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Recent Progress in Histamine and Antihistamine Research[1]

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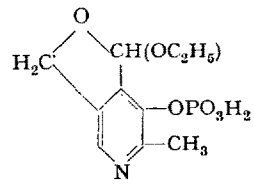
Introduction

In the following paper some of the publications are reviewed which have appeared since 1946 on the subject of histamine and antihistaminics and which are of particular interest to those working in these fields[3]. Not only the clinical and commercial importance of the antihistaminic substances has contributed to a rich yield of publications but also the stimulus provided by international conferences, such as the "Congrès médicale" in Paris and the Meeting at the New York Academy of Sciences, both held in October 1947.

Looking over these papers, one is surprised to find that rather little fundamental work has been done during the last two years concerning histamine metabolism, as compared to *histidine* which has been studied extensively from the viewpoints of distribution[4], requirements[5], its relationship to folic acid[6], toxicity[7], metabolism[8], physiological activity[9], elimination[10], histidase[11], and finally histidine decarboxylase[12].

While it has been possible to resolve lysine and tyrosine into a specific coenzyme and a common decarboxylase, this was *not* possible with histidine decarboxylase which apparently does not contain codecarboxylase[1]. The codecarboxylase of tyrosine has been synthesized in crystalline form by KARRER[2]. GUNSALUS, however[3], claimed that the compound synthesized by KARRER, namely the 3-phosphate of Pyridoxal (I), does not have codecarboxylase activity. Additional evidence in favor of KARRER's original contention is presented in a recent paper[4].



codecarboxylase (?)

(I)

Publications on *histamine* on the other hand (here, of course, the antihistaminics are *not* included) have been restricted to the technique of histamine determination and to histamine determinations in skin and other organs in normal and pathological conditions.

But before discussing these, let us summarize some of the main-results obtained since the fundamental discoveries of BARGER and DALE[5], DALE and LAIDLAW[6], LEWIS[7] etc.

Histamine

The origin of histamine which is found in the animal body in sometimes surprisingly large quantities, is still not quite clear. It might derive from the essential amino acid histidine (to a small extent) by

[1] Taken in part from a paper presented at the combined Meeting of the A.A.A.S. and the A.C.S., Chicago, December 26, 1947. Revised October 1948.

[2] Warner Institute for Therapeutic Research, New York, N.Y.

[3] Literature on histamine has been thoroughly reviewed till 1930 in FELDBERG and SCHILF's[13], and till 1940 in GUGGENHEIM's book[14]. Quite recently, an excellent book has been published by D. BOVET and F. BOVET-NITTI (S. Karger, Basel, 1948), which covers the here discussed field in great detail.

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[5] G. BARGER and H. H. DALE, Zbl. Physiol. *24*, 885 (1910).

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[7] T. LEWIS, *The blood vessels, etc.* (London, 1927).

the activity of an amino acid oxidase or histidase[1], and (to a larger extent) by the activity of decarboxylases, such as are found in mammalian tissues[2] or produced by bacteria[3]. The presence of histidine decarboxylase in the human body, however, has not been definitely proven[4]. Most of the histamine is immobilized and probably pharmacologically inactivated, being bound to protein. The mechanism by which histamine is inactivated and by which it is released is unknown. Histamine *can* be released by the junction of antigen-antibody or by ultra-violet rays, by skin irritation (extreme cold or heat, etc.), by muscle contraction, under the influence of ascorbic acid, cobra venom, and in many other conditions. Particularly important, from the practical point of view, was the observation that histamine is released during, and most likely to a great extent responsible for certain anaphylactic and allergic manifestations[5]. Consequently, the mechanism of histamine release in anaphylactic, peptone, and ascaris shock was subject of intensive studies[6]. ROCHA and SILVA came to the conclusion that histamine is released in shock from the blood platelets under the influence of activated plasma trypsin. This, however, has lately been questioned by GEIGER[7]. According to DANIELOPOLU[8] histamine release is only secondary to the prior release of acetylcholine. The *distribution* of histamine in plants, animals, tissues, blood under normal and pathological conditions has been widely studied (GUGGENHEIM[9], p. 362). Blood histamine was found to be increased by 100 times in chronic myeloid leucemia[10], 456 times in insulin shock[11], 100–200 times in the blood of smokers[12], increased in the blood during scarlet fever[13], in blood during menstruation[14] and menstrual fluid[15], 200 times increased in the skin after adrenalectomy[16], to cite just a few examples.

Histamine determination in most of the cases was carried out, using the method of BARSOUM-GADDUM, modified by CODE PARROT, and RICHET[1] published a bioassay method of histamine determination in organic fluids, based on the pharmacological action of anextract. Compared with that of a known quantity of histamine, HALPERN and WALTHERT[2] described a method which permitted determination of histamine in presence of histidine. CANTONI[3] criticized the usual guinea-pig gut method by showing that large doses of histamine will depress temporarily the contractile responsiveness of the gut.

The physiological activity of histamine has been subject of intensive investigation. Its contracting effect on the smooth muscles, dilating effect on capillaries, its secretory stimulating effect, hemocontraction, triple response of the skin, the similarities and differences of histamine and anaphylactic shock, are all well known and thoroughly reviewed by GUGGENHEIM (l. c.). It was found, furthermore, that histamine in low concentrations can accelerate the regeneration of wounded guinea-pig tissues[4], that histamine increases the permeability of erythrocytes for trypanblue[5] and for CNS[6]. Ulcers produced by histamine were photographed[7], and gastric ulcers induced by cinchophen were found to have lead to a simultaneous elevation of the blood histamine level[1]. In men, histamine injection produced gastric juice of high acidity but low peptic activity[8], and gastric acidity induced by histamine was much higher in men suffering from ulcers than in women patients[9]. During histaminic cephalgia the stomach acid curve was found to be elevated[10]. Histamine induced ulcers could not be prevented by vagotomy[11], and nitroglycerin accelerated the occurrence of such ulcers. Histamine as a possible mediator of pain, was studied by KOCHTOYANTS *et al.* in U.S.S.R.[12]. Histamine injection was made responsible for changes in the epinephrine content of the adrenals[13], and the action of histamine and acetylcholine on the

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secretion of epinephrine was thoroughly studied[1] (see later STAUB[2]).

The mechanism of histamine activity was investigated by chemists, pharmacologists and immunologists as well. The observation that 2-pyridylethyl amines had histamine-like activity, while 3- and 4-pyridylethyl amines had *no* such activity[3], led to the conclusion that the group:- CH–N–C($CH_2CH_2NH_2$)–C–CH– is "essential" for histamine-like activity.

The pharmacodynamic effects of histamine were attributed to the NH_2-group, while the imino group supposedly should act as the anchoring group, fixing histamine to the cell receptors[4]. This, however, was contradicted on the ground that arginine (claimed to be a specific histamine antagonist) also counteracts acetylcholine and pilocarpine, which do *not* have free imino groups[5].

It has been stated repeatedly[6] that histamine acts on isolated muscles and in shock not directly but by intervention of released acetylcholine (see later[7]). According to PARROT and RICHET[8] histamine is pre-existing in the tissues bound to protein which at the same time plays the role of a "fixed antibody". As soon as the antigen is introduced, it combines with the protein which simultaneously would release histamine and also heparin and perhaps acetylcholine. This interpretation is of course the opposite to DANIELOPOLU'S[6] findings.

To begin with the technique we should mention that the accuracy of the classical BARSOUM-GADDUM-CODE method has been questioned by BRAM ROSE[9]. Of new methods we could mention BARAUD'S[10] chemical determination of histamine (diazotization and colorimetric measurement) and HALPERN'S electrophotometric method[11] which is based on PAULY'S color reaction. Particularly important is MCINTIRE'S[12] method of histamine purification which is suitable for quick determinations in series of samples, f. i. in blood plasma.

The histamine is extracted from an aqueous tissue extract with butanol and recovered from the same by means of cottonacid succinate, a new cation exchange medium. From this, the histamine is eluted with diluted HCl and neutralized with NaOH to give an isotonic solution ready for bioassay. Recoveries are quantitative.

