the value of pA_2 by simply measuring the ratio of slopes (β) of the lines of the reciprocals of (responses-doses) and deducing, from the above equation, by the following formula:

$$-pA_2 = \log(I) - \log(\beta - 1)$$

By using this method we have calculated the pA_2 for the pair benadryl-histamine, and the values obtained agree with those of previous investigators, using more direct methods of determination.

Since such deductions depend upon the validity of the main arguments involved in Clark's and Gaddum's equations, their agreement with the experimental findings have, as a consequence, the rejection of Stephenson's hypothesis and a confirmation of the postulate invoking linearity between the number of receptors occupied by the drug and the effect as measured upon the smoked drum. Also the idea that a maximum contraction can be produced by a small number of receptors occupied by the drug should be rejected. There is no reason to suppose that the interrelationship between agonist and antagonist, when competition is established, will not follow Clark's and Gaddum's equations.

METABOLITE ANTAGONISMS IN BACTERIA

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Perhaps by historical accident this symposium on drug antagonism has been based largely on experiments on vertebrate tissues. In order to bring antagonisms in bacteria into the same picture, I would like to describe recent work (35) on the relations of growth inhibitors to purines in a strain of *Escherichia coli* (NCTC 8242) that requires purine. In this strain, the curve of growth plotted against log concentration of adenine follows a sigmoid course, but after reaching a peak turns downwards because excess adenine inhibits. The general antibacterial compound Dequadin (decamethylene-bis-4-aminoquinaldinium) (18) vertically depresses this curve, except where lack of adenine limits growth. On the other hand, the antipurine 6-mercaptopurine (39) shifts the log adenine-growth curve along the horizontal axis of the graph without changing its height or its eventual downward turn, so that the ascending portions of curves obtained in the presence and absence of 6-mercaptopurine run roughly parallel. If the extent of the horizontal shift, which characterizes competitive inhibition, is plotted against the negative log molar concentration of 6-mercaptopurine, a straight line is obtained. From this line the pA values of Schild (131) may conveniently be read off. For example, the pA_{10} of 6-mercaptopurine against adenine for *Esch. coli* (8242) is 3.12. It thus seems that in bacteria metabolite antagonisms may be analysed on similar lines to those described for vertebrate tissues.

REFERENCES

1. AGARWAL, S. L. AND HARVEY, S. C.: Mechanism of long duration of action of dibenzyline. J. Pharmacol. 117: 106–111, 1956.
2. AMBACHE, N.: The use and limitations of atropine for pharmacological studies on autonomic effectors. Pharmacol. Rev. 7: 467–494, 1955.
3. ARIËNS, E. J.: Het Verband tussen de Chemische Structuur en de Pharmacodynamie van Sympatho-mimetische Phenylalkyl-amines. Deel II. Thesis, Utrecht 1950.
4. ARIËNS, E. J.: Affinity and intrinsic activity in the theory of competitive inhibition. Part I. Problems and theory. Arch. int. Pharmacodyn. 99: 32–50, 1954.
5. ARIËNS, E. J. AND DE GROOT, W. M.: Affinity and intrinsic activity in the theory of competitive inhibition. Part III. Homologous decamethonium-derivatives and succinyl-choline-esters. Arch. int. Pharmacodyn. 99: 193–205, 1954.
6. ARIËNS, E. J. AND SIMONIS, A. M.: Affinity and intrinsic activity in the theory of competitive inhibition. Part II. Experiments with para-aminobenzoic acid derivatives. Arch. int. Pharmacodyn. 99: 175–188, 1954.
7. ARIËNS, E. J. AND SIMONIS, A. M.: The biosynthesis of folic-acid homologues from 2-amino-5-carboxy-pyridine and other para-amino-benzoic acid substitutes by E. coli. Schweiz. Z. allg. Path. 18: 71–81, 1955.
