ADVENTURES IN PHYSIOLOGY

WITH EXCURSIONS INTO AUTOPHARMACOLOGY

A selection from the scientific publications of

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With an Introduction and recent comments by the author

PERGAMON PRESS · LONDON

PUBLISHED IN 1953 IN GREAT BRITAIN
BY THE PERGAMON PRESS LTD.
2, 3 & 5 STUDIO PLACE
KINNERTON STREET
KNIGHTSBRIDGE
LONDON
S.W.1

PRINTED IN GREAT BRITAIN BY
THE LEWES PRESS
FRIARS WALK
LEWES SUSSEX

ADVENTURES IN PHYSIOLOGY

To T. R. Elliott,

who had so much to do with the beginning of these adventures and, long after they have ended, is still my counsellor and friend.

INTRODUCTION

1

FAVOURED with opportunities such as few of my own generation enjoyed, I have been able to make scientific research, on problems mainly of my own choosing, the central activity of my working life. And now, some ten years after my direct part in such enterprises came to a natural end, I am asked to allow a collection of my papers to be republished, so as to make them more readily accessible to students of the matters with which they deal. It would not have occurred to me to suppose that my writings would have such a special interest, or that they were not sufficiently easy of access, in libraries containing the journals in which they first appeared. Friends and colleagues assured me, however, that a selection from them in handy form would be really useful; and they carried their conviction to more than one publisher, with the eventual result that the Pergamon Press have come to me with an insistent request to be allowed to publish such a volume. I cannot think of a more flattering proposal to one in my position, and I am deeply grateful to all who have taken part in making the suggestion, and in giving effect to it.

I should very gladly have left the choice of papers for inclusion to those who could judge, from their own experience of students' needs, which were the most likely to be in demand. I find myself further honoured, however, by requests to make the selection myself, and to add, in cases where I judge them to be suitable, such new comments as may help to make clear the relation to present knowledge, and to theories now prevalent, of evidence and ideas which I published at different earlier dates, extending over a period which began more than 45 years ago.

Apart from what my own experience may suggest to be reasonable, in bulk or cost, no limit has been set to the number of papers I may include, or to the number of pages I may fill. I am keenly conscious of the generosity of this proposal and, at the same time, not a little embarrassed by it. Any author, I suppose, given a free hand thus to select items from his own writings, might find it difficult to hold the balance between what he would like to keep alive, or to bury, and what was likely, on the other hand, to be most useful to anybody who referred to the collection. The author might feel constrained, perhaps, by such evidence as the number of requests for reprints of them, to include some papers in which his own interest had long faded; on the other hand, he might be reluctant to relinquish others, because of some personal or even humorous associations which would hardly be likely to commend them to the serious student.

I tried, then, to hold this balance evenly, between an author's fancy and a reader's probable interests; and I came to the conclusion that I could make the compromise most easily, if I limited my choice to papers having some relevance to

what became, during more than 30 years, my two main lines of activity in research, which have led me to traverse, or to touch upon, scientific areas commonly allotted to physiology, pharmacology and experimental pathology, and the borderlands between all of these. These two lines of enquiry have led, on the one hand, by way of studies which involved the specific actions of adrenaline and of acetylcholine, to a widening application of the conception of a chemical phase in the transmission of excitation from nerve-fibre endings to responsive cells; and, on the other hand, by way of studies of the actions of histamine and of its distribution in the animal body, to evidence for its contribution to local and general reactions, by which the organism as a whole and its separate tissues respond to various chemical, immunological, or physical assaults upon the integrity of their living cells.

Even when I had decided thus to restrict my choice, I had some difficulty in deciding what to omit. The first paper which I have included deals with a peculiar, preferentially paralytic effect, produced by a number of partially purified preparations from ergot on the actions of sympathetic nerves and adrenaline, which gives it a relevance to one of the general themes of the collection. On the same principle, however, I felt bound to exclude, though with some reluctance, a long paper by my late colleague George Barger and myself, dealing in a much more general way with all the actions and the distribution of an alkaloid, ergotoxine, which had soon afterwards been found to be responsible for this special paralytic action. In order to lighten the total load, again, and to keep a better balance between exposition, review and theory, on the one hand, and records of original observation on the other, I have also felt obliged, though again with reluctance, to omit some sets of lectures, though admitting some others. I have tried on the other hand to refer, in my notes on the papers included, to points in those omitted which still seem relevant and worthy of such notice.