*Anti*histamine levels can be determined by the same method and actually included in the same procedure. In this case, the aqueous tissue extract (before being treated with butanol) is extracted with ether. All amines, except histamine, will go nto the ether which should *not* be filtered through the cation exchanger but worked up separately. MCINTIRE and his coworkers give no data on antihistamine determinations. Their data on blood histamine concern animals only. This method was improved upon by ROSENTHAL and TABOR[1]. Shortly afterwards MCINTIRE reported the discovery of a new quantitative reaction for histamine with 2:4-dinitrofluorobenzene[2].

PELLERAT[3] was the first one, to our knowledge, to do systematic histamine (and also antihistamine) determinations in *human* beings under normal and pathological conditions *and* also under antihistamine treatment.

According to PELLERAT, the skin of the normal human adult contains an average of about 20 mg/kg histamine, determined by CODE'S method. This is lowered: in old age, after application of cold or heat, as a result of a TB-cuti-reaction, and in certain dermatoses.

Cooling by chlorethyl anesthesia e.g. reduced the histamine content of human skin from 15 or 19 mg to 3 mg (at the same time the histamine in the blood plasma was increased!). Consequently, skin which had been anesthetized did *not* react to *heat* with the usual wheal formation as normal skin did, since most of the histamine had disappeared. Further experiments indicated that skin histamine, displaced in this way, is fairly rapidly replaced, namely within about one hour. PELLERAT made the interesting observation (l. c., p. 16) that two of his guinea-pigs 5 minutes after chlorethyl anesthesia developed asthmatic dyspnœa, very similar to the one produced by a histamine aerosol. Later on, a possible explanation for this phenomenon will be discussed. According to DEKANSKI[4], the histamine content of the skin of the rat is increased after moderate burns (60°), while it is decreased after severe burns (80°). Examinations of the blood by PELLERAT showed that human subjects have practically no histamine in their plasma, and about 55–66 γ/l in total blood while under certain pathological

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Table I
Pathological cases influenced by histamine (PELLERAT, l. c.)

Disease	Total blood (γ/l)	Plasma (γ/l)
Urticaria	90	30
Urticaria	115	25
Cured urticaria	90	traces
Prurigo	260	20
Artificial dermatite	128	32
Artificial dermatite	60	4
Zoster	160	traces
During Brocq	100	0
Pruritus with eczema	125	50
Pruritus after itches	100	45
Pruritus by itches	82	15
Pruritus by itches	85	15
Pruritus by cutaneous irritation	120	26
Pruritus by cutaneous irritation	150	28

conditions the blood showed an increase of plasma histamine up from zero to 50 and in total blood from 60–260 γ/l.

CODE and MACDONALD[1] had found 1937 a 100-fold increase of blood histamine in a case of chronic myeloid leucemia, and recently ROSE[2] reported a case with a 500-fold increase of total blood histamine. This patient, however, was neither allergic nor in shock. All or most of his histamine was evidently bound to the leucocytes.

PELLERAT (l. c.) does not give figures on asthma cases, and ROSE did not find an increase in blood histamine of asthma patients, while RANDOLPH and RACKEMANN[3] *did* find it.

The distribution of histamine over the different blood constituents has been studied by PARROT and GABE[4]. BUSINCO[5] determined the histamine content of the stomach wall of patients with gastric or duodenal ulcers. And VANDELLI[6] found considerable amounts (2·04 γ/cc) of histamine in human sperm.

Physiological effects of interest were noted by DESCHIENS and POIRIER[7]. They found that the damaging effects of repeated intramuscular injections of histamine into guinea pigs (in lung, liver, kidneys) are similar to those produced by poisoning with extracts of either *Ascaris megalocephala* or *Tænia saginata*.

Data on histamine liberation deserve particular attention. According to EISA[8] smooth, and particularly striated muscles, uterus, bladder, esophagus, heart, etc., all produce measurable amounts of histamine. Production of histamine by the heart is increased whenever the heart is made to work harder as f. i. during high arterial pressure, after adrenaline administration, during anoxemia, or under influence of small amounts of carbon dioxide.

Histamine liberation from muscles (EISA, l. c.)

Gastrocnemius of dog (40 g) contracted 10 sec produced	3·5 γ histamine
Heart at 50 mm Hg arterial blood pressure produced	0·6 γ histamine
Heart after 0·1 mg adrenaline, at 150 mm Hg produced	40·6 γ histamine
Heart supplied with fully oxygenated blood produced	0·34 γ histamine
Heart during anoxemia produced	26·0 γ histamine

In this connection it is also interesting that GOODMAN *et al.*[1] found increased capillary permeability under the influence of anoxemia. It has been reported by BOVET[2] that histamine is released also after administration of stilbamidines and of curare. The latter observation was confirmed by GROB *et al.*[3]. (Liberation of a histamine-*like* substance from muscle by curare had previously been reported by ALAM *et al.*[4].) Histamine liberation from the lung after adrenaline administration has been predicted (but not experimentally proven) by BURN and DALE in 1926[5]. EICHLER and BARFUSS[6] have shown strong histaminemia in *cats* after toxic doses of adrenaline. And STAUB[7] found histaminemia in *human* subjects after adrenaline administration. He also noticed that this histaminemia can be prevented by previous administration of an antihistaminic drug, such as Antistin—and finally formulated the thesis that histamine and adrenaline are partners in a compensatory mechanism, regulating the blood pressure. Consequently, blood pressure increase or vasoconstriction due to adrenaline would immediately be compensated by increased histamine production or release, and vice versa. BAUR and STAUB[8] found recently that the sympathomimetic drug Sympatol increased the histamine level of human blood plasma, just as adrenaline. According to GROSS[9] adrenalectomized animals withstand histamine shock almost as good as normal animals if balanced by

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[3] T. G. RANDOLPH and F. M. RACKEMAN, J. Allergy *124*, 50 (1941).
[4] J. L. PARROT and M. GABE, C. r. Soc. biol. *139*, 965 (1945).
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[9] F. GROSS, Helv. physiol. acta *6*, 114 (1948).

desoxycorticosterone (desoxy itself gives only little protection, according to DOBY[1]).

It has further been stated by DANIELOPOLU[2], AMBACHE[3], and later supported by CRAVER[4] that histamine (as well as barium) acts probably by releasing acetylcholine. AMBACHE's conclusions, however, have been quite recently severely criticized by EMMELIN and FELBERG[5]. Epinephrine, acetylcholine and histamine appear nevertheless, to be the principal actors involved in the intricate play of regulatory mechanism, which might be dependent of, or influenced by a number of other factors as yet unknown.

Antihistaminics

Before discussing recent progress in this field, let us summarize some of the results prior to 1946:–

(a) *Natural histamine antagonists:*– Histamine is –in the organism–subject to oxidative deamination by histaminase (diaminoxydase of ZELLER[6]). This enzyme leaves the imidazol ring of histamine intact and needs oxygen for its activity[7]. The question as to whether it is a flavoprotein, is not yet settled[8]. Histaminase has been purified by LASKOWSKI[8] until his product was 24 times stronger than the commercially available preparation (Torantil), but it was too toxic to be used in men against allergic manifestations, and *per os* administration proved useless, since it is inactivated by pepsin and trypsin. According to LASKOWSKI, l. c., the hydrogen peroxide formed by the activity of histaminase in the reaction

$$R\cdot CH_2CH_2NH_2 + O_2 + H_2O \rightarrow R\cdot CH_2CHO + NH_3 + H_2O_2$$

cannot be demonstrated experimentally, because even the purest histaminase preparations available are contaminated with catalase which immediately would destroy any H_2O_2 formed during the reaction.

Quantitative changes of histaminase in the blood and urine during pregnancy and particularly toxemic pregnancy have been thoroughly investigated[9,10] and have resulted in methods of rather accurate pregnancy determinations[10,11], and better insight into the histidinuria of normal pregnancy, which is replaced by histaminuria in certain toxemic pregnancies[12].

Other natural histamine antagonists are certain amino acids, such a arginine, spermine, which, however, are 100,000–1 million times *less* active than the synthetic antihistaminic substances. The mechanism of their activity started a long controversy[1]. In therapeutically effective amounts (their effectiveness *in vivo* has never been proven), these aminoacids would be much too toxic for human beings.

(b) *Synthetic histamine antagonists:*– In 1941 FELL, SHELDON *et al.*[2] coupled histamine with azoproteins and were able to stimulate *in vivo* the formation of histamine antibodies by repeated administration. With one of their products, marketed as „Hapamine", occasional relief was obtained in allergic conditions. Similar compounds were also prepared by WENT and KESTYÜS, 1942[3]. The specificity of the antibodies so formed, has, however, been questioned[4].

