries of immature monkeys to the gonadotropic hormone of pregnant mare's serum has been produced by chronic treatment with the purified hormone. We believe this condition is related to the presence in the serum of the monkeys of a substance which prevents the action of the gonad-stimulating hormone.

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THE CONTROL OF BRONCHIAL ASTHMA[1]

IN fifty cases of bronchial asthma the attacks of paroxysmal dyspnea have been prevented by a régime of treatment based upon elimination, by postural drainage, of the accompanying bronchial and pulmonary exudate.

It is our conception that the fundamental pathological change in bronchial asthma is chronic, nontuberculous pulmonary infection with characteristic[2] hypertrophic and inflammatory change in the lymphoid tissue, thickening and hyalinization of the bronchial and bronchiolar basement membrane, sacculation and ulceration of the bronchial mucosa with marked cellular infiltration. The products of this infectious process are the causative factors in the provocation of the asthmatic attack. When these products are not permitted to accumulate in the bronchii and lungs the asthmatic attack never occurs.

The first therapeutic step is reduction of the viscidity of the bronchial and pulmonary exudate in order to facilitate its evacuation. For this purpose elixir of terpene hydrate, guiacol, sodium iodide, potassium iodide, ammonium chloride and compound tincture of benzoin by steam inhalation have been used singly or in combination.

After the viscidity of the exudate is reduced the patient is instructed to kneel on a chair or stool and place both hands on the floor. The more nearly the thorax approximates an inverted vertical position the more nearly ideal are the results. Compromise positions can be devised for the enfeebled patient. While in this position the patient coughs as nearly continuously as possible and peroral drainage of the exudate is thus accomplished through the combined agencies of the tussive squeeze, ciliary drainage and the bechic blast.[3] The exudate is then expectorated. The inverted position is maintained for a minimum of three minutes regardless of productivity. This procedure is carried out at least twice daily, preferably on arising and retiring. Coughing during the interval between drainage procedures is the signal that insufficient evacuation of the bronchial passages has been accomplished, and the frequency of the drainage procedure is then increased.

The clinical and autopsy evidence available indicates that sinusitis, tonsillitis and possibly dental abscess are highly important factors in the production and perpetuation of the inflammatory bronchial and peribronchial process resulting in paroxysmal dyspnea. It seems probable that although such focal infections are extremely common they are productive of bronchial asthma only when constitutional thymicolymphatic stigmata are present.

Although it is possible by the above procedure to prevent asthmatic attacks where active infectious foci are present, total and permanent quiescence of the bronchial and peribronchial inflammation will occur only after ablation of these foci. Under this treatment régime the laboratory and physical signs of bronchial asthma disappear. Some of our patients have been asymptomatic for four years without treatment.

Our series consists of a group of severe and recalcitrant cases ranging in age from six to seventy-five years. Strict adherence to the régime has not yet failed to keep our patients free from asthmatic attacks.

Further studies are in progress regarding other factors which appear important in the provocation of the asthmatic attack and in the perpetuation of the disease process.

NOEL F. SHAMBAUGH[4]
SAM M. ALTER

[1] Preliminary report.

[2] Ian G. Macdonald, *Annals of Internal Medicine*, vi: 253, 1932.

[3] C. Jackson and C. L. Jackson, *American Journal of Medical Science*, clxxxvi, 849, 1933.

[4] From the Department of Internal Medicine, University of Southern California.

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