2

If anybody were to read through the papers in this collection consecutively, he would be likely to notice the recurrent mention of the drug ergot, as a source for me of a succession of substances with remarkable, and widely different, pharmacological actions. Such a reader would probably guess, indeed, that my accidental encounters with these different types of activity had been largely responsible for determining the direction of my activities and interests in research; and there might be some who would be curious to know something of the circumstances, in which I thus came to receive what I have always recognized as more than my proper share of scientific windfalls.

When I had finished my formal studies and examinations at Cambridge, and began to try my hand as a research worker in Physiology, I had the inestimable privilege of regular access for guidance and inspiration to some of the great physiologists of those days—W. H. Gaskell, J. N. Langley, H. K. Anderson and others; and this privilege was renewed in London when, with medical qualification completed, I held a research studentship and worked in daily contact with E. H. Starling and W. M. Bayliss.

In 1904, however, at the age of 29, faced with what then seemed a rather bleak academic prospect, I accepted a research post in the Wellcome Physiological Research Laboratories, then at Herne Hill. These laboratories did a number of important services to the business of Burroughs Wellcome & Co., but they were also rather a pet project of the sole proprietor of that business, Mr. (later Sir) Henry S. Wellcome, who told me that it was his wish that research of permanent value to science might be done there. Though many friends advised me against it, I believe that I was attracted to the offer, not only by a conscious desire to earn a marrying income, but also by an instinctive feeling that it would be a good thing for me, at that stage, to be obliged to stand scientifically on my own feet, to find my own problems, to plan my own experimental attacks upon them, to learn and devise methods for myself, and to make my own mistakes. When I accepted the appointment, Mr. Wellcome said to me that, when I could find an opportunity for it without interfering with plans of my own, it would give him a special satisfaction if I would make an attempt to clear up the problem of ergot, the pharmacy, pharmacology and therapeutics of that drug being then in a state of obvious confusion. Pharmacological research was for me a complete novelty, and I was, frankly, not at all attracted by the prospect of making my first excursion into it on the ergot morass. I found George Barger, however, a former Cambridge acquaintance and a very able and enterprising chemist, working in the Wellcome Laboratories; and Barger, in response, no doubt, to a similar prompting, had already prepared from ergot a number of the substances which then figured in the pharmacological literature, with claims made for each to be ergot's "active principle." I thought that I might make a beginning by testing some of these, for the kind of pharmacological activity which was within reach of my limited technical competence. So I began with their effects on the arterial blood-pressure of the anaesthetized, or, more commonly, the spinal cat. All of them, as Paper No. 1 (p. 1) in this collection makes clear, showed an initial, noteworthy pressor action on the spinal preparation. That observation, however, would not have added much, by itself, to earlier knowledge, or to my independent experiences; and, if nothing more had happened, I should only have complied in a rather perfunctory manner with the request to do something about ergot. By one of my greatest strokes of good fortune, however, it was to give me an immediate opportunity of making a mistake of my own—a really shocking "howler." I was finishing one of these experiments on a spinal cat, to which I had given successive doses of one of Barger's ergot preparations, when a sample of dried suprarenal gland substance was delivered to me from the Burroughs Wellcome factory, with a request that I would test it for the presence of a normal proportion of adrenaline. The moment seemed opportune; a boiled extract was easily prepared, and there was a cat most suitable, as it seemed, for the required test. Successive injections of the extract elicited, to my surprise, only falls of the arterial pressure, and, with the confidence of inexperience, I condemned the sample without hesitation. And then, by another and almost incredibly fortunate coincidence, the same sequence of events was repeated in detail a week later. Again I was finishing an experiment on a spinal cat, which again had been heavily dosed with an ergot preparation, when a sample of suprarenal gland substance was again delivered for testing. Quite possibly it was from the same batch again, sent to control not only the quality of the material, but

also the competence of the new young pharmacologist; but that was never revealed to me. The result was, of course, the same as on the earlier occasion; but reference to my notes now raised the question whether the cat's response to adrenaline might have been so altered, by the heavy doses of ergot given in both cases, that the normal, pressor action had been reversed. It seemed unlikely, but control tests showed promptly that, in an animal not thus treated with ergot, both samples of the suprarenal material had the usual pressor action, representing a normal content of adrenaline, and then that treatment with ergot reversed this action of pure adrenaline itself. My first, tottering attempt at practical pharmacology had thus ended in what might have been merely a humiliating crash. My immediate recall of my first report, however, was received with what seemed to me a remarkable equanimity; while the kindly fate which is supposed to watch over the uncertain steps of children, and of some others, intervened to enable me to pick up the pieces and to recover something from the apparent disaster, with the result that I was soon launched upon the studies recorded in Paper No. 1.

