CIBA FOUNDATION SYMPOSIUM

Jointly with

THE PHYSIOLOGICAL SOCIETY

and

THE BRITISH PHARMACOLOGICAL SOCIETY

on

HISTAMINE

in honour of

SIR HENRY DALE, O.M., G.B.E.,
M.D., F.R.C.P., F.R.S.

Editors for the Ciba Foundation


and

CECILIA M. O'CONNOR, B.Sc.

With 133 Illustrations

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HISTAMINE
Ciba Foundation Symposia

General Volumes:

Visceral Circulation – – – – –
Mammalian Germ Cells – – – – –
Preservation and Transplantation of Normal Tissues – – – – – –
Hypertension: Humoral and Neurogenic Factors – – – – – –
Leukæmia Research – – – – –
Chemistry and Biology of Pteridines – –
Experimental Tuberculosis – – – –
Porphyrin Biosynthesis and Metabolism –
Extrasensory Perception – – – –

A leaflet giving fuller details of these volumes, also of the Ciba Foundation Colloquia on Endocrinology and Colloquia on Ageing, is available from the Publishers.
SIR HENRY DALE, O.M., G.B.E.
M.D., F.R.C.P., F.R.S.
THE suggestion of a symposium on Histamine originated in the Biological Council’s Co-ordinating Committee for Symposia on Drug Action, of which Sir Charles Harington is Chairman. It was taken up by the Physiological Society and the British Pharmacological Society, and a joint committee was formed of which the members were Prof. J. H. Gaddum, Dr. W. Feldberg, Prof. W. D. M. Paton, Dr. H. O. Schild and Dr. D. Wood.

In the hope of making the symposium an international occasion, this committee approached the Director of the Ciba Foundation, who very willingly agreed to hold a small conference on some aspects of the same subject in the days following the Societies’ symposium, and thereby invite, with some contribution towards their travelling expenses, a number of workers from overseas to both meetings. The committee obtained the use of the auditorium in the Wellcome Institute for the Societies’ symposium, and the Wellcome Foundation Ltd. further added generous financial support towards the attendance of members from overseas.

Sir Henry Dale honoured the Ciba Foundation by graciously consenting to have its symposium named in his honour.

On Sir Henry’s advice, formal papers were restricted to the Societies’ symposium, and the proceedings for the much smaller group at the Ciba Foundation were so arranged that only two speakers were invited briefly to open each of the four sessions, and the remainder of the time available was given up to group discussion. Some 300 people were present at the Wellcome, whereas attendance at any one session at the Ciba Foundation was necessarily limited to 30.

The Ciba Foundation undertook to publish, in the usual book form adopted for all its conferences, the papers presented at the Societies’ symposium in addition to the full
Preface

proceedings of its own symposium. This book is the result, and it is, therefore, a work in which many people have had a hand. The Director most gratefully acknowledges the essential help given in the original organization of the meetings by the Societies’ Committee, in particular by Dr. Schild, and by the Wellcome Foundation Ltd., mainly in the person of Dr. Adamson, and in the publication of this volume by Mr. J. and Mr. J. A. Rivers of J. & A. Churchill Ltd., whose unfailing and courteous co-operation makes even editorial work a pleasure.

To those to whom this book serves as an introduction to the activities of the Ciba Foundation it should be explained that it is an international centre, which is established as an educational and scientific charity under the laws of England. It owes its inception and support to its founder, CIBA Ltd., of Switzerland, but is administered independently and exclusively by its distinguished British Trustees.

The Foundation provides accommodation for Scientific workers who visit London from abroad, organizes and holds international conferences, conducts (in conjunction with the Institut National d’Hygiène) a postgraduate medical exchange scheme between England and France, arranges informal meetings for discussions, awards an annual lectureship, has initiated a scheme to encourage basic research relevant to the problems of ageing, assists international congresses and scientific societies, is building up a library service in special fields, and generally endeavours to give aid in all matters that may promote international co-operation in scientific research.

Leading research workers from different countries and in different disciplines are invited to attend the symposia or colloquia. The size of the group is, however, very strictly limited, as indicated above, in order to obtain a free conversational manner of discussion—although the basic timetable of the programme is strictly observed. The smallness of the groups means the exclusion of many workers active and interested in the subjects discussed, and therefore the
proceedings of these conferences are published and made generally available.