8. ARIËNS, E. J., SIMONIS, A. M. AND DE GROOT, W. M.: Affinity and intrinsic activity in the theory of competitive and non-competitive inhibition and an analysis of some forms of dualism in action. Arch. int. Pharmacodyn. 100: 298–322, 1955.
9. ARIËNS, E. J. AND VAN ROSSUM, J. M.: pD_x, pA_x and pD'_x values in the analysis of pharmacodynamics. Arch. int. Pharmacodyn. 109: 468–492, 1957.
9a. ARIËNS, E. J. AND VAN ROSSUM, J. M.: Affinity, intrinsic activity and the all or none response. Arch. int. Pharmacodyn., in press.
10. ARIËNS, E. J., VAN ROSSUM, J. M. AND SIMONIS, A. M.: A theoretical basis of molecular pharmacology, Part I: Interactions of one or two compounds with one receptor system. Arzneim.-Forsch. 6: 282–293, 1956.
11. ARIËNS, E. J., VAN ROSSUM, J. M. AND SIMONIS, A. M.: A theoretical basis of molecular pharmacology. Part II. Interactions of one or two compounds with two interdependent receptor systems. Arzneim.-Forsch. 6: 611–621, 1956.
12. ARIËNS, E. J., VAN ROSSUM, J. M. AND SIMONIS, A. M.: A theoretical basis of molecular pharmacology. Part III. Interactions of one or two compounds with two independent receptor systems. Arzneim.-Forsch. 6: 737–746, 1956.
13. ARUNLAKSHANA, O. AND SCHILD, H. O. Brit. J. Pharmacol. 1957, in press.
14. AUGUSTINSSON, K.-B.: Substrate concentration and specificity of choline-ester-splitting enzymes. Arch. Biochem. 23: 111–127, 1949.
15. AUGUSTINSSON, K.-B.: The enzymic hydrolysis of organophosphorus compounds. Biochim. biophys. acta 13: 303–304, 1954.
16. AUGUSTINSSON, K.-B. AND NACHMANSOHN, D.: Studies on cholinesterase. VI. Kinetics of the inhibition of acetylcholine esterase. J. biol. Chem. 179: 543–559, 1949.
17. AXELROD, J., ARONOW, L. AND BRODIE, B. B.: The physiological disposition and biotransformation of dibenamine and a method for its estimation in biological tissues. J. Pharmacol. 106: 166–179, 1952.
18. BABBS, M., COLLIER, H. O. J., AUSTIN, W. C., POTTER, M. D. AND TAYLOR, E. P.: Salts of decamethylene-bis-4-aminoquinaldinium ("Dequadin"), a new antimicrobial agent. J. Pharm., Lond. 8: 110–119, 1956.
19. BERALDO, W. T. AND ROCHA E SILVA, M.: Biological assay of antihistaminics, atropine and antispasmodics upon the guinea pig gut. J. Pharmacol. 97: 388–398, 1949.
20. BERKSON, J.: Application of the logistic function to bio-assay. J. Amer. statist. Ass. 39: 357–365, 1944.
21. BIGGER, J. W.: Synergism and antagonism as displayed by certain antibacterial substances. Lancet 2: 46–50, 1950.
22. BRODIE, B. B., ARONOW, L. AND AXELROD, J.: The fate of dibenzyline in the body and the role of fat in its duration of action. J. Pharmacol. 111: 21–29, 1954.
22a. BRÜCKE, F.: Dicholinesters of α,ω-dicarboxylic acids and related substances. Pharmacol. Rev. 8: 265–335, 1956.
23. BRÜCKE, F., KOBINGER, W. AND KRAUPP, O.: Über den Antagonismus von Kongorot und anderen Substanzen gegenüber quaternären Ammoniumbasen. Arch. exp. Path. Pharmak. 224: 123–136, 1955.