In 1943, ROCHA e SILVA[5] prepared several amino-acid conjugates which upon tryptic or acid hydrolysis liberated histamine. The most active compound of this series was only 3 times as active as arginine, and consequently no clinical tests have been made with these compounds.

The first synthetic preparations which deserve the name of *true* antihistaminic substances, were prepared at the Fourneau Institute in Paris and reported by BOVET and STAUB, 1937[6], and STAUB[7]. They were rather simple chemicals such as *N,N*-diethyl-N^1-phenyl-N^1-ethyl-ethylenediamine (F 1571) or thymoxyethyl-diethylamine (F 929). Within a series of 17 analogous amines and 21 ethers, the above two compounds were the most active. Given in doses of 10–20 mg/kg intravenously to guinea-pigs, they protected them against 2–6 otherwise lethal doses of histamine given subcutaneously. Similarly, the animals were protected against histamine aerosol and against anaphylactic shock. These compounds, however, were extremely toxic for men and could therefore not be used clinically. In 1940 intensive antihistamine research at the Rhône-Poulenc Laboratories in France, led to the discovery and marketing of R.P. 2339 (Antergan), which is *N,N*-dimethyl-N^1-phenyl-N^1-benzyl-ethylenediamine. This compound was about 4–5 times as active as the previous Fourneau compounds and at the same time far less toxic. Clinically, if provided effective relief in allergic manifestations, particularly in hay-fever and urticaria.

[1] T. DOBY, Schweiz. med. Wschr. *76*, 485 (1946).
[2] D. DANIELOPOLU, Schweiz. med. Wschr. *78*, 567 (1948).
[3] N. AMBACHE, J. Physiol. *104*, 266 (1946).
[4] B. N. CRAVER, N. Y. Acad. Sci., in press (1947).
[5] N. EMMELIN and W. FELDBERG, J. Physiol. *106*, 482 (1947).
[6] E. A. ZELLER, Helv. chim. acta *21*, 880 (1938).
[7] E. WERLE, Biochem. Z. *311*, 329 (1942).
[8] M. LASKOWSKI, J. M. LEMLEY, and C. K. KEITH, Arch. Biochem. *6*, 105 (1945).
[9] G. V. ANREP, G. S. BARSOUM, and A. IBRAHIM, J. Obstetr. Gynecol. *54*, 619 (1947).
[10] R. KAPELLER-ADLER, Brit. Med. J. 717 (1947).
[11] A. AHLMARK (Sweden), see Biol. Abstr. *21*, 8534 (1947).
[12] R. KAPELLER-ADLER, Wiener klin. Wschr. *60*, 395 (1948).

[1] D. ACKERMAN and W. WASMUTH, Z. physiol. Chem. *260*, 155 (1939); *258*, 28 (1939). – S. EDLBACHER, P. JUCKER, and H. BAUR, Z. physiol. Chem. *247*, 63 (1937).
[2] J. M. SHELDON, N. FELL, J. N. JOHNSTON, and H. A. HOWES, J. Allergy *13*, 18 (1941). – N. FELL, G. RODNEY, and D. E. MARSHALL, J. Immunol. *47*, 237 (1943).
[3] L. KESTYÜS (Debrecen), see Chem. Abstr. *38*, 3731 (1944). – I. WENT and L. KESZTYÜS (Debrecen, 1946), see: Chem. Abstr. *42*, 3062 (1948).
[4] G. S. COFFIN and E. A. KABAT, J. Immunol. *52*, 201 (1946).
[5] M. ROCHA e SILVA, J. Pharmacol. *77*, 198 (1943); *80*, 399 (1944).
[6] D. BOVET and A. M. STAUB, C. r. Soc. biol. *124*, 547 (1937).
[7] A. STAUB, Ann. Inst. Past. *63*, 400, 420, 485 (1939).

Since that time a number of other products have been marketed in Europe and in U.S.A. known by their trade-names as Neoantergan, Antistin, Pyribenzamine, Benadryl, etc. (Antergan has lately been withdrawn). Most of these compounds are strong local anesthetics; Neoantergan f. i. was found by DEWS *et al.*[1] to be 3 times as potent as Procaine. The local anesthetic properties (as well as the adrenergic potentiating effect[2] are independent of the antihistamine activity[3].

As to the possible mechanism of antihistamine activity, the following can be said:— these drugs do not enhance the activity of histaminase, they do not combine chemically with histamine[4], they most likely do not interfere with the formation of antibodies[5]. Some of the experimental results, however, seem to indicate that junction of antigen and antibody might be hindered by antihistaminics[6]. The most generally accepted theory is that antihistaminic substances displace histamine from the cell receptors rendering the tissues—in some as yet unknown way—less susceptible to the activity of histamine. According to STAUB[7] antihistaminics might be capable of preventing the formation of histamine. PAYOT[8] reported that they also hinder the enzymatic splitting of acetylcholine.

The name "antihistaminic substances" has been repeatedly criticized, and GILMAN has proposed to call them *histaminolytic* substances, because they do not interfere with the release of a chemical mediator but prevent him from reaching the receptor mechanism of receptor cells; consequently they ought to be considered not as physiological antagonists but rather as blocking agents[9].

Let us again begin with the technique:—

(i) *Technique of evaluation.*—Considerable time and effort has been spent to find reliable methods which would permit correct evaluation of the different synthetic antihistaminics. LEVY and SEABURY[10] described a spirometric method, and CASTILLO and DE BEER[11] used the so-called tracheal chain for evaluation of antihistaminic drugs. TRAUB *et al.*[12] determined the activity by measuring the ability of the drug to suppress histamine action on the skin capillaries of the rabbit. WELLS at the N.Y. Academy of Sciences[1] proposed to evaluate them by the help of a mathematical equation which would relate the affinity constant of histamine for the cell receptor to the affinity constant of the antihistaminic drug for the cell receptor.

$$\frac{HR}{RT} = \frac{H}{H—\alpha + \frac{\alpha}{\alpha'} B + \frac{\alpha}{\alpha'\alpha''} B^2}$$

Very exact results were obtained by SCHILD[2] who developed an idea of CLARK and RAVENTOS[3] which had proposed to measure drug antagonism by using as measure of activity the concentration which would neutralize the effect of a 10-fold increase of active drug. SCHILD determined such values and called them p_A which stands for the negative logarithm to base 10 of the molar concentration of an antagonistic drug which will reduce the effect of a multiple dose x of an active drug to that of a single dose. Each drug-antagonist pair is characterized by four p_A-values, and this gives a more complete picture as the usual one which is influenced by duration of action and by concentration. His graphs show that Neoantergan is an extremely discriminating antagonist being 40,000 times as active against histamine as against acetylcholine. Atropine is 1000 times as active against acetylcholine as it is against histamine. And Pethidine (ethyl-4-phenyl-1-methyl-piperidino-4-carboxylic acid, prepared by SCHAUMANN) hardly discriminates between the two.

STAUB[4] had noticed already 1939 that the stronger antihistaminic a given compound, the poorer anti-acetylcholine it was, and vice versa. This point can be seen quite clearly on SCHILD's pictures.

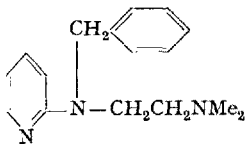
SCHILD's method has recently been improved by MILLER and coworkers[5]. ROCHA e SILVA, however[6], considers the dynamics of recovery of the isolated intestinal strip as a more reliable basis for quantitative determinations of drug antagonism.

BUKANTZ and DAMIEN[7] discovered that antihistaminic activity can be measured *in vivo* by means of fluorescein. In *normal* subjects fluorescein disappears rapidly under the influence of histamine, and antihistaminic substances always neutralize this effect. In *allergic* subjects fluorescein alone is visible only for a short time (probably due to presence of histamine), but when antihistaminics are added, fluorescence is visible for a prolonged period of time.