Research on Histamine seems to be at a point at which important advances can be anticipated. It is hoped that the papers and discussions held at the symposia organized by the Physiological and Pharmacological Societies and the Ciba Foundation, with the assistance of the Wellcome Foundation Ltd., will prove informative and stimulating to workers in this field throughout the world. In the progress of their research they will be honouring Sir Henry Dale in the manner which he would surely like best.
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Chairman: J. H. GADDUM

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List of those participating in or attending the Symposium on "Histamine" held at the Ciba Foundation, 6th-7th April, 1955

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C. F. Code . . . Mayo Foundation and Mayo Clinic, Rochester, Minnesota
Sir Henry Dale . . . The Wellcome Trust, London
U. S. von Euler . . . Dept. of Physiology, Karolinska Institute, Stockholm
W. Feldberg . . . National Institute for Medical Research, Mill Hill, London
J. H. Gaddum . . . Pharmacology Laboratory, University of Edinburgh
D. C. Hardwick . . . Institute of Animal Physiology, Babraham, Cambridge
G. Kahlson . . . Dept. of Physiology, University of Lund
R. Kapeller-Adler . . . Dept. of Clinical Chemistry, Royal Infirmary, Edinburgh
F. C. MacIntosh . . . Dept. of Physiology, McGill University, Montreal, Canada
F. C. McIntire . . . Abbott Laboratories, North Chicago
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J. L. Parrot . . . Physiology Laboratory, Hôpital Boucicaut, Paris
W. D. M. Paton . . . Dept. of Pharmacology, Royal College of Surgeons, London
J. J. Reuse . . . Laboratory of Pharmacodynamics, University of Brussels
J. F. Riley . . . Dept. of Radiotherapy, Royal Infirmary, Dundee, Scotland
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R. W. Schayer . Rheumatic Fever Research Institute, Northwestern University Medical School, Chicago
H. O. Schild . Dept. of Pharmacology, University College, London
H. Tabor . Section on Biochemical Pharmacology, National Institutes of Health, U.S. Public Health Service, Bethesda
U. Trendelenburg . Dept. of Pharmacology, University of Oxford
E. Werle . Surgical Clinic, University of Munich
G. B. West . Dept. of Pharmacology and Therapeutics, Queen's College, Dundee, Scotland
C. W. M. Wilson . Dept. of Pharmacology, Middlesex Hospital, London
E. A. Zeller . Dept. of Biochemistry, Northwestern University, Chicago
SYMPOSIUM OF THE PHYSIOLOGICAL AND PHARMACOLOGICAL SOCIETIES AT THE WELLCOME FOUNDATION
CHAIRMAN'S OPENING REMARKS

W. FELDBERG

National Institute for Medical Research, Mill Hill, London

It is most gratifying to see that the idea of a symposium on histamine has been so well received and that so many have come. As Chairman of the opening session it is my pleasant duty to welcome you. We are delighted that so many of our colleagues from abroad could come, and I would like to extend a special welcome to all those who have come from overseas—from South America, Canada and the States—to those who have come from the Continent, and naturally also to those who came from Scotland.

The idea of a symposium on histamine was suggested at a meeting of the Biological Council's Co-ordinating Committee for Symposia on Drug Action held in July 1953. The Chairman of the Committee, Sir Charles Harington, undertook to bring the suggestion to the notice of the British Physiological and Pharmacological Societies.

The suggestion was welcomed by these Societies, who appointed a joint sub-committee to organize the symposium. It consisted of Prof. Gaddum, Prof. Paton, Dr. Schild, Dr. Wood and myself and had at least one bright idea, although it was actually not a very original one, namely that of getting Dr. Wolstenholme from the Ciba Foundation interested in the matter. The result was that we now have two symposia, that the contents of both will be published by the Ciba Foundation, and that many more guests from abroad could be invited. On behalf of the organizing Committee I should like to express our thanks to the Ciba Foundation and to Dr. Wolstenholme personally, who has probably more experience in arranging symposia than anyone else in this country and on whose help and advice, I can assure you, we
could always rely. The meeting should also know that we are greatly indebted to Dr. Schild who cheerfully carried the main burden of organizing this symposium. Finally, on behalf of the organizing Committee—and I think you would wish me to do so also on your behalf—I should like to express our most sincere thanks to the Wellcome Foundation for their hospitality. We are fortunate that we can meet here in this fine hall for our symposium on histamine and, as mentioned by Mr. Perrin, the Chairman of the Wellcome Foundation, in his speech at the reception lunch party, this is indeed the most appropriate place, because it was in the Wellcome Research Laboratories that Sir Henry Dale carried out his pioneer work on histamine, and we are proud and glad to have him with us today.
If I had to shorten my contribution to the utmost, I could just say: histamine is very widely distributed in the body. In fact, if we look up its distribution in the book by Guggenheim (1951), we find there is scarcely any organ which does not contain at least some histamine. It occurs in the skin, in the subcutaneous tissue, in skeletal muscle, in all the viscera so far examined, and in the peripheral and central nervous systems. There are two tissues which, as far as I know, have not yet been examined: bone and cartilage, so I do not know if they contain histamine. Histamine occurs also in tumours and not only in those consisting of mast cells. It has been found in sarcoma of mice and rats but not in the Rous sarcoma of chicken, and histamine also appears to be absent in carcinoma, or to be present in these tumours in traces only (Rosenthal, 1949).