24. BUCHER, K.: Zum Wirkungsmechanismus der Antihistaminica. Arch. int. Pharmacodyn. 79: 336–342, 1949.
25. CAVANAUGH, D. J. AND HEARON, J. L.: The kinetics of acetylcholine action of skeletal muscle. Arch. int. Pharmacodyn. 100: 68–79, 1954.
26. CHAPMAN, N. B., JAMES, J. W., GRAHAM, J. D. P. AND LEWIS, G. P.: Chemical reactivity and pharmacological activity among 2-haloethylamine derivatives with a naphthylmethyl group. Chem. & Ind. (Rev.) pp. 805–807, 1952.
27. CHEN, G. AND RUSSELL, D.: A quantitative study of blood pressure response to cardiovascular drugs and their antagonists. J. Pharmacol. 99: 401–408, 1950.
28. CHEN, G. AND RUSSELL, D.: The antagonistic action of adrenergic blocking agents on the vasopressor effect of epinephrine. Arch. int. Pharmacodyn. 84: 176–180, 1950.
29. CLARK, A. J.: The antagonism of acetylcholine by atropine. J. Physiol. 61: 547–556, 1926.
30. CLARK, A. J.: General pharmacology. In: Heffter's Handbuch der experimentellen Pharmakologie, ed. by W. Heubner and T. Schüller, Erg. vol. 4. Springer, Berlin 1937.
31. CLARK, A. J.: The mode of action of drugs on cells. Williams & Wilkins, Baltimore 1937.
32. CLARK, A. J. AND RAVENTOS, J.: The antagonism of acetylcholine and of quaternary ammonium salts. Quart. J. exp. Physiol. 26: 375–392, 1937.
33. COHEN, J. A. AND POSTHUMUS, C. H.: The mechanism of action of anticholine-esterases. Acta physiol. pharm. néerl. 4: 17–36, 1955.

34. COHEN, J. A., WARRINGA, M. G. P. J. AND BOVENS, B. R.: Protection of true cholinesterase against diisopropyl fluorophosphonate by butyrylcholine. Biochim. biophys. acta 6: 469–476, 1951.
35. COLLIER, H. O. J. AND HUSKINSON, P. L.: The effects of potential antipurines on a purine-requiring strain of *Escherichia coli*. In: CIBA Found. Symp. on Chemistry and Biology of Purines, p. 146. Churchill, London 1957.
36. DAGLEY, S., FREEMAN, L. O. AND TATTON, O'G.: The kinetics of growth of *Bact. lactis aerogenes* in the presence of phenol, alcohols, ketones and acetates. Biochem. J. 43: iv, 1948.
37. DE HAAN, P. J.: Het werkingsmechanisme van sulfanilamide. Thesis, Utrecht 1950.
38. DODGSON, K. S., SPENCER, B. AND WILLIAMS, K.: Examples of anti-competitive inhibition. Nature, Lond. 177: 432–433, 1956.
39. ELION, G. B., BURGI, E. AND HITCHINGS, G. H.: Studies on condensed pyrimidine systems. IX. The synthesis of some 6-substituted purines. J. Amer. chem. Soc. 74: 411–414, 1952.
39a. EVANS, D. H. L. AND SCHILD, H. O.: Unpublished.
40. FELLER, W.: On the logistic law of growth and its empirical verifications in biology. Acta biotheor., Leiden 5: 51–65, 1940.
41. FERGUSON, F. C., Jr. AND WESCOE, W. C.: The pharmacology of N,N-dimethyl 2-chloro-2-phenylethylamine. J. Pharmacol. 100: 100–114, 1950.
42. FERGUSON, J.: The use of chemical potentials as indices of toxicity. Proc. Roy. Soc., s.B. 127: 387–404, 1939.
43. FILDES, P.: The mechanism of the anti bacterial action of mercury. Brit. J. exp. Path. 21: 67–73, 1940.
44. FLECKENSTEIN, A.: A quantitative study of antagonists of adrenaline on the vessels of the rabbit's ear. Brit. J. Pharmacol. 7: 553–562, 1952.