[1] P. B. DEWS and J. D. P. GRAHAM, Brit. J. Pharmacol. *1*, 278 (1946).
[2] E. R. LOEW, Physiol. Rev. *27*, 542 (1947).
[3] B. N. HALPERN, G. PERRIN and P. B. DEWS, C. r. Soc. biol. *141*, 1125 (1947).
[4] A. STAUB, Ann. Inst. Past. *63*, 400, 420, 485 (1939).
[5] A. LEYA, C. r. Soc. biol. *140*, 194 (1946). – R. L. MAYER, PH. C. EISMAN, and K. ARONSON, J. Bacteriol. *52*, 257 (1946).
[6] P. VALLERY-RADOT, B. N. HALPERN, and A. HOLTZER, C. r. Soc. biol. *141*, 229 (1947). – S. W. LANDAU, H. L. HARRIOTT, and L. N. GAY, Bull. Johns Hopkins' Hosp. *83*, 343 (1948).
[7] H. STAUB, Schweiz. med. Wschr. *76*, 818 (1946); Helv. physiol. acta *4*, C 54 (1946); *4*, 539 (1946).
[8] P. PAYOT, Schweiz. med. Wschr. *76*, 1159 (1946).
[9] A. GILMAN, J. Allergy, *19*, 281 (1948).
[10] L. LEVY and J. H. SEABURY, J. Allergy *18*, 244 (1947).
[11] J. C. CASTILLO and E. J. DE BEER, J. Pharmacol. *89*, 104 (1947).
[12] F. B. TRAUB, U. FRIEDEMANN, and D. LANDSTADT, J. Allergy *18*, 273 (1947).

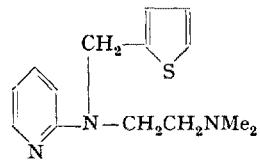
[1] J. A. WELLS, N. Y. Acad. Sci. Meetings, October 1947, in press.
[2] H. O. SCHILD, Brit. J. Pharmacol. *2*, 189 (1947).
[3] A. J. CLARK and J. RAVENTOS, Quart. J. Exp. Physiol. *26*, 375 (1937).
[4] A. STAUB, Ann. Inst. Past. *63*, 400, 420, 485 (1939).
[5] L. C. MILLER, T. J. BECKER, and M. L. TAINTER, J. Pharmacol. *92*, 260 (1948).
[6] M. ROCHA e SILVA, and W. T. BERALDO, J. Pharmacol. *93*, 457 (1948).
[7] S. C. BUKANTZ and G. DAMIEN, Science *107*, 224 (1948).

(ii) *New antihistaminics and related compounds.*—In discussing the new antihistaminics and some related compounds published during 1946/7, we have to mention the *thiophen* analogs of Pyribenzamine (PBZ) reported almost simultaneously from the Laboratories of



(II)

Pyribenzamine (Ciba)
(PBZ)

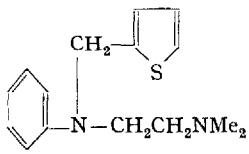


(III)

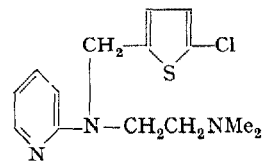
Thenylene (ABBOTT)
Histadyl (ELI LILLY)
W-53 (WM. R. WARNER)

ABBOTT[1], AMERICAN CYANAMID[2], MONSANTO[3] (in collaboration with ELI LILLY[4]), and WM. R. WARNER[5].

LICHTFIELD *et al.*[6] found superior activity and diminished toxicity in animal experiments with the chloro and bromo substituted thiophen derivatives (V) and (VI), as compared with the unsubstituted compound (III), which has about the activity of PBZ[7]. Diatrin (IV), the phenyl analog of Thenylene, has been reported by VIAUD[8] as being completely inactive

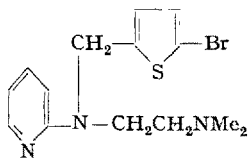


Diatrin (WARNER)
(IV)

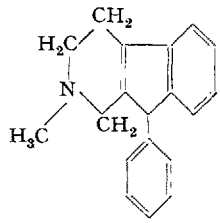


Chlorothen (AMERICAN CYANAMID)
(V)

(R.P. 2740), but when prepared by LEONARD and SOLMSSEN[9] and tested by ERCOLI *et al.*[10] (all of the Warner Institute for Therapeutic Research, New



Bromothen
(AMERICAN CYANAMID)
(VI)

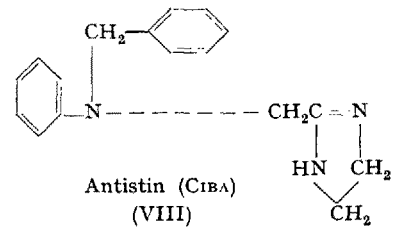


Thephorin (HOFFMANN-LA ROCHE)
(VII)

[1] A. W. WESTON, J. Amer. Chem. Soc. *69*, 980 (1947).
[2] R. C. CLAPP *et al.*, J. Amer. Chem. Soc. *69*, 1549 (1947).
[3] H. M. LEE, W. G. DINWIDDIE, and K. K. CHEN, J. Pharmacol. *89*, 183 (1947).
[4] L. P. KYRIDES, F. C. MAYER, and F. B. ZIENTY, J. Amer. Chem. Soc. *69*, 2239 (1947).
[5] N. ERCOLI, R. J. SCHACHTER, F. LEONARD, and U. V. SOLMSSEN, Arch. Biochem. *13*, 407 (1947).
[6] J. T. LICHTFIELD Jr., *et al.*, Bull. Johns Hopkin's Hosp. *81*, 44 (1947).
[7] S. M. FEINBERG and T. B. BERNSTEIN, J. Lab. Clin. Med. *32*, 1370 (1947).
[8] P. VIAUD, Produits pharmac. *2*, 53 (1947).
[9] F. LEONARD and U. V. SOLMSSEN, J. Amer. Chem. Soc., in print (1948).
[10] N. ERCOLI, R. J. SCHACHTER, W. C. HUEPER, and M. LEWIS, I. pharmocol. *93* 210 (1948).

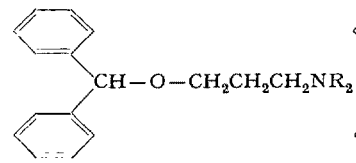
York, N.Y.), it was found to be about as active as Antergan, and of considerably lower toxicity. Pharmacological findings were born out by clinical reports (to be published shortly).

Thephorin of HOFFMANN-LA ROCHE[1] can be interpreted as a substance in which the aliphatic chain $-CH_2CH_2NMe_2$ has participated in ring closure, somewhat similar to Antistin (VIII). The clinical evaluation is still in progress, but in 25% of human allergy cases studied by KESTEN *et al.*[2] the side-effects were strong enough to warrant discontinuation.

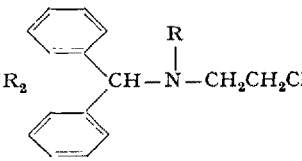


Antistin (CIBA)
(VIII)

According to LEHMANN[1], Thephorin antagonizes epinephrin-induced responses, reduces the incidence of duodenal ulcers caused in dogs by continuous histamine administration, and influences the histamine-stimulated gastric secretion in dogs.

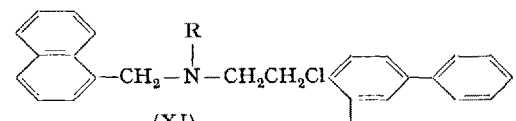


U.S. P. 2427878
RIEVESCHL (PARKE DAVIS)
(IX)

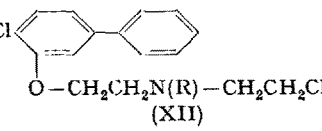


(X)

Reduction of histamine-induced gastric secretion is also claimed for RIEVESCHL'S propyl ether of benzhydrol (IX), a Benadryl analog which is covered by U.S.P. 2427878[3].

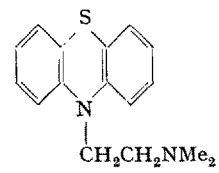


(XI)

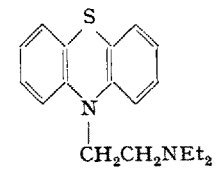


(XII)

Several of the chloroethylamine derivatives (X, XI, XII) prepared by RIEVESCHL *et al.* were found by LOEW[4] to block and even reverse the pressor response



(R.P. 3015)
(XIII)



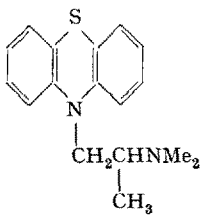
(R.P. 2987) Diparcol
(XIV)

[1] G. LEHMANN, N.Y. Acad. Sci., October Meetings 1947, in press.
[2] B. M. KESTEN and C. SHEARD, Jr., J. Invest. Dermat. *9*, 65 (1947).
[3] G. RIEVESCHL, U.S.P. 2427878.
[4] E. R. LOEW, Physiol. Rev. *27*, 542 (1947).

