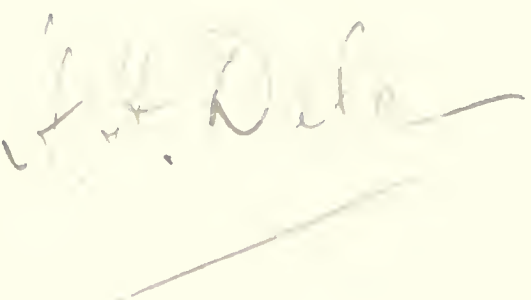

ERGOT AND ERGOTISM

ERGOT AND ERGOTISM

A MONOGRAPH

BASED ON THE DOHME LECTURES DELIVERED
IN JOHNS HOPKINS UNIVERSITY, BALTIMORE

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A LA MEMOIRE DE

CHARLES TANRET

1847-1917

PHARMACIEN FRANÇAIS

à qui sont dues les découvertes de
l'ergotinine et de l'ergothionéine avec
l'exacte description de l'ergostérine

PREFACE

THIS book was planned more than twenty years ago, during a happy partnership in research, but the claims of the laboratory caused the joint project to be abandoned. When in 1928 Johns Hopkins University honoured me with an invitation to deliver the Dohme Lectures, instituted "to promote the development of a more intimate relationship between chemistry, pharmacy and medicine," I considered that this purpose might be served best by choosing ergot as my subject.

During the subsequent writing for publication, the three lectures have grown into a monograph, in which I have attempted to deal fully with the subject in all its aspects. The bibliography has received special attention; in particular I have consulted in continental libraries the contemporary accounts of ergotism, and in the United States the earliest clinical publications; thus I hope that little of importance has escaped.

My thanks are due to numerous colleagues: to Dr M. Wilson of Edinburgh for reading Chapter III. and for photographs (Figs. 17 and 21-23); to Dr E. Rothlin of Basle for reading Chapter V. and for reprints; to Professor E. Mellanby of Sheffield for private communications and for Fig. 6, I.-III.; to Professor E. Rost of Berlin for Figs. 7, 9, and 10; to Professor R. Eder of Zürich for Figs. 12 and 13; to Professor F. T. McFarland of the University of Kentucky for Figs. 18 and 19; to Professor A. Stoll of Basle and Dr Raymond Hamet of Paris for the loan of blocks for Figs. 32 and 34-37. I am further indebted for permission to reproduce: to Messrs Macmillan & Co. for Fig. 20, to the U.S. Department of Agriculture for Fig. 31, to the Chemical Society for Fig. 33, to the Biochemical Society for Fig. 38, and to the *Journal of Pharmacology and Experimental Therapeutics* for Fig. 39. Mr N. A. Johns, of the firm of Messrs F. W. Berk & Co. and Messrs Burroughs, Wellcome & Co. have kindly supplied information relating to ergot in commerce,

Dr G. Tanret of Paris has furnished me with specimens and information. Various libraries have given me special facilities, in particular those of the Imperial Bureau of Mycology, Kew, and of the Faculté de Pharmacie, Paris; I am also indebted to the authorities of the Staatsbibliothek, Berlin, and to Dr J. Briquet, Geneva.

Finally, I wish to express my thanks to the Committee of the Dohme Lectureship, who provided the occasion for the writing of this book, and especially to Dr H. H. Dale of London, who greatly stimulated my interest in the subject. Besides giving criticism and advice on many points, he has, throughout the preparation of this work, encouraged me to believe that the detailed treatment adopted was worth the labour involved.

G. BARGER.

EDINBURGH, *September* 1931.

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ERGOT AND ERGOTISM

CHAPTER I

ERGOT: HISTORICAL

A LARGE number of grasses are attacked by one or other of the several species of *Claviceps;* of these *C. purpurea* is particularly liable to infect rye and is therefore of outstanding importance. Other cereals are much more resistant to this fungus; thus wheat, barley and oats are attacked comparatively rarely. The history and distribution of ergot are therefore especially associated with those of rye.

History and distribution of rye.—Detailed and valuable information on this subject will be found in a recent book by Sir William Ashley [1928]; also in one by Maurizio [1919; not quoted by Ashley]. The Ancients hardly knew rye; the Greeks were used to wheaten bread and objected to the black, malodorous product of Thrace and Macedonia (Maurizio); in classical Latin rye was called *secale* (Pliny, lib. 18, cap. 16), from which word the modern French and Italian names are derived, but rye seems to have been grown to some extent only in cis- and trans-alpine Gaul and not further south. In medieval Latin rye was called *siligo*, by which the Romans, however, meant fine wheat.

Rye was essentially the bread corn of the Teutons; according to Hoops, it was not introduced into Southern Europe until the beginning of the Christian era, although it was known to the ancient Germans at least four centuries earlier.[1] It seems likely that in Roman Britain wheat was chiefly cultivated, at least in the south, and that rye was first introduced by the Teutonic invaders, to the sandy soil of East

[1] Husemann (in Neuburger und Pagel, *q.v.*) seems to be in error in considering that rye was first introduced into Europe by the Huns.