45. FRASER, T. R.: An experimental research on the antagonism between the actions of physostigma and atropia. Proc. roy. Soc. Edinb. pp. 506–511, 1870–71.
46. FRASER, T. R.: The antagonism between the actions of active substances. Brit. med. J. pp. 457–459 and 485–487, 1872.
47. FREI, W.: Versuche über Kombination von Desinfektionsmitteln. Z. Hyg. InfektKr. 75: 433–496, 1913.
48. FURCHGOTT, R. F.: Dibenamine blockade in strips of rabbit aorta and its use in differentiating receptors. J. Pharmacol. 111: 265–284, 1954.
49. FURCHGOTT, R. F.: The pharmacology of vascular smooth muscle. Pharmacol. Rev. 7: 183–265, 1955.
50. GADDUM, J. H.: The action of adrenaline and ergotamine on the uterus of the rabbit. J. Physiol. 61: 141–150, 1926.
51. GADDUM, J. H.: The quantitative effects of antagonistic drugs. J. Physiol. 89: 7P-9P, 1937.
52. GADDUM, J. H.: Discussion on the chemical and physical bases of pharmacological action. Proc. roy. Soc., s. B 121: 598–601, 1937.
53. GADDUM, J. H.: Symposium on chemical constitution and pharmacological action. Trans. Faraday Soc. 39: 323–121: 332, 1943.
54. GADDUM, J. H.: Pharmacology. Oxford University Press, London 1944, 2nd ed.
55. GADDUM, J. H., HAMEED, K. A., HATHWAY, D. E. AND STEPHENS, F. F.: Quantitative studies of antagonists for 5-hydroxytryptamine. Quart. J. exp. Physiol. 40: 49–74, 1955.
56. GEISSMAN, T. A., HOCHMAN, H. AND FUKUTO, R. T.: β-Dialkylaminoethyl esters with adrenergic blocking activity. J. Amer. chem. Soc. 74: 3313–3318, 1952.
57. GINZEL, K. H., KLUPP, H. AND WERNER, G.: Die Wirkung einiger aliphatischer α-ω-Bis-quaternärer Ammonium-Verbindungen auf die Skelettmuskulatur. Arch. exp. Path. Pharmak. 213: 453–466, 1951.
58. GINZEL, K. H., KLUPP, H. AND WERNER, G.: Methoden zur biologischen Wertbestimmung und Charakterisierung von neuromuskulär lähmenden Stoffen. Sci. pharm. 19: 821–835, 1951.
59. GOLDSTEIN, A.: The mechanism of enzyme-inhibitor-substrate reactions. Illustrated by the cholinesterase-physostigmine-acetylcholine system. J. gen. Physiol. 27: 529–580, 1944.
60. GOLDSTEIN, A.: Interactions of drugs and plasma proteins. Pharmacol. Rev. 1: 102–165, 1949.
61. GOODMAN, L. S. AND GILMAN, A.: The pharmacological basis of therapeutics. Macmillan, New York 1955, 2nd ed.
62. GRAHAM, J. D. P. AND LEWIS, G. P.: The antihistamine and antiadrenaline properties of a series of N-napthylmethyl-2-haloethylamine derivatives. Brit. J. Pharmacol. 8: 54–61, 1953.
63. GRAHAM, J. D. P. AND LEWIS, G. P.: The role of the cyclic ethyleneiminium ion in the pharmacological activity of the 2-haloethylamines. Brit. J. Pharmacol. 9: 68–75, 1954.
64. HALDANE, J. B. S.: Enzymes. Longmans, Green and Co., London 1930.
65. HALDANE, J. B. S. AND STERN, K. G.: Allgemeine Chemie der Enzyme. Steinkopff, Dresden 1932.
66. HARROW, B. AND MAZUR, A.: Textbook of biochemistry. W. B. Saunders, London 1954, 6th ed.
67. HARVEY, S. C. AND NICKERSON, M.: The chemical transformations of dibenamine and dibenzyline and biological activity. J. Pharmacol. 109: 328–339, 1953.