My interest in the more general ergot problem was now genuinely aroused; but, though the alkaloid ergotoxine was soon afterwards isolated by George Barger and another chemical colleague and friend of many years, Francis H. Carr, then of the Wellcome Chemical Works, and was found to be responsible for this highly specific action, and even though its primary effects included a tonic action on the plain muscle of the uterus, I soon became doubtful whether a claim could be sustained for it, as the constituent of ergot mainly responsible for the traditional value of that drug in obstetrics. The accoucheurs were, in general, satisfied with the efficacy of the old-fashioned, watery liquid extract of ergot, as described in the British and several other Pharmacopoeias, and it was very easy to show that normal samples of this had practically none of the characteristic activity of ergotoxine; while, on the other hand, Barger failed to detect in this extract any other kind of alkaloid, to be tested for the so-called "oxytocic" activity. And, indeed, this problem of the practical use of ergot in obstetrics was to remain unsolved for another quarter of a century, although in that period a whole series of some six or seven other alkaloids had been discovered in ergot, differing from ergotoxine in minor details of chemical constitution and physical properties, but all of them practically indistinguishable from it in their actions, and none of them significantly represented in the watery extracts so widely used in obstetrics. And then at last, in 1932, I had the great satisfaction of being in touch with Dr. (now Professor) Chassor Moir, when he succeeded in demonstrating experimentally the presence in such extracts of an active substance, readily absorbed when administered by the mouth, and promptly stimulating the puerperal human uterus to vigorous activity. And, in 1935, I had the further joy of seeing my then chemical colleague, the late H. W. Dudley, working with the close control of Moir's clinical tests, isolate the water-soluble alkaloid which they named "ergometrine"; and I was even able then to take a hand in the pharmacological analysis of its actions. This was, beyond doubt, the long-sought, obstetrically important constituent of ergot, which Barger and I had started to look for three decades earlier, but had never come near to finding. So clear, indeed, was its claim to this important therapeutic rôle, that three other groups of workers, in Switzerland and the U.S.A., who must all have been independently on the track

of it, described the same alkaloid, though under different names, within a few months of Dudley and Moir's first publication; so that it acquired an unusual wealth of competitive synonyms.

This tale of the later development of the ergot story, however, must be regarded as told in parenthesis, and as outside the scope of the papers chosen for this collection. Nothing like it could have been predicted in 1908, when it was clear only that, if the value claimed for ergot in obstetrics had any reality, the preparation most commonly used in Britain for such purposes must owe its activity to something very different from the only active alkaloid, ergotoxine, then known to occur in the drug. We needed a new line of attack; and this was suggested by information, received from those responsible for the manufacture on a large scale of the official "Liquid Extract of Ergot," that its preparation was inevitably accompanied by an obvious putrefaction. At about the same time there had been more than one publication showing that pressor substances of some kind, bases apparently, were formed when materials like meat, or human placenta, were allowed to putrefy. I suggested to Barger, therefore, that identification of some of these products of putrefaction might give us clues to active constituents of the ergot extract. These, in fact, we obtained; and, though they led to nothing of lasting importance for the uses of ergot in medicine, they eventually started new enquiries of a greater general interest, I believe, to physiology and pathology. The first bases which Barger and Walpole found in putrefying meat were the amines formed by the decarboxylation of leucine and tyrosine—*iso*amylamine and tyramine. Both had pressor activities of a type for which I coined the name "sympathomimetic," to signify reproducing by peripheral action the effects of sympathetic nerves, and recalling thus the actions of adrenaline, but doing this with different degrees of fidelity. The fact that we then found such bases also in ergot extracts did no permanent service to the practical ergot problem; but the recognition of the type of their activity led me to embark, with Barger's chemical collaboration, on a comparative study of the different degrees and kinds of sympathomimetic action exhibited by a long series of such amines, most of them produced by artificial synthesis. The results of this study were assembled and discussed in Paper No. 5 of the collection. It was, I think, the first of a series of many such, by workers in different countries.