Anglia. During the Middle Ages rye bread, baked from rye or from a mixture of rye and wheat, was largely eaten by the poor. According to Rogers, wheat already (again) predominated in 1150 (with some oats in the north of England). "Rye was scantily cultivated. An occasional crop on many estates, it is habitually sown on few. It is regularly sown in Cambridgeshire and some other eastern counties. As the period before us passes on [1259-1400] it became still more rare." Ashley's elaborate investigation of this subject led him to the conclusion that more rye was grown in England than is commonly supposed. Yet about the time of the Peasants' Rising of 1381 the labourers were demanding wheaten bread, and it seems clear that the bread of the poor was never made exclusively from rye, as it was in many parts of the Continent. Gerarde [1597] states that rye grew well in most places in England, especially in the north, and plentifully in Germany and Poland, whence it was brought to England in years of scarcity [*e.g.* 1596]. In the seventeenth century it was still grown in many places in this country, but the improvements in agriculture in the eighteenth (particularly by "marling," *i.e.*, mixing the subsoil of clay with the sandy surface layers) resulted in rye being almost entirely displaced by wheat, for instance in Norfolk. Michell [1828] states that the oldest thatch consisted of rye straw in counties where rye was then no longer grown.[1] In 1925 rye was limited to 50,000 acres, chiefly in Yorkshire, Lancashire, Cheshire, Monmouth and Essex; only 30,000 acres were allowed to ripen, the rest being ploughed-in as green manure.

In France, during the Middle Ages and in modern times, there was always much more rye than in England. Wheat was for a long time regarded almost as a luxury crop, but the improvements in agriculture, particularly between 1770 and 1800 (Maurizio) brought about a great change, and early in the nineteenth century wheat began to predominate. Rye (and ergotism) became largely restricted to such barren districts as the Sologne; but even there drainage, the digging up of the chalk subsoil, and the planting of trees have within the last sixty years enabled rye to be replaced by wheat; incidentally in the Sologne the death-rate has been reduced

[1] I have been informed that, owing to the difficulty of importing straw, small plots of rye are now being grown on Scottish farms for thatching purposes.

from 26 to 16 per thousand and the population has increased considerably (Fallex and Mairey).

Rye is still the chief cereal in a large belt of Europe, extending from Holland across Northern Germany, Czechoslovakia, Austria, Poland and Central Russia to the Ural Mountains, as is evident from the following table, showing the production in millions of bushels :—

RELATIVE IMPORTANCE OF RYE AND OF WHEAT.

	Rye.	Wheat.	Ratio.
Poland	246	60	4·1
Germany	321	123	2·6
Netherlands	13	4·7	2·1
Austria	19	11·6	1·6
Czechoslovakia	64	48	1·3
Russia	756	783	0·96
Sweden	16	19	0·87
Denmark	10	12	0·87
Norway	0·56	0·73	0·77
Belgium	11	16	0·68
Portugal	5·3	11	0·48
Hungary	33	72	0·46
Spain	23	149	0·15
Rumania	13	100	0·13
France	39	320	0·12
United States	41	807	0·050
Canada	13	294	0·045
Italy	6·8	261	0·025
England and Wales	0·65	46·5	0·014

The first two columns (millions of bushels) have been rounded-off from data in the *Year Book of Agriculture* [1930] *of the U.S. Department of Agriculture*, except those for England and Wales, for which I am indebted to the Ministry of Agriculture and Fisheries. They apply to 1929, except those for Russia, which apply to 1928. The last column, showing the ratio rye : wheat has been calculated from the exact data. In certain countries this ratio was formerly much higher, and if Northern Germany and the northern cultivated portion of Russia were considered separately, it would also be much higher. Although Spanish and Portuguese ergot is commercially important, the combined production of rye of these countries is less than that of Hungary, France, or the United States and is only one twenty-seventh of that of Russia. Spanish ergot comes almost entirely from the moist north-west

corner of the Iberian Peninsula. The amount of rye now produced in the United States is about 1½ times that of 1909, but only half the average of 1918-1922; by far the most important rye-producing state is N. Dakota. Until the end of the eighteenth century the ratio rye : wheat was in France greater than unity, but in Italy it must always have been very low.

Ergot in England.—The rather limited distribution of rye explains to some extent why ergot was hardly known in England until it was introduced into medicine in the nineteenth century; but to my mind the explanation is not quite adequate. Some other factor, perhaps the climate, must have contributed to make ergot comparatively rare, for its very name is foreign. After a Latin reference to "Muttercorn" taken by John Ray from a German flora in 1677, the word *ergot* appears for the first time in the English language, or more accurately, in an English context, in 1683 (in *Weekly Memorials for the Ingenious*, p. 151). "That malignity . . . breeding in the ears of corn certain black grains call'd in Sologne Ergots and in Gastinois Bled Cornu." This passage is simply a translation of a review in the *Journal des Sçavans* (for 29th June 1682) of a book by Bernier (*q.v.*) on the county of Blois. In the *Philosophical Transactions* of 1762 ergot is still a foreign word (*v.* Bones); it was becoming anglicised in 1791 when Erasmus Darwin used it in his *Botanic Garden* (Part I, canto 4, lines 511-514):—

> Shield the young Harvest from devouring blight,
> The Smut's dark poison, and the mildew white;
> Deep-rooted Mould, and Ergot's horn uncouth,
> And break the Canker's desolating tooth.

Darwin found it, however, necessary to explain in a footnote that "there is a disease affecting the rye in France, and sometimes in England in moist seasons, which is