68. HARVEY, S. C. AND NICKERSON, M.: Reactions of dibenamine and some congeners with substances of biological interest in relation to the mechanism of adrenergic blockade. J. Pharmacol. 112: 274–290, 1954.
69. HITCHCOCK, D. I.: The formal identity of Langmuir's adsorption equation with the law of mass action. J. Amer. chem. Soc. 48: 2870, 1926.
70. HOBBIGER, F.: Effect of nicotinhydroxamic acid methiodide on human plasma cholinesterase inhibited by organophosphates containing a dialkylphosphate group. Brit. J. Pharmacol. 10: 356–362, 1955.
71. HOFSTEE, B. H. J.: On the mechanism of inhibition of xanthine oxidase by the substrate xanthine. J. biol. Chem. 216: 235–245, 1955.
72. HOROWITZ, R. M. AND NICKERSON, M.: Distribution and persistence of dibenzyline-C^{14} in the body. Fed. Proc. 13: 367, 1954.
73. HUNT, C. C.: The adrenergic blocking effect of certain β-choloroethyl amines. J. Pharmacol. 95: 177–184, 1949.
74. ING, H. R.: Chemical constitution and pharmacological action. Trans. Faraday Soc. 39: 372–383, 1943.

75. JOHNSON, F. H., EYRING, H. AND POLISSAR, M. J.: The kinetic basis of molecular biology. Wiley, New York and Chapman & Hall, London 1954.
76. KAHANE, E. AND LÉVY, J.: Sur quelques nouvelles amines inversant l'action de l'adrénaline. Bull. Soc. Chim. biol., Paris 27: 562–570, 1945.
77. KENSLER, C. J.: The antagonism of curare by congo red and related compounds. J. Pharmacol. 95: 28–45, 1949.
78. KERWIN, J. F., HALL, G. C., NICKERSON, M., GUMP, W. S., MCLEAN, R. A., FELLOWS, E. J. AND ULLYOT, G. E. The reported adrenergic blocking action of β-haloethylammonium compounds. Science 113: 315–317, 1951.
79. KIRSCHNER, L. B. AND STONE, W. E.: Action of inhibitors at the myoneural junction. J. gen. Physiol. 34: 821–835, 1951.
80. KOELLE, G. B.: Protection of cholinesterase against irreversible inactivation by diisopropyl fluorophosphate *in vitro*. J. Pharmacol. 88: 232–237, 1946.
81. LÄSER, S.: Untersuchungen über den Antagonismus Aneurin-Acetylcholin am Froschherzen. Int. Z. Vitaminforsch. 20: 94–108, 1948.
82. LANGLEY, J. N.: On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J. Physiol. 33: 374–413, 1905.
83. LANGMUIR, I.: The adsorption of gases on plane surfaces of glass, mica and platinum. J. Amer. chem. Soc. 40: 1361–1403, 1918.
84. LINEWEAVER, H. AND BURK, D.: The determination of enzyme dissociation constants. J. Amer. chem. Soc. 56: 658–666, 1934.
85. LOCKETT, M. F. AND BARTLETT, A. L.: A method for the determination of pA_2 at two minutes. J. Pharm., Lond. 8: 18–26, 1956.
86. LOEWE, S.: Die quantitativen Probleme der Pharmakologie. Ergebn. Physiol. 27: 47–187, 1928.
87. LOEWE, S.: Antidyname Arzneigemische. Festschrift E. BÜRGI. Benno Schwabe, Basel 1932.
88. LOEWE, S.: Coalitive effects of drug combinations. J. Pharmacol. 63: 24, 1938.
89. LOEWE, S.: Duration of drug action. Proc. Soc. exp. Biol., N. Y. 81: 596–598, 1952.
90. LOEWE, S.: The problem of synergism and antagonism of combined drugs. Arzneim.-Forsch. 3: 285–290, 1953.
91. LOEWE, S.: Isobols of dose-effect relations in the combination of pentamethylenetetrazole and phenobarbital. J. Pharmacol. 114: 185–191, 1955.