Histamine occurs, further, in many physiological and pathological body fluids: in blood, plasma, bile, gastric juice, urine, in the secretion of the nose, in blister fluid, sputum, and pus, but it has not been found in pancreatic juice and is usually absent in saliva, although Ungar and Pocoulé (1937) detected minute quantities occasionally.

Mention might be made that histamine is also a naturally occurring constituent of various plants such as nettles, spinach, tomatoes, Chenopodia and others, and it is sometimes present in plant tissues in extremely high concentrations. Werle and Raub (1948) found, in growing seeds of spinach, concentrations of nearly $0.5 \text{ mg./g.}$ fresh tissue, and even higher values in the flowers of the spinach plant.
which had survived the winter. In one specimen a value of $1.34 \text{ mg./g.}$ was found.

When discussing the distribution of histamine in the body, I must avoid as far as possible touching those aspects which are reviewed by the other speakers of this session and of the following, and this naturally imposes a restriction on the subject. My main object will therefore be to underline some of the striking and puzzling facts concerning the distribution of histamine in animal tissues.

First of all, we are not in the position to say that this or that organ has a high or low histamine content, because the distribution of histamine varies in different species. For instance, if we take the liver: in guinea pigs it contains usually only traces, in rats it has an average histamine content of less than $1 \mu\text{g./g.}$, whereas in dogs and horses values between 8 and 110 $\mu\text{g./g.}$ histamine have been found. Similar species differences for the histamine content occur in other organs. Thus the organs which are rich in histamine vary in different species.

I said that the histamine content of liver varies in dogs and horses between 8 and 110 $\mu\text{g./g.}$. I want to emphasize this wide range because it illustrates the tremendous individual variations which exist in the histamine content of so many organs. Anyone who wants to study changes in histamine content of organs and is not aware of these variations is apt to draw wrong conclusions. I myself once erred badly in this respect. The great individual variations make it difficult also to compare the histamine contents of different organs. I have tried to overcome this difficulty in Table I, by giving plus and minus signs instead of figures. The blank spaces do not mean that the organs contain no histamine but only that I did not find values in the papers I looked at.

The liver we have discussed. Another organ with a high histamine content in many species is the lung, except in rats. Skeletal muscle contains, in general, relatively small amounts of histamine except in rats.

When we consider the histamine content of skin, we have to consider not only species differences but also regional
Table I

DISTRIBUTION OF HISTAMINE

<table>
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<th>Rat</th>
<th>G Pig</th>
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<th>Cattle</th>
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**Code for histamine values**

- +++ often 40 - 100 \( \mu g/g \) or more
- +++ 20 - 40 \( \mu g/g \)
- ++ 10 - 40 \( \mu g/g \)
- + 10 - 20 \( \mu g/g \)
- ++ 1 - 10 \( \mu g/g \)
- less than 1 \( \mu g/g \)

...
ears, face and paws are normally the regions with the highest histamine values. Miles and I (1953) found that the skin of the cat's ear contains between 95 and 120 µg./g. The regional differences in the guinea pig's skin are illustrated diagrammatically in Fig. 1. The histamine content of the abdominal skin which is 3.2 µg./g. is taken in this diagram as unity. Skin from the ears contains five times as much histamine, and skin from many parts of the face and head and around the nipples has high histamine values; high histamine values
are also obtained from the skin of the feet. The large regional differences in skin histamine probably reflect regional differences in the mast cell content, and perhaps we shall hear more about this problem from Dr. West, and during the discussion.

Concerning the gastro-intestinal wall, I think it is not generally realized that the intestinal mucosa, in many species, has a very high histamine content, and to some extent this applies to the mucosa of the stomach as well. The distribution of histamine in the wall of the digestive tract of the dog is shown in Fig. 2. The wall of the oesophagus has a low histamine content. In the stomach wall the histamine content is high, at least in the body; in the pyloric region the value falls to half the level. When we come to the duodenum, the value becomes very high again and then there is a gradual decrease from duodenum to ileum and colon. The greater part of the histamine in the wall of the digestive tract resides in the mucosa; here the concentration of histamine is even higher than that given for the whole wall. For the gastric mucosa, values of over 100 µg./g. are often obtained for the body of the stomach and the values for the mucosa from the pyloric region are about half as high.

The mucosa of the digestive tract consists of many different cellular elements, and in order that these figures and differences, for instance the difference between the body and

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**Fig. 2.** Diagram of digestive tract to illustrate the position of pieces taken for extraction and histamine assay. The figures below the diagram are µg. histamine per g. of entire wall of the respective areas. (Douglas, Feldberg, Paton and Schachter, 1951.)
Fig. 3. Histamine profiles and microphotographs of mucosa and submucosa from the body and the pyloric region of the stomach of a dog. (Feldberg and Harris, 1953.)