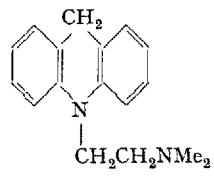
to epinephrine, just as Thephorin and F 929, but to a lesser degree than Dibenamine. The naphthyl derivative (XI) is as active as Neoantergan in preventing fatal histamine and anaphylactic shock in guinea-pigs, and these compounds have prolonged activity which is rapid in onset.

By far the most active antihistamine compounds known, belong to the series of phenothiazines, synthesized by CHARPENTIER of the Rhône-Poulenc Laboratories and described by HALPERN *et al.*, 1946[1]. Their activity is about 15 times that of PBZ, and the duration of action is 3 times that of Antergan or PBZ.

By means of compounds, such as R.P. 3277, HALPERN *et al.*[1] were able to protect guinea-pigs against 1500 lethal doses of histamine. These high doses led shortly afterwards to death, due to perforating stomach ulcers[2]. While R.P. 3015 and particularly R.P. 3277



(R.P. 3277) Phenergan
(XV)

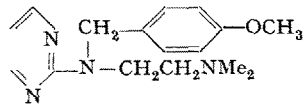


(Searle No. 1675)
(XVI)

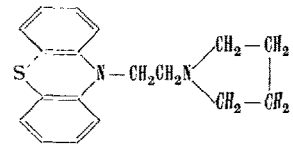
(Phenergan, XV) deserve great interest for their prolonged antihistamine activity, compound R.P. 2987 (Diparcol, XIV) was found to be useful in the treatment of Parkinsonism[3]. This compound (XIV) has originally been synthesized by GILMAN and SHIRLEY[4]. It was recently shown to be also a specific inhibitor of pseudo-cholinesterase[5]. Extremely high antihistamine activity is claimed for the acridan derivative (XVI). Its high toxicity, however, excludes clinical application[6].

We should also mention Neohetramine (XVII), Pyrrolazote (XVIII), Decapryn (XIX), compound C-5581-H (XX), Trimeton (XXI), and finally the thiazolyl analog of PBZ (XXII). All of these compounds are now in clinical investigation, and not enough material has been published to permit their correct evaluation.

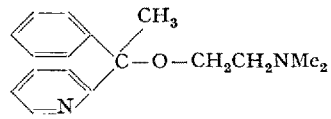
Combined medications are represented by Hydryllin (Searle), which is a chemically stable mixture of Benadryl-base with aminophylline[7]—and by Antistine/



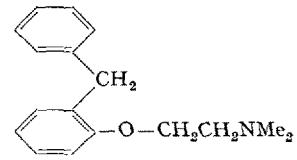
NH-188, Neohetramine
(NEPERA) marketed by WYETH
(XVII)



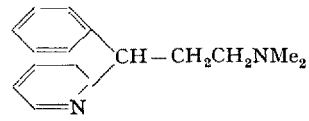
Pyrrolazote
(UPJOHN)
(XVIII)



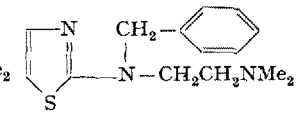
Decapryn (MERRELL)
(XIX)



C-5581-H (BRISTOL)
(XX)



Trimeton (SCHERING)
(XXI)



U.S. Pat. 2440703
(WHITE Laboratory)
(XXII)

Privine—a mixture marketed by CIBA and claimed to be useful for topical application (in the eye and against insect bites). Evidence was found by KOEPF and coworkers for a synergistic effect between PBZ and ephedrine[1] and STAVRAKY reported that it is possible to potentiate the activity of antihistaminics by simultaneous administration of ferrous sulfate[2]. This is understandable in view of TRETHEWIE's previous observation that the mortality of phosgene-poisoned animals could be reduced by administration of ferrous sulfate and ascorbic acid[3].

In the future we may well expect a number of mixtures made to enhance f. i. the weak antiasthma effect of antihistaminic substances, or to strengthen capillary resistance.

In this connection we should perhaps mention a few substances which do not have antihistaminic, but which may have some anti-anaphylactic activity:— f. i. rutin which was shown by WILSON *et al.*[4] to have protective effect against anaphylactic shock but only slight protective activity against histamine shock when given 10–30 minutes before the shocking dose. RAIMAN *et al.*[5] confirmed essentially WILSON's result and came to the conclusion that rutin might prevent liberation of endogenous histamine. (Quite recently, however[6], these and other reports on the physiological

[1] B. N. HALPERN and R. DUCROT, C. r. Soc. biol. *140*, 361 (1946).
[2] B. N. HALPERN and J. MARTIN, C. r. Soc. biol. *140*, 830 (1946).
[3] J. SIGWALD, D. BOVET, and G. DUMONT, Rev. Neurol. France *78*, 581 (1946). – J. SIGWALD, A. GROSSIORD, and P. DUREL, Rev. Neurol. *79*, 683 (1947). – J. SIGWALD, Rev. Neurol. *79*, 776 (1947).
[4] H. GILMAN and D. A. SHIRLEY, J. Amer. Chem. Soc. *66*, 888 (1944).
[5] J. J. GORDON, Nature *162*, 146 (1948).
[6] D. L. COOK, W. E. HAMBOURGER, and M. M. WARBURG, Feder. Proc. *7*, 212 (1948). – H. B. FREESE, W. E. HAMBOURGER, and P. M. MICHIELS, Feder. Proc. *7*, 219 (1948).
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[1] G. C. KOEPF, C. E. ARBESMAN, and A. LENZNER, Feder. Proc. *5*, 56 (1946).
[2] G. W. STAVRAKY, Feder. Proc. *7*, 257 (1948).
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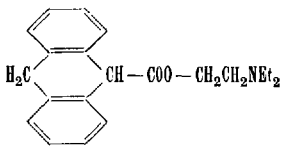
[5] R. J. RAIMAN, E. R. LATER, and H. NECHELES, Science *106*, 368 (1947).
[6] T. A. GEISSMAN, Amer. Chem. Soc. Nat. Med. Chem. Sympos. Ann. Arbor, June 1948. – B. A. LEVITAN, Proc. Exp. Biol. Med. *68*, 569 (1948). – L. W. ROTH and I. M. SHEPPERD, Science *108*, 410 (1948).

activity of rutin have been questioned.) According to LAVOLLAY and coworkers[1] and lately confirmed by ROYLE and PAPAGEORGE[2]. Rutin as well as ascorbic acid inhibit the autoxidation of adrenaline. CLARK and GEISSMAN, however, discovered certain simple hydroxyphenols which were more active in this respect then rutin or citrin[3]. Thorotrast, which is stabilized colloidal thorium dioxide (containing 24–26% ThO_2 by volume), was found by GOTH and HOLMAN[4] to be effective in protecting dogs against anaphylactic but not against histamine shock. FRANK[5] found that anaphylactic but not histamine shock can also be prevented by crotaline in 63% of sensitized guinea-pigs, if given repeatedly before the shocking dose. Since Crotalin liberates histamine, the beneficial effect of crotaline is supposedly due to development of histamine tolerance.

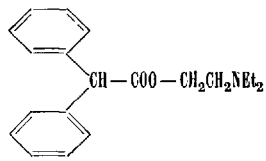
The antiacetylcholine and antihistamine action of cocaine, procaine, and percaine (against histamine aerosol) was studied on guinea-pigs by FROMMEL *et al.*[6] and found to be considerable. The compound 9,10-dihydroanthracene-9-carboxylate (XXIII), (prepared by BURTNER and CUSIC[7]) a musculotropic compound, obtained from the neurotropic Trasentine (XXIV) by ring closure between the two phenyl rings, had been reported in 1945[8] to have antihistamine activity, which, however, was not considered to be specific. HARTMAN[9] recently stated that this compound, which was only 20 times more potent than papaverine against histamine shock, was quite strongly hypnotic and gave 80% benefit in bronchial asthma with optimum dosages of 100–200 mg. Another compound, the use of which is claimed to be as effective and much safer than aminophyllin, is Khellin (XXV).