92. LOEWE, S.: Isobols of dose-effect relations in the combination of nikethamide (Coramine) and phenobarbital. J. Pharmacol. 115: 6–15, 1955.
93. LOEWE, S.: Combined drug effect. Paper presented at Symposium on Drug Synergism, Fed. Meetings, Atlantic City, 1956; to appear in Arzneim.-Forsch.
94. LOEWE, S., ALDOUS, R. A., FOX, S. R., JOHNSON, D. G. AND PERKINS, W.: Isobols of dose-effect relations in the combination of trimethadione and pentylenetetrazole. J. Pharmacol. 113: 475–480, 1955.
95. LOEWE, S. AND MUISCHNEK, H.: Über Kombinationswirkungen I. Hilfsmittel der Fragestellung. Arch. exp. Path. Pharmak. 114: 313–326, 1926.
MAANEN, E. F. VAN see 143.
96. MACKWORTH, J. F. AND WEBB, E. C.: The inhibition of serum cholinesterase by alkyl fluorophosphonates. Biochem. J. 42: 91–95, 1948.
97. MARSHALL, P. B.: Some chemical and physical properties associated with histamine antagonism. Brit. J. Pharmacol. 10: 270–278, 1955.
98. MARTIN, G. J.: Biological antagonism. Blakiston Co., New York 1951.
99. MASON, D. F. J. AND WIEN, R.: The actions of heterocyclic bisquaternary compounds especially of a pyrrollidinium series. Brit. J. Pharmacol. 10: 124–133, 1955.
100. MATSUMOTO, H., MIYAKE, T. AND KANAZAWA, J.: The concentration-action curves of various drugs. Kobe J. med. Sci. 1: 197–209, 1954.
101. MATSUMOTO, H., MIYAKE, T., MISAWA, H., MATSUDA, H. AND KUMOI, T.: The concentration-action curves of various drugs with special reference to the study of the mode of drug antagonism by means of the curve analysis. Kobe J. med. Sci. 2: 347–363, 1955.
102. MATTHES, K.: The action of blood on acetylcholine. J. Physiol. 70: 338–348, 1930.
103. MAZUR, A. AND BODANSKY, O.: The mechanism of *in vitro* and *in vivo* inhibition of cholinesterase activity by diisopropyl fluorophosphate. J. biol. Chem. 163: 261–276, 1946.
104. MCLEAN, F. C., HASTINGS, A. B., EICHELBERGER, L. AND HALL, J. L.: On the ionization of calcium citrate. Proc. Soc. exp. Biol., N. Y. 30: 1136–1137, 1933.
105. MICHAELIS, D. AND MENTEN, M. L.: Die Kinetik der Invertinwirkung. Biochem. Z. 49: 333–370, 1913.
106. MONGAR, J. L. AND SCHILD, H. O.: Inhibition of the anaphylactic reaction. J. Physiol. 135: 301–319, 1957.
107. NACHMANSOHN, D., ROTHENBERG, M. A. AND FELD, E. A.: The *in vitro* reversibility of cholinesterase inhibition by diisopropyl fluorophosphate (DFP). Arch. Biochem. 14: 197–211, 1947.
108. NICKERSON, M.: The pharmacology of adrenergic blockade. Pharmacol. Rev. 1: 27–101, 1949.
109. NICKERSON, M.: Activation of vascular smooth muscle receptors by sympathomimetic amines. Rev. canad. Biol. 14: 275, 1955.