While our review of amines with this general type of action had been making rather intermittent progress, ergot had afforded us another clue, leading eventually in a very different direction. At a Physiological Congress in Heidelberg, in 1907, Dr. Kehrer gave the first demonstration of the behaviour of the horn of a cat's uterus as a surviving, isolated organ, using the method which Magnus had introduced a few years earlier for loops of intestine. Kehrer demonstrated the immediate and very powerful tonic action on this preparation of a particular ergot extract; and it was obvious to me that there must be an active substance in this, of a different kind from any which we had yet identified. The nature of the extract further suggested that this unknown substance might be another product of putrefaction, and probably from another amino-acid. Barger and I accordingly resumed the quest, and were able to isolate this intensely active substance and to identify it as the now familiar histamine, produced by decarboxylation of the diamino-acid, histidine. Our identification was greatly assisted by the fact that Ackermann, in Germany, had obtained

histamine from putrefying pancreas, while we were engaged in isolating it from ergot. Ackermann and Kutscher, indeed, also ran neck-and-neck with us in obtaining it from ergot, though they hesitated over the identification, through a misinterpretation of some physiological effects. Histamine again had, in the long run, no permanent interest for the therapeutic use of ergot; on the other hand, a detailed study of its actions revealed a remarkable correspondence between the contrasted symptoms which it produced in different animal species, and those which had then recently been described as constituting, in those same species, the central syndromes of their respective anaphylactic reactions—a group of phenomena which was even then acquiring a position of central interest for workers in a particular range of experimental pathology. And thus the recognition of this base and its actions, again as an accidental outcome of our search for active substances in ergot, opened the way to one of the main lines of research illustrated by this collection, which can be followed in Papers Nos. 5, 6, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22.

Yet once again, about 1913, it was an accidental observation of the unusual activity of a particular extract of ergot, which quickened anew my interest in phenomena suggesting a chemical, pharmacodynamic transmission of excitation at the junctional contacts between nerve-endings and cells. What was supposed to be an ordinary liquid extract of ergot had been sent to me for a routine control of its activity. When a conventional dose of this was injected into the vein of an anaesthetized cat, it caused a profound inhibition of the heart-beat; I suspected, indeed, a fatal accident of injection, till recovery set in, and successive repetitions of the injection then caused the same sequence at every trial. Tests of this extract on other biological reagents, such as isolated loops of intestine, confirmed the presence in it of an unusual constituent, with actions suggestively resembling those of muscarine; and muscarine, I thought, might perhaps turn up occasionally in a fungus like ergot. It was obviously impossible to pass an extract with such properties for therapeutic use, and I secured the whole batch of it for further investigation. My chemist colleague at that time, A. J. Ewins, succeeded thus in obtaining and purifying a few milligrammes of the abnormal active constituent, as a platinum salt; but, when it was freed from this combination and tested, it became clear that it could not be the stable muscarine; it was something with the properties, rather, of a very labile ester. There seemed little hope then of further progress with the minute amount in hand, till I recalled into conscious memory an observation made some 8 years earlier by my late friend Dr. Reid Hunt, then in Washington. Hunt and Taveau had found that, when choline was acetylated, its depressor activity was enormously intensified, the unstable ester, acetylcholine, being some ten-thousand times as active as the parent choline. When Ewins, accordingly, made me some acetylcholine, its identity with our substance from the ergot extract was immediately put beyond doubt; and thus I was led to make the experiments described and discussed in Paper No. 10. As the date shows, this was published just after the outbreak of the first world war, and my own transfer to the national service of the Medical Research Committee (now Council).

Soon after that war came to an end, and while I was busy for some years with resettlement under new conditions and then with researches in other directions, ideas

concerning a chemical transmission of nervous effects had been raised to a new level of significance by the work of Otto Loewi and his co-workers in Graz, on the frog's heart. Their direct evidence had given such ideas for the first time an experimental reality, and had even revealed two transmitters, with properties indistinguishable from those of acetylcholine and adrenaline. And thus it was not till 1929, after an interval of some 15 years, but then in a new atmosphere of generally awakened interest in its possible significance, that my direct participation in experiments with acetylcholine was renewed; and this was stimulated, again, by another accidental encounter with that substance. As a late item in a series of studies on the distribution of histamine in normal tissues and organs, I was engaged, with the late H. W. Dudley, in investigating, and eventually proving, its presence in the spleen. Incidentally to this, and quite unexpectedly, we found that extracts from the spleens of oxen and horses also contained something having the activity and the chemical properties of acetylcholine, and were thus led to the first chemical isolation of that ester from an animal tissue. And, having acetylcholine thrust, as it were, again upon my notice, I was led to embark, with a succession of good colleagues, on studies of the wider physiological significance of its activities, as a transmitter of nervous effects; and all the later papers chosen for this collection, from No. 23 onwards, have this as a principal theme.

