

# CORTISONE AND HEPARIN

BY

CLAUDIO CERVINI, ELIA CERIMELE, and SALVATORE LUCÀ

*Istituto di Semeiotica Medica dell' Università di Roma, Centro di Reumatologia (Prof. T. Lucherini)*

(RECEIVED FOR PUBLICATION FEBRUARY 25, 1953)

Though the abundant data published in the literature concerning the influence of cortisone on the thrombo-plastic powers of the blood is varied and sometimes even contradictory, we have concentrated our attention on the eventual influence of cortisone on heparin, the main factor of the circulating anti-coagulating substances. This decision was taken in consideration of the supposed existence of correlations between heparin, hyaluronic acid, and the enzymes of collagenasic, hyaluronidasic types, etc., of connective tissues.

In fifteen patients of different age and sex, received at the Institute of Medical Semiology of the University of Rome, who were affected with evolutive rheumatoid arthritis, we performed the "heparin tolerance test" during a period of therapeutical rest of at least 5 days. This was the test proposed by De Takats (1943) and De Takats and Gilbert (1943) to check the heparin reactivity in individuals who had to be submitted to anti-coagulating therapy.

## Technique

After having checked the coagulation time (C.T.) of the patient's blood *in toto*, we made an intravenous injection of 50 mg. heparin exactly measured (instead of the 10 mg. indicated in the original method of De Takats), and again measured the C.T. after 15, 30, 45, and 60 minutes. De Takats classified the different individuals as hypo-reactive, normo-reactive, and hyper-reactive. There was some criticism of this test, but this did not lessen its practical and theoretical value (Menghini and Costantini, 1950). The test was praised by Marmont and Palmieri (1949, 1951) as being sensitive, sure, and simple.

We used Burker's method in determining the C.T., as this is judged one of the most exact. Its method and application were described by Ferrio (1948).

## Results

In our fifteen cases of rheumatoid arthritis, the heparin tolerance test gave constant results, the curves being almost identical with those of healthy normal individuals. But the average curve traced

after treatment with cortisone, applied for 5 days with a daily dosage of 50-150 mg., shows a markedly flattened trend, expressing a state of hyporeactivity to heparin. Our investigations also showed that cortisone causes great changes in heparin tolerance, and brings about a constant hyporeaction.

## Discussion

This part of our results is confirmed by the clinical observations, already published in many countries, of the appearance of blood hyper-coagulability during treatment with ACTH or cortisone.

Our clinical investigations have made a fresh contribution to the complicated problem of the relationship between heparin, hyaluronidase activity, and adrenocortical therapy.

The fact that cortisone appears to cause hyporeaction to heparin may be ascribed to an increase of substances capable of inactivating or neutralizing heparin, of the type of thromboplastin and thrombin. Such an increase could, in theory, easily be ascribed to cortisone, as this substance shows the power of enhancing blood coagulability (see the thrombo-embolic incidents referred to). The possibility that the diminished tolerance is equal to an increased need of heparin, as we observed after cortisone administration, cannot be rejected; it may be ascribed to a greater consumption or neutralization of heparin. A third, and perhaps better, theory must also be kept in mind, *i.e.* a reduction in the formation of heparin is caused by the number reduction of the mast-cells and their morphologic and histochemical alterations (Asbøe-Hansen, 1950; Cavallo and Sala, 1950).

Even if the interpretation of this problem appears extremely complicated, every new piece of research into the nature and effects of cortisone is interesting.

## Summary

The influence of cortisone on heparin, the main factor of the circulating anti-coagulating substances, was studied in fifteen cases of rheumatoid arthritis.

The coagulation time was measured before, and 15, 30, 45, and 60 minutes after, an intravenous injection of 50 mg. heparin; this was done first during a period of therapeutical rest, and then after 5 days' treatment with cortisone (daily dosage 50-150 mg.).

The reaction to heparin was much less after the course of cortisone in every case. The reasons for this hyporeaction are discussed.

## REFERENCES

- Asbøe-Hansen, G. (1950). *Scand. J. clin. Lab. Invest.*, 2, 271.  
 De Takats, G. (1943). *Surg. Gynec. Obstet.*, 77, 31.  
 —, and Gilbert, N. C. (1943). *J. Amer. med. Ass.*, 121, 1246.  
 Cavallero, C., and Sala, G. (1950). *Comunicaz. Soc. Ital. Patol., Centro Triveneto (Sez. Riunite)*, Padova, Nov. 26, 1950.  
 Ferrio, L. (1948). "Semeiotica delle malattie interne," p. 446. "U.T.E.T.", Turin.  
 Marmont, A., and Palmieri, A. (1949). *Minerva med., Torino*, 40 (2), 510.  
 —, — (1951). *Ibid.*, 42 (1), 58.  
 Menghini, C., and Costantini, A. (1950). *Boll. Soc. ital. Biol. sper.*, 26, 1288.

## Cortisone et héparine

## RÉSUMÉ

Dans quinze cas d'arthrite rhumatismale on étudia l'influence de la cortisone sur l'héparine, facteur anticoagulant principal du sang circulant.

Le temps de coagulation fut déterminé avant, ainsi que 15, 30, 45 et 60 minutes après une injection intraveineuse de 50 mg. de héparine. Ce procédé fut appliqué une fois pendant le repos thérapeutique et répété après une cure de 5 jours de cortisone (50 à 150 mg. par jour).

Dans tous les cas la réaction à la héparine fut diminuée après le traitement par la cortisone. On discute les raisons de cette hyporéaction.

## Cortisona y heparina

## SUMARIO

La influencia de la cortisona sobre la heparina, factor principal de las substancias anticoagulantes del riego sanguíneo, fué estudiada en quince casos de artritis reumatoide.

El tiempo de coagulación fué medido antes, así como 15, 30, 45 y 60 minutos después de una inyección endovenosa de 50 mg. de heparina, aplicando este procedimiento durante un período de reposo terapéutico y repitiéndole al cabo de una cura de cinco días de cortisona (50 a 150 mg. diarios).

En todos los casos hubo una disminución de la reacción a la heparina después del tratamiento con la cortisona. Se discuten las razones de esta hiporreacción.