Its structure has been elucidated by SPAETH and GRUBER[10] to be a dimethoxy-methyl-furanochromone and its structure is shown here next to Amethone[11],



β-diethylaminoethyl-9,10-dihydroanthracene-9-carboxylate

(XXIII)



Trasentine

(XXIV)

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[3] W. C. CLARK and T. A. GEISSMAN, Proc. Exp. Biol. Med. *7*, 1 (1948).

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[6] E. FROMMEL *et al.*, Arch. int. Pharmacodyn. *73*, 355 (1947).

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[9] M. M. HARTMAN, Ann. Allergy, in press (1948).

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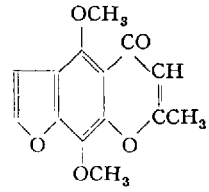
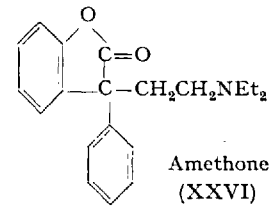
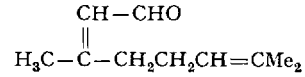


Khellin (XXV)



Amethone (XXVI)



Citral (XXVII)

another furane derivative which is used against bronchial asthma and at the same time has slight antihistamine activity. Khellin has up to now been extracted from the Egyptian plant *Ammi visnaga* L., but recently its complete synthesis has been announced by DAVIS[1], having been accomplished by BAXTER, RAMAGE, and TIMSON[2]. According to this report, some of the synthetic analogs of Khellin were even more potent than Khellin itself.

From the Moscow Central Institute of Ophthalmology came news[3] that Citral (XXVII), a fragment of vitamine A, neutralizes the contraction of guinea-pig small intestine, produced by 1 γ of histamine: partially in solution 1:100,000, and completely in solution 1:50,000. ERCOLI[4] of our Laboratories tried Citral *in vivo* on guinea-pigs, but doses as high as 2 cc/kg subcutaneously and 5 cc/kg *per os* did not protect the animals against 2 lethal doses of histamine injected intravenously.

Quite recently a new antihistaminic substance was reported to have been isolated, for the first time, from a plant, *Euphorbia pilulifera*. It was found to be active on the isolated gut test, against histamine intoxication and also against anaphylactic shock. No further details have been published so far[5].

(iii) *Pharmacology.*—In regard to pharmacological work on antihistaminics we should mention first of all the excellent review recently published by LOEW[6]. There it is pointed out that some reactions attributed by MENKIN to Leukotaxine might be actually due to histamine, LOEW mentioned that it would be of great importance to obtain quantitative data relating to the inhibition of histamine and anaphylactic shock. Similarly, KABAT[7] recently stressed the necessity for quantitative immunochemical studies, measuring the amounts of antigen and antibodies required to elicit allergic reactions. (An attempt in this direction has

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[2] R. A. BAXTER, G. A. RAMAGE, and J. A. TIMSON, J. Chem. Soc. Lond., in press.

[3] S. D. BALAKHOVSKII, V. V. BARODATOV, and E. V. BUDNITSKAIA (U.S.S.R.), see: Chem. Abstr. *41*, 5176-g (1947).

[4] N. ERCOLI, unpublished.

[5] L. W. HAZELTON and R. C. HELLERMAN, Amer. Pharmac. Ass. Meetings, San Francisco, 1948.

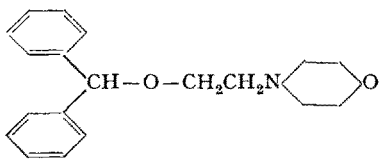
[6] E. R. LOEW, Physiol. Rev. *27*, 542 (1947).

[7] E. A. KABAT, Amer. J. Med. *3*, 535 (1947).

just been published by MARCUS[1] who studied the quantitative aspects of inhibition of anaphylactic shock in guinea-pigs.) This is important since larger doses of antihistaminic substances are required to prevent anaphylactic shock than to prevent histamine shock. LOEW believes that in anaphylactic shock histamine might be released in a more intimate contact with the effector portion of the reacting cells. (But here, experimental evidence is still lacking.) LANDAU and coworkers[2] are inclined to believe that the larger amount of antihistaminics required for antagonizing anaphylactic phenomena can be understood by assuming that simultaneously with histamine, *other* substances are released which, too, are antagonized by antihistaminics.

DALE, however, believes, in accordance with LOEW, that one has probably to differentiate between extrinsic histamine—which is extracellular and carried by the circulation—and intrinsic histamine which is liberated within the sensitized cell[3]. LOEW was able to show with the chloroethylamine derivatives (X, XI, XII) that antihistamine action is not only *independent* of adrenergic stimulation but can even be found in compounds which have epinephrine-blocking activity; on the other hand, epinephrine-blocking agents, such as Dibenamine or Priscol, are known which are devoid of antihistamine activity.

Evaluations of antihistamine activities of different preparations have been published by WINTER[4], GRAHAM[5], PRATT[6], SHERROD[7], KYSER *et al.*[8], LEGER[9], LAST[10], their coworkers and many others. ELLIS[11] and GRUHZIT[12] studied different Benadryl analogs, and the latter author reported that the morpholine analog of Benadryl (Linadryl) (XXVIII) was less active and *half* as toxic as Benadryl.



Linadryl (Parke Davis)
(XXVIII)

A clinical paper on this compound was published recently[13]. In a great number of papers the physiological activity of antihistaminics were studied. While antihistaminic substances do not antagonize histamine-induced gastric secretion, nor the hematological effects of histamine[1] they block or diminish most other secretory effects of histamine[2]. The effect of antihistaminic substances on the capillary permeability is probably the most important criterion for their effectiveness in human therapy[3,4]. Closely connected with the capillary permeability effect is the protection afforded by antihistaminics against the pulmonary edema induced by adrenaline or war gases, such as picryl chloride[5].

TRETHEWIE found that it is possible to reduce the mortality of guinea-pigs due to snake venoms by administration of antihistaminic substances together with heparin[6]. MAYER and KULL reported that antihistaminics are capable of antagonizing the spreading effect of hyaluronidase[7] and WINTER discovered that antihistaminic drugs have a potentiating effect on the sedative action of barbiturates[8]. Protection of rabbits against experimentally induced myocarditis by antihistaminic substances has been reported; the study of this phenomenon might shed new light on the etiology of rheumatic fever[9]. MAYER and BROUSSEAU[10] e.g. found in a study of mouse anaphylaxis that in this animal (which is 1000 times more resistent to histamine than the guinea-pig) antihistaminics act as synergists to histamine in histamine-poisoning. LOEW (l. c.), however, attributed the synergistic effect to the large amounts of acidic solutions injected. ERSPAMER and PAOLINI[11] reported that administration of antihistaminics to rats slowed down the purgative action of castor oil, colocynth, and senna. These authors were inclined to conclude that the purgative action of these agents was due—at least in part—to release of histamine. The negative phototaxis of *Daphnia* against uviol was shown to be probably due to the release of histamine, and is reversible by antihistaminic substances[12].

(iv) *Clinical work and mechanism of antihistamine activity.*—The therapeutic effectiveness of antihist-

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[2] S. W. LANDAU, H. J. L. MARRIOTT, and L. N. GAY, Bull. Johns Hopkin's Hosp. *83*, 343 (1948).
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[5] J. D. P. GRAHAM, J. Pharmacol. *91*, 103 (1947).
[6] H. J. PRATT and R. BEUTNER, Feder. Proc. *6*, 363 (1947).
[7] T. R. SHERROD, E. R. LOEW, and H. F. SCHLOEMER, J. Pharmacol. *89*, 247 (1947).
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[10] M. R. LAST and E. R. LOEW, J. Pharmacol. *89*, 81 (1947).
[11] F. W. ELLIS, J. Pharmacol. *89*, 214 (1947).
[12] O. M. GRUHZIT and R. A. FISKEN, J. Pharmacol. *89*, 227 (1947).
[13] T. H. MCGAVACK *et al.*, J. Allergy *19*, 141 (1948).