When the succession of such events is thus viewed in retrospect, I think that it will be understood why the frequency, with which accident has provided new directions and opportunities for my efforts in research, should appear to me to have been quite unusual; and anybody who has the curiosity to examine for that purpose the papers here collected, and my recent notes upon them, will there find records of yet other cases, in which accident seems to have favoured, or even to have prompted some scientific enterprise of mine. At the very beginning of all that is here on record, I had, as I have mentioned already, the good fortune to be offered by Mr. Wellcome the kind of opportunity which was probably, at that juncture, the most suited to my particular need. And he did me the further service of suggesting a problem, with hopes of a kind, no doubt, which had to wait for real fulfilment until some twenty years after I had finished my work in his laboratories; but the problem had meanwhile provided a remarkable succession of other and unexpected clues, and I was given freedom to follow these. And then the freedom to pursue them further was continued, in a wider field of opportunity and through nearly thrice as many years, under the Medical Research Council. And in all this I have had the crowning good fortune of working in intimate association with a large number of distinguished colleagues. The names of many of these appear with my own, as jointly responsible with me for one or more of the papers in this collection; but there were many other researches, for which these and other colleagues of mine had the full responsibility, and which cannot therefore be included here, though they came from the same laboratories in the same period, and provided chapters of at least equal importance to the development of what was, essentially, one story.

I have been looking once again at the papers chosen for reproduction here, and at the comments which I have made on changes in the intervals, varying from 46 to 15 years, between the dates at which they were first published and this time of writing. And, in doing so, I have seen how incomplete and capriciously selective

these comments must appear, to any reader who is keeping pace with the rush of modern developments in these fields of research. Even as I have been writing these recent comments, additional points have continued to crowd upon my notice, in new numbers of the relevant journals or in verbal reports made to recent scientific meetings; and many of these call for a further reconsideration of conclusions which had appeared for the time to be settled, or offer new and more decisive evidence in favour of others. And it became clear that, if I left my commentary thus open to further additions or amendments, I should never be finished with the attempt to correct it, or to make it more complete. Fully conscious, therefore, of the gaps in it and of its lack of balance, I have been obliged to call a halt to further effort at its improvement, and to reconcile myself to a decision just to stop it, with the knowledge that it could never be finished. And thus I leave these papers and comments, puzzled, as at the outset, to discover a reason why they should have been singled out for such an honour.

The republication has, of course, given me an opportunity to eliminate or to make good, in the new proof, such minor errors or omissions in printing as had escaped correction before these papers first appeared. I have thus been able to incorporate into the text of one paper an "erratum" which had been required when it was first published; and in another case I have had a first opportunity of correcting an unusual abundance of printing errors, due to the interruption of postal communication by war in 1914, which had led to the appearance of this paper, in an American journal, without any proof-revision by me. Apart, however, from such minor corrections of obvious oversights and printing errors, I have passed the original texts for reprinting exactly as they were. The natural itch to revise, in the light of later knowledge and larger experience, has been allayed only by the attachment to the papers of my recent comments.

H. H. DALE.

London, March 1952.

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Originally published in J. Physiol., Vol. XXXIV, No. 3, 1906 (pp. 163-206)

1

ON SOME PHYSIOLOGICAL ACTIONS OF ERGOT

H. H. DALE

From the Wellcome Physiological Research Laboratories

A PRELIMINARY note on the phenomena dealt with more completely in this paper was entitled, "The Physiological Action of Chrysotoxin"[1]. Since the date of that publication further experiment has shown that the action is due to a principle or combination of principles, which, by the aid of the physiological test, can be recognised in the various substances for which the title of "active principle" has been claimed, and indeed in all preparations of ergot possessing therapeutic activity. The active resin extracted from chrysotoxin, and called by Jacobj[2] "sphacelotoxin," gives the effect in doses of a few milligrammes. So also do preparations corresponding in mode of extraction and solubility to the "cornutine" of Kobert, and differing from that substance only in their failure to elicit the spasms in frogs, described by Kobert[3] as characteristic—a failure by no means unique in the experience of those who have worked with "cornutine" since Kobert. A resinous substance separated from commercial ergotinine also gives the reaction very typically and in small dosages; while, in large quantities, many specimens of the ordinary pharmacopœial extracts produce the same effects, complicated only by the presence of depressant impurities.

