to below. The screenings were essentially free from noxious weed seeds and from ergot sclerotia.

Experiments were initiated to determine the suitability of rats as a means of tracing the causative agent. It was definitely established in July, 1944, that the material in question contained something which is highly toxic to rats. Sixty parts of normal stock ration mixed with forty parts of powdered screenings killed rats in an average of about ten days. Subsequent experiments have involved a study of the symptoms produced at different levels of intake and a search for the causative factor.

The symptoms observed varied with individual animals and with the level at which the toxic material was fed. Frequently observed symptoms in rats were:

(1) Incoordination to complete paralysis of rear quarters.

(2) Extreme swelling and discoloration (dark red) of usually one rear leg only, frequently followed by sloughing of affected tissues.

(3) Dark blue discoloration of tails, frequently followed by tail eating.

(4) Extensive tissue hemorrhages.

Preliminary experiments with 2-week-old chicks indicate that they are even more sensitive to the toxic material than are rats.

No decrease in toxicity has been observed in screenings stored at room temperature since July, 1944. The toxic factor is largely insoluble in ethyl ether and in petroleum ether but is largely, if not entirely contained in boiling alcohol extracts. Results obtained to date with several lots of screenings fed to over 150 rats, strongly suggest a causal relationship between toxicity and the degree of nematode (*Anguina agrostis*) infestation of the fescue seed.

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SIGNIFICANCE OF NEGATIVE RESULTS IN SMALL SAMPLES

AT the recent Gibson Island Conference on Cancer, reports were made on the failure to cause regression of tumors by the use of various chemotherapeutic agents. It was stated that from 10 to 25 animals were used in each experiment. The question was raised whether such numbers were always adequate to test therapeutic effect, particularly since, in cancer, true effectiveness of as little as 10 per cent. may have practical importance. The reply made was that the types of tumor employed never regress spontaneously and consequently regression in even one animal would be highly significant. During the discussion it appeared that other investigators were following this line of reasoning. It seems desirable, therefore, to point out that while a single positive result in a small group of animals bearing tumors which do not regress spontaneously would be significant, in the sense that it would lead to further testing, the converse is not true, *i.e.*, failure to observe a single regression in 10 to 25 animals does not always conclusively demonstrate the absence of therapeutic power. If a therapy were capable of causing 10 per cent. regressions, then, in samples of 25 animals, no regressions might be observed by chance in $.90^{25}$ or 7 out of a hundred trials. One may question whether a possibility as important as effective cancer therapy should be dismissed with so high a margin of error.

Following the convention of considering a chance probability of over .05 as too great to be reliable, Table 1 states the various sizes of sample (n) for which the probability of no successes would be .05, for various values of true effectiveness (p).

TABLE 1

PROBABILITY OF NO SUCCESSES = .05 = $(1-p)^n$ FOR VARIOUS VALUES OF p AND n

p	.10	.15	.20	.25	.30	.35	.40	.45	.50
n (to nearest whole number)	28	18	13	10	8	7	6	5	4

In experiments with groups of 10 animals one might easily miss chemotherapeutic agents which had an effectiveness of less than 25 per cent. This is, of course, elementary probability, but it is of interest that in this instance the considerations of elementary probability may have been ignored because of failure to distinguish between the significance of a single positive result not noted before and the significance of the absence of this result. The crucial experiment when successful may be conclusive, but, if it is unsuccessful, one must still ask whether the experiment as performed allowed the positive event sufficient opportunity to occur. Since we are about to witness great activity in the field of experimental chemotherapy of cancer, it is to be hoped that none of this work will be rendered inconclusive on such well-recognized grounds.

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THE RUMBLING OF THUNDER

THE rumbling of thunder certainly does not arise from any single cause. Among possible causes Humphreys[1] lists (*a*) inequalities in the distance from the

[1] W. J. Humphreys, "Physics of the Air," McGraw-Hill, ed. 3, pp. 379, 441. 1940.

observer to various points in the path of the lightning; (*b*) crookedness of the path; (*c*) succession of discharges; and (*d*) reflection.

On the morning of August 30, 1945, there was in Northampton, Massachusetts, a thunder storm in which there was very little noticeable lightning, and the number of sharp claps of thunder was small, but the sky was very dark, and there was an irregular rumbling that was sometimes loud and was almost incessant. In this case there must have been many discharges—probably along many different paths, occurring at varying intervals of time, and perhaps along paths that were not as long as when there are vivid flashes of lightning and sharp claps of thunder.

Perhaps such a case is really included under (*c*) in the list of causes given by Humphreys, although his emphasis seems to be on successive discharges along a single path. Is it not entirely possible that successive discharges along a considerable number of short paths in different parts of the cloud may often account for a part of the rumbling?

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SCIENTIFIC BOOKS

THE THEORY OF RESONANCE

The Theory of Resonance and its Application to Organic Chemistry. By GEORGE WILLARD WHELAND. 14.5 × 21.5 cm. Illustrated. vi + 316 pages. New York, N. Y.: John Wiley and Sons, Inc. 1944. $4.50.

FEW chemists are better equipped to write a book on "The Theory of Resonance and its Application to Organic Chemistry" than Wheland, who has made notable contributions to both organic chemistry and quantum mechanical resonance. It is no easy task to write the first monograph about a theory, the applications of which are growing steadily and extending into all branches of organic chemistry. The book of Wheland is a conspicuous success and should be read by all scientists interested in the new concepts of organic chemistry. The author has divided the material into eight chapters, which are very well organized, and has presented it in a simple and clear style without going into the actual mathematical calculations, but also without any oversimplifications.

In the first chapter the meaning and significance of resonance are explained, and conditions are defined under which resonance occurs. In this chapter also is the amusing but very fitting analogy between a resonance hybrid and a mule, which is not "a horse part of the time and a donkey the rest of the time. Instead it means that a mule is a new kind of animal, neither horse nor donkey, but intermediate between the two and partaking to some extent of the character of each." This picture should prove quite useful in explaining the meaning of resonance to first-year organic chemistry students who still very often associate resonance with the vague notion of an equilibrium of independent compounds.

After a short discussion of the different types of valence in the second chapter, resonance energy is taken up in the third. Some of the values recorded for the resonance energies are admittedly different from values reported elsewhere (usually somewhat higher), but the chapter is particularly valuable because of the inclusion of detailed formulae and methods by which resonance energies can be computed from thermochemical data and from Pauling's values for the bond energies and because of the critical statements made about the importance of the different methods. Steric effects of resonance, resonance and dipole moments, and resonance and molecular spectra are discussed in the following chapters, in the last two of which the physical basis of dipole moments and spectroscopy is explained in simple terms. The last two chapters, on resonance and chemical equilibrium, and resonance and chemical reaction, are possibly the best ones, and also the ones most likely to be of greatest actual interest to the organic chemist, for whose benefit the book is written primarily. Problems such as acid and base strength, free radicals, tautomerism, addition to olefinic double bonds and the carbonyl group, aromatic substitution, and others are discussed in the light of resonance. Not only known interpretations are presented in these two chapters, but many original and unpublished ideas are expressed on questions of current interest and controversy. This makes the two chapters particularly interesting and stimulating; they contain quite a number of suggestions for future research.

The problems of hyperconjugation and steric inhibition of resonance are scattered throughout the book and may, after some future research in those two fields, warrant two special chapters in a later edition. An appendix, containing all interatomic distances determined before June, 1943, is a useful addition.

The book is not beyond the comprehension of a senior or first-year graduate student, and will certainly be read with pleasure by students, teachers and research workers. It is a most welcome addition to every scientific library.

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