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[4] DELLA SANTA, *et al.* Rev. méd. Suisse rom. *67*, 716 (1947). – B. N. HALPERN and J. P. LAUBSCHER, Sem. hôp. Paris *24*, 667 (1948). – B. N. HALPERN and J. HAMBURGER, Canad. M. A. J. *59*, 322 (1948).
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[6] E. R. TRETHEWIE and A. J. DAY, Austral. J. Exp. Biol. Med. Sci. *26*, 153 (1948).
[7] R. L. MAYER and F. C. KULL, Proc. Exp. Biol. Med. *66*, 392 (1947).
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[9] F. A. KYSER and J. C. MCCARTER, Proc. Inst. Med. Chicago, March 16, 396 (1947).
[10] R. L. MAYER and D. BROUSSEAU, Proc. *63*, 187 (1947).
[11] V. ERSPAMER and A. PAOLINI, Exper. *2*, 455 (1946).
[12] O. POUPA, Nature *161*, 235 (1948).

aminic substances in allergic manifestations, such as urticaria, hay-fever, angioneurotic edema, and numerous others, has been very widely studied, and enumeration of even a few of the clinical reports would lead us too far. Instead, we shall mention here a few of the lesser known papers which are of particular interest, because the successful administration of antihistaminics in some of these cases was unexpected and could not have been anticipated on the basis of theoretical considerations or even animal experimentation.

The effectiveness of the phenothiazine derivatives in Parkinson disease has been mentioned before. Benadryl too, gave relief in Parkinson, while PBZ did not[1]. Benefit was obtained by using antihistaminic substances in the treatment of glomerulonephritis[2], gout[3], lepra[4], chickenpox[5], angina pectoris[6], and irradiation sickness[7].

Antihistaminics have been used successfully to treat skin manifestations caused by sulfonamides or mold products, such as penicillin[8] or antirabic vaccine[9]. They prevented side-effects due to curare[10] and adrenaline[11], and their use has been suggested to break any adrenaline refractoriness existing in status asthmaticus[12]. Antihistaminics offset sensitiveness to liver and insulin[13], and side-effects due to blood transfusions[14].

They were effectively used for the rapid increase in antibody production[15], and to promote wound-healing[16].

They relieved pain in amputees and different war casualties[17] and were found useful adjuncts in the control of the morphine withdrawal-syndrome[18].

Antihistaminics have finally also found application in veterinary medicine, and were useful in the treatment of laminitis[19] and of alveolar emphysema of horses[20].

[1] J. BUDNITZ, New England J. Med. *238*, 874 (1948).
[2] F. REUBI, Helv. med. acta *12*, 547 (1945).
[3] P. L. VIOLLE, Presse méd. *55*, 882 (1947).
[4] L. A. BOX, Hawaii Med. J. *7*, 303 (1948).
[5] H. GROSS, Schweiz. med. Wschr. *78*, 159 (1948).
[6] J. MCEACHERN, Canad. Med. Ass. J. *58*, 503 (1948).
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[9] A. SLIPYAN, Ann. Allergy *6*, 428 (1948).
[10] D. GROB, J. L. LILIENTHAL, and A. M. HARVEY, Bull. Johns Hopkin's Hosp. *80*, 299 (1947).
[11] H. STAUB, Schweiz. med. Wschr. *76*, 818 (1946).
[12] F. F. YONKMAN, N. Y. Acad. Sci. Meetings, May 14 (1948).
[13] E. BARTELHEIMER and T. AFENDULIS, Z. exp. Med. *104*, 31 (1938). – C. F. GASTINEAU and M. D. LEAVITT, Proc. Mayo Clin. *21*, 316 (1946). – R. B. HUNTER and D. M. DUNLOP, Brit. Med. J. 547 (1947).
[14] L. S. BLUMENTHAL and M. H. ROSENBERG, J. Amer. Med. Ass. *135*, 20 (1947).
[15] R. MEIER and K. BUCHER, Exper. *2*, 140 (1946). – A. LEYA, Rev. thérap. *3*, 1 (1946).
[16] M. J. DRIESSENS and Y. YEUDEVILLE, Lille Chirurg. *3*, 92 (1948).
[17] M. WAHL, Thérapie, Paris *2*, 17 (1947).
[18] P. KELLS, South. Med. J. *41*, 134 (1948).
[19] W. F. KOCHAN, Veter. Rec. Lond. *60*, 257 (1948).
[20] N. J. OBEL and C. G. SCHMITERLÖW, Acta pharmacol. toxicol. *4*, 71 (1947).

This list which could be extended almost *ad libitum*, will suffice to show that antihistaminic substances have invaded the most diversified fields of clinical medicine.

One of the outstanding characteristics of antihistaminic drugs is that they seem to have usually insignificant physiological effects beside their specific antihistamine activity. They are not particularly toxic in therapeutic doses, they are not habit-forming and do not give rise to addiction. Side-effects are frequent, but usually of minor importance. The nature, occurrence, and prevention of the side-effects have been the subject of more then extensive studies. (Considering the time and the patience spent by many clinicians in assembling huge statistics on rather insignificant side-effects, one is tempted to hope that at least the same amount of time, energy, and money would be spent—to greater avail—for the study of some fundamental problems of which so many are still in the dark.)

Let us finally report on one French publication which has been printed already in 1945 but for some reason has not been properly evaluated in the literature which was to follow.

It is the thesis by PELLERAT[1] in which he described histamine and antihistamine determinations in the blood of patients treated with antihistaminics. The technique has been elaborated by WALTHERT[2] and consists in determining the minimum quantity of the solution in question capable of releasing the histamine spasm of an isolated guinea-pig gut (first having determined the amount antihistamine necessary to produce the same effect). PELLERAT found that after ingestion or injection of Antergan or Neoantergan the blood-histamine level was increased in both the total blood *and* in the blood plasma.

These histamine determinations were followed up for some time in the same patient and so it was found that f. i. before treatment with Antergan there were 90 γ histamine in total blood and 30 γ in the plasma (this was an urticaria case!). One day *after* adminis-

Table II

(from PELLERAT, *Thesis*, l. c., p. 48)

Before R. P. 2339			After	
			2 hours	24 hours
Pel	Total blood 65 γ 0·20 gram *per os*	Total blood	180 γ	115 γ
Rau	Urticaria	Total blood	90 γ	
	0·5 gram 1 day	Plasma	30 γ	
	0·5 gram 5 days	Total blood	335 γ	
		Plasma	154 γ	
	0·6 gram 3 days	Total blood	366 γ	
		Plasma	162 γ	

[1] J. PELLERAT, *Thesis* (Lyon, 1945) and Congrès méd. français, Paris, Oct. 1947.
[2] F. WALTHERT, C. r. Soc. biol. *138*, 437 (1944); see also: PELLERAT, *Thesis* (Lyon, 1945), pp. 46 and 62.

Table III
(from PELLERAT, *Thesis*, l. c., p. 49)

Before R. P. 2339		After 2 hours	After 24 hours
Mich Total blood 35 γ	Total blood	500 γ	280 γ
Plasma 6 γ	Plasma	190 γ	62 γ

Table IV
Histaminemic concentrations after injection of 0·1 gram of R.P.2786 given intramuscularly (from PELLERAT, *Thesis*, l. c., p. 51)

Before R. P. 2786		After 2 hours	After 24 hours
Rui Total blood 56 γ	Total blood	1050 γ	450 γ
Plasma 5 γ	Plasma	350 γ	120 γ

tration of 0·5 g Antergan, there were 335 γ in total blood and 154 γ in the blood plasma. The same increase of blood histamine was observed after injection of Antergan, Neoantergan, and R. P. 2325 intramuscularly given.

Finally, PELLERAT determined the amounts of *antihistamine* in the blood, and again:— most of it was concentrated in the blood plasma!

Table V
(from PELLERAT, *Thesis*, l. c., p. 67)

		After 2 hours	After 24 hours
Mich injection of 0·1 g R.P.2339	Total blood	725 γ	500 γ
	Plasma	500 γ	400 γ
Bui injection of 0·1 g R.P.2786	Total blood	280 γ	150 γ
	Plasma	160 γ	95 γ
Pel injection of 0·1 g R.P.2325	Total blood	1800 γ	1200 γ
	Plasma	1350 γ	900 γ

After injection of 0·1 g Antergan he found 725 γ in total blood, 500 γ in the plasma. In the same subject 24 hours later, 500 γ in total blood and 400 γ in the plasma.