110. NICKERSON, M.: Mechanism of the prolonged adrenergic blocking action of dibenzyline. Fed. Proc. 15: 463, 1956.
111. NICKERSON, M.: Receptor occupancy and tissue response. Nature, Lond. 178: 697–698, 1956.
112. NICKERSON, M.: Unpublished results.
113. NICKERSON, M. AND GOODMAN, L. S.: Pharmacological properties of a new adrenergic blocking agent: N,N-dibenzyl-β-chloroethylamine (dibenamine). J. Pharmacol. 89: 167–185, 1947.
114. NICKERSON, M. AND GOODMAN, L. S.: Pharmacological and physiological aspects of adrenergic blockade, with special reference to dibenamine. Fed. Proc. 7: 397–409, 1948.

115. NICKERSON, M. AND GUMP, W. S.: The chemical basis for adrenergic blocking activity in compounds related to dibenamine. J. Pharmacol. 97: 25–47, 1949.
116. NICKERSON, M. AND HARRIS, F. B.: Antihistaminic properties of the β-haloalkylamine (dibenamine) series of adrenergic blocking agents. Fed. Proc. 8: 321–322, 1949.
117. NICKERSON, M., HENRY, J. W. AND NOMAGUCHI, G. M.: Blockade of responses to epinephrine and norepinephrine by dibenamine congeners. J. Pharmacol. 107: 300–309, 1953.
118. NICKERSON, M. AND NOMAGUCHI, G. M.: Adrenergic blocking action of phenoxyethyl analogues of dibenamine. J. Pharmacol. 101: 379–396, 1951.
119. NYMAN, E.: A sympatholytic (adrenergic blocking) substance (dibenzyl-β-chloroethyl ethyl ammonium bromide) with rapid action and high activity in animal experiments. Nature, Lond. 164: 269–270, 1949.
120. PARROT, J.-L. AND REUSE, J.: Role physiologique et physiopathologique de l'histamine. J. Physiol. Path. gén. 46: 99–221, 1954.
121. PHILIPS, F. S.: Recent contributions to the pharmacology of bis(2-haloethyl) amines and sulfides. Pharmacol. Rev. 2: 281–323, 1950.
122. QUIVY, D., BERTRAND, I. AND GAYET-HALLION, I.: Étude pharmacodynamique de l'action conjointe de diverses substances; antagonisme et synergie. Ann. pharm. franç. 8: 217–225, 1950.
123. RENTZ, A.: Zur Systematik und Nomenklatur der Kombinationswirkungen. Arch. int. Pharmacodyn. 43: 337–361, 1932.
124. RHOADS, C. P.: Antimetabolites and cancer. Amer. Ass. Advanc. Science, Washington 1955.
125. ROCHA E SILVA, M.: The mechanism of recovery of the guinea pig gut from inhibition by atropine and anti-histaminics. Exp. Med. Surg. 8: 346–356, 1950.
126. ROCHA E SILVA, M. AND BERALDO, W. T.: Dynamics of recovery and measure of drug antagonism. Inhibition of smooth muscle by lysolecithin and antihistaminics. J. Pharmacol. 93: 457–469, 1948.
127. Ross, W. C. J.: Aryl-2-haloalkylamines. Part VI. Reactions with certain organic sulfur compounds. J. chem. Soc. pp. 815–818, 1950.
128. ROSSUM, J. M. VAN AND ARIËNS, E. J.: Chemical structure and biological activity of decamethonium derivatives. Acta physiol. pharm. néerl. 5: 261–262, 1956.
129. ROSSUM, J. M. VAN AND ARIËNS, E. J.: From parasympathomimetics to parasympatholytics by homologous substitution. Experientia 8: 161–163, 1957.
130. ROUGHTON, F. J. W., OTIS, A. B. AND LYSTER, R. L. J.: The determination of the individual equilibrium constants of the four intermediate reactions between oxygen and sheep haemoglobin. Proc. roy. Soc., s. B 144: 29–67, 1955.