These facts make it impossible to speak of the action any longer as that of chrysotoxin. On the other hand, the wide acceptance of Kobert's[4] view as to the difference between sphacelotoxin (in sphacelinic acid) and cornutine would render the attribution of the effects to either of those substances misleading. The introduction of new names on the strength of physiological results, and in default of chemical isolation of principles, would inevitably add to the existing confusion, and I have thought it better to speak of the action as that of "ergot," and to mention in the body of the paper the particular preparations used. This seemed the more desirable in view of the possibility that the effects are due, not to one but to two closely associated principles. Dr. G. Barger is investigating the matter from the chemical side, and in a later joint paper we hope to deal with the nature of the active substance or substances, their distribution in ergot preparations, and the therapeutic application of our results. This paper is concerned with the action only in so far as it appears to be of general physiological interest.

Since the various preparations used in the experiments here described, while free from ergotinic acid, choline and the other depressant impurities of galenical preparations, contain varying proportions of inert matter, it will be understood that

[1] *Proc. Phys. Soc.* p. lviii. 1905. *J. Physiol.*, xxxii.
[2] *Arch. f. exp. Path. u. Pharm.* xxix. p. 85. 1897.
[3] *Arch. f. exp. Path. u. Pharm.* xviii. p. 316. 1884.
[4] *loc. cit.*

indications as to dosage can be no more than rough approximations. Chrysotoxin, which generally contains about 99% of inactive but harmless material, was the form of administration in all the earlier experiments. In many cases the chrysotoxin was dissolved in the smallest possible volume of ethyl alcohol, just enough sodium hydrate added to prevent precipitation on the addition of water, and the solution then diluted with water to a strength of 1% chrysotoxin. In other cases the preformed water-soluble sodium salt was used, prepared by precipitation from a solution in dry ether by means of sodium ethylate. This preparation possesses a good deal of the activity of the original chrysotoxin, but not all, nor even a constant proportion of it. Preparations corresponding to Jacobj's sphacelotoxin and to Kobert's cornutine were used in many of the later experiments, and were similarly dissolved in dilute sodium hydrate. Their activity varied from 20 up to 100 times that of the average specimen of chrysotoxin.

The experiments here discussed are concerned only with such prompt effects of intravenous injection as can be observed directly, or with the aid of mechanical methods of recording, in the anæsthetised or pithed animal. No new observations have been made on the slowly developed effects of administration by the mouth or hypodermically to the intact animal, and these will be dealt with only incidentally. Most of the experiments were made on cats: a few also on rabbits, dogs, monkeys, ferrets, and fowls, the purpose for which each species was used being indicated in dealing with the results of particular experiments. The animals were always anæsthetised with chloroform, ether, or A.C.E. mixture, unless or until the cerebrum was pithed.

The effects of intravenous injection, the mode of administration used throughout these experiments, are divisible into two classes, corresponding to a primary or stimulant, and a secondary or paralytic stage of the drug's action. It will be convenient, however, as giving a more connected picture of the sequence of events, to deal, in the first place, separately with each organ or system on which observations have been made.

1. The Circulatory System

Primary or stimulant action. The first definite laboratory demonstration of the stimulant effect of ergot on the peripheral arteries was given by Kobert[1]. The gangrenous phenomena which he observed in the comb and other peripheral structures of the fowl and the pig, as the result of administering sphacelinic acid, were attributed by v. Recklinghausen, who investigated the phenomena histologically, to "powerful and persistent constriction of the arterioles." In contrast to this repeatedly confirmed and now familiar action on the cock's comb, the results of observing the effect on blood-pressure have been very variable and unsatisfactory. Setting aside, as merely misleading, the numerous observations on the depressant effect of crude extracts given intravenously[2], the recorded results with such comparatively pure preparations as sphacelotoxin and cornutine are surprisingly inconclusive. Kobert gave an intravenous injection of the sodium salt of sphacelinic

[1] *loc. cit.*

[2] *Cf.* a recent paper by Sollmann and Brown (*Journal American Med. Assoc.*, 22nd July 1905), who give references to most of the papers dealing with similar experiments.