PELLERAT came to the conclusion—and this is in accord with the generally accepted view—that tissue-histamine is displaced by antihistaminic substances from the cell receptors, and is liberated into the blood, where it is found circulating in the plasma and gradually adsorbed to, and thereby detoxified by the cellular elements of the blood. Part of the plasma-histamine will be neutralized by antihistamine, which is *also* circulating in the plasma, provided it is there in sufficiently high concentration.

PELLERAT has tried to explain the so-called "histaminoide accidents" which sometimes occur after antihistamine treatment (and also the asthma of his guinea-pigs after chlorethylanesthesia, mentioned in the beginning), in the following way:— It is well known that different tissues of one and the same organism are sensitive to histamine to a different degree. One could now imagine f. i. that the *skin* of a patient treated for urticaria with an antihistaminic drug would be more sensitive to the antihistamine than it is to histamine. The cell receptors of the skin will then accept the antihistamine, and the free blood plasma histamine will, now increased, reach the pulmonary tissue, which might be *more* sensitive to histamine than to the antihistamine which is also present in the blood plasma. If such is the case, and *not enough* antihistamine is circulating in the blood plasma of such a patient, we might actually *produce* asthma, or other symptoms which can be classified as "histaminoide accidents".

Since it also has been shown that the more powerful an antihistaminic compound is, the more it is retained in the tissue, and the less circulating in the blood (PELLERAT, l.c., p.65), we may well expect from the advent of new and more powerful antihistaminics an increase of such "histaminoide accidents".

Several cases of severe side-effects have been reported after antihistamine treatment[1], and in order to understand and possibly to avoid them, it will be advisable to use the new methods which permit rapid blood plasma histamine and antihistamine determinations in series of samples. Quantitative determinations of sulfonamides and other drugs in the blood have been done routinely for years, and it might now be important to extend the clinical hematological work with antihistaminics in certain selected cases to *blood chemistry*, and not to restrict it to the examination of possible pathological changes in the number of cellular elements. Even if we believe that the actual mechanism of antihistamine action is much more complicated and most likely quite different from the one pictured by PELLERAT, his experiments if repeated on a larger scale and with improved methods, may help to a better understanding of the actual mechanism.

Zusammenfassung

Die vorliegende Arbeit ist ein Versuch, den Fortschritt der Histamin- und Antihistaminforschung während der letzten zwei Jahre zu beschreiben. Da die Literatur in GUGGENHEIMS Buch, *Die biogenen Amine*, bis 1940 berücksichtigt ist, erschien es notwendig, die Lücke von 1940–46 mit einer Übersicht zu schließen, welche die in dieser Zeit entstandenen Arbeiten umfaßt.

Die *Histamin*forschung der letzten Jahre hat sich nicht so sehr auf fundamentale Probleme konzentriert als vielmehr auf die Vervollkommnung der Technik der Histaminbestimmung im Gewebe und Blut unter normalen und pathologischen Bedingungen. Arbeiten, welche die physiologischen Wirkungen und den Mechanismus der Freisetzung des Histamins betreffen, wurden besonders eingehend behandelt.

Die *Antihistamin*forschung der letzten Jahre hatte nicht nur die Entdeckung mehrerer neuer Produkte zur Folge, sondern eine weitgehende Vervollkommnung der

[1] W. H. BLANTON and M. E. B. OWENS, J. Amer. Med. Ass. *134*, 754 (1947). – F. G. CRANDALL, in: Forman's letters Int. Corresp. Soc. of Allergists, 11th ser., p. 2/3 (1947). – E. C. KERN, J. Med. Soc. New Jersey 347 (1947).

Methoden zur vergleichenden Bestimmung. Da Antihistaminika nicht sehr wirksam gegen Asthma sind, wurden hier auch solche (*nicht* antihistaminische) Drogen behandelt, welche Antiasthma-Aktivität besitzen und möglicherweise als Zusatzdrogen für Antihistaminika in Frage kommen.

Einige pharmakologische und klinische Resultate wurden erwähnt, mit spezieller Berücksichtigung der Histamin- und Antihistaminspiegel-Bestimmungen im menschlichen Blut sowie PELLERATS Theorie der «accidents histaminoïdes».

Die Bibliographie umfaßt 174 Arbeiten.

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Observation sur la diffraction de la lumière par les tissus

L'étude de la diffraction de la lumière par des tissus du genre de la mousseline, tulle et surtout soie à bluter, fournit de jolies expériences, propres à illustrer la théorie de la formation des spectres de Fraunhofer.

La diffraction est produite par les trous du tissu qui sont disposés aux nœuds d'un réseau à mailles rectangulaires de dimensions $a\,b$ (fig. 1). Les rayons parallèles issus d'une source monochromatique ponctuelle

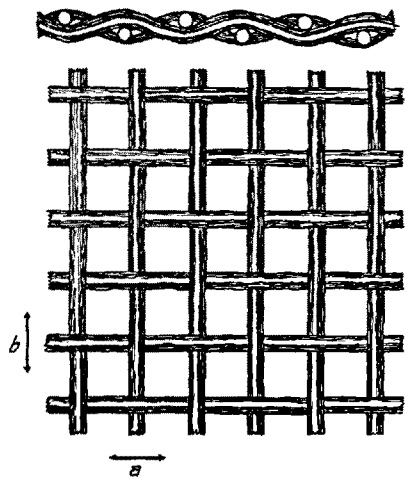

Fig. 1.

donnent dans le plan focal d'une lentille à long foyer placée derrière la toile, un système de points lumineux (fig. 2) distribués aux sommets d'un réseau dont la maille a les dimensions

$$A = \frac{\lambda f}{a}, \quad B = \frac{\lambda f}{b}$$

(λ = longueur d'onde, f = distance focale de la lentille). L'intensité d'un point lumineux de coordonnées hA, kB (h et k = nombres entiers) peut être calculée par les formules classiques en tenant compte des dimensions et de la forme des trous. Si l'on incline le plan du réseau par rapport à l'axe optique du système, la figure de diffraction change. En inclinant d'un angle α (fig. 3) le réseau, par rotation autour d'une de ses directions principales (p. ex. b), les points lumineux du plan focal sont placés pratiquement aux nœuds d'un réseau de maille

$$A = \frac{\lambda f}{a \cos \alpha}, \quad B = \frac{\lambda f}{b},$$

c'est-à-dire que les rangées verticales s'espacent d'autant plus que l'angle α devient plus grand. Quand on fait croître l'angle α, on est surpris de constater, à partir d'une certaine valeur de α, *l'apparition de nouveaux points lumineux placés sur des rangées intermédiaires* correspondant à des valeurs

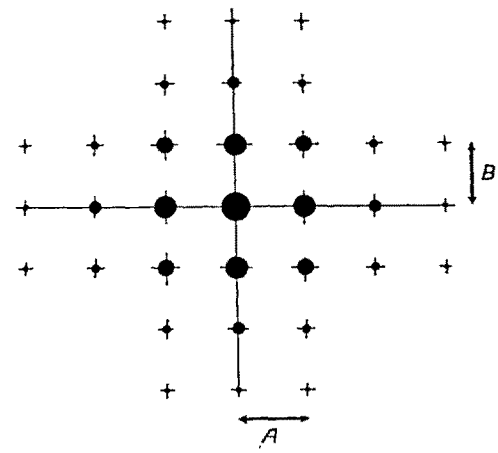

Fig. 2.

$$h = \frac{1}{2}, \; h = \frac{3}{2} \ldots, \; k = \frac{1}{2}, \; k = \frac{3}{2}, \text{ etc.}$$

On peut expliquer l'apparition de ces nouveaux spectres (fig. 4) en considérant la projection du réseau de la toile sur un plan perpendiculaire à l'axe du système. En effet, la figure de diffraction d'un réseau incliné est en première approximation, la même que celle qu'on obtiendrait avec un réseau ayant la forme de cette projection. La projection, à cause de l'entrelacement des fils du tissu, ne présente plus un système uniforme de trous, mais un ensemble de *trous différemment orientés*, T et T' (fig. 3). La figure suppose un réseau à maille centrée de dimensions $a^* = 2\,a \cos \alpha$, $b^* = 2\,b$.

Si nous prenons comme origine le centre d'un trou T,