131. SCHILD, H. O.: pA, a new scale for the measurement of drug antagonism. Brit. J. Pharmacol. 2: 189–206, 1947.
132. SCHILD, H. O.: The use of drug antagonists for the identification and classification of drugs. Brit. J. Pharmacol. 2: 251–258, 1947.
133. SCHILD, H. O.: pA_x and competitive drug antagonism. Brit. J. Pharmacol. 4: 277–280, 1949.
134. SCHILD, H. O.: Non-competitive drug antagonism. J. Physiol. 124: 33P–34P, 1954.
135. SEED, J. C. AND MCKAY, E. A.: Inhibition by piperidinomethyl-3-benzodioxane (933F) of epinephrine vasopressor blockade produced by dibenzyl-β-chlorethylamine. Proc. Soc. exp. Biol., N. Y. 70: 724–726, 1949.
136. SEXTON, W. A.: Chemical constitution and biological activity. Spon, London 1949.
137. SHACKELL, L. F., WAYNE WILLIAMSON, DEITCHMAN, M. M., KATZMAN, G. M. AND KLEINMAN, B. S.: The relation of dosage to effect. J. Pharmacol. 24: 53–65, 1924.
138. SHAW, E. AND WOOLLEY, D. W.: Yohimbine and ergot alkaloids as naturally occurring antimetabolites of serotonin. J. biol. Chem. 203: 979–984, 1953.
139. STEPHENSON, R. P.: Acetylcholine receptors and alkyltrimethylammonium salts. Abstr. Comm. XIX Internat. Physiol. Congress, Montreal 1953, pp. 801–802.
140. STEPHENSON, R. P.: Personal communication. XX Internat. Physiol. Congress, Brussels, 1956.
141. STEPHENSON, R. P.: A modification of receptor theory. Brit. J. Pharmacol. 11: 379–393, 1956.
142. THESLEFF, S. AND UNNA, K. R.: Differences in mode of neuromuscular blockade in a series of symmetric bisquaternary ammonium salts. J. Pharmacol. 111: 99–114, 1954.
143. VAN MAANEN, E. F.: The antagonism between acetylcholine and the curare alkaloids d-tubocurarine, c-curarine-I, c-toxiferine-II and β-erythroidine in the rectus abdominis of the frog. J. Pharmacol. 99: 255–264, 1950.
VAN ROSSUM, J. M. AND ARIËNS, E. J. see 128 and 129.
144. WELLS, J. A.: Anti-histamines in allergy. General discussion I. Ann. N. Y. Acad. Sci. 50: 1202–1206, 1950.
145. WESTERFIELD, W. W.: Biological response curves. Science 123: 1017–1019, 1956.
146. WILSON, I. B.: Acetylcholinesterases XI. Reversibility of tetraethyl pyrophosphate inhibition. J. biol. Chem. 190: 111–117, 1951.
147. WOOLLEY, D. W.: A study of antimetabolites. Wiley and Sons, New York 1952.
148. WORK, T. S. AND WORK, E.: The basis of chemotherapy. Oliver and Boyd, London 1948.
149. ZAIMIS, E. J.: Motor end-plate differences as a determining factor in the mode of action of neuro-muscular blocking substances. J. Physiol. 122: 238–251, 1953.
150. ZIPF, H. F.: Kombinationsversuche mit zwei Stoffen. Arzneim.-Forsch. 3: 398–404, 1953.
151. ZIPF, H. F. AND ALSTAEDTER, R.: Die hypnotische Wirkung von Luminal und Evipan in Kombinationen mit Megaphen und anderen Phenothiazin-Derivaten. Arzneim.-Forsch. 4: 14–19, 1954.
152. ZIPF, H. F. AND HALBEISEN, T.: Bakteriostatische und bakterizide Kombinationswirkungen verschiedener Antibiotika in vitro. Arzneim.-Forsch. 4: 463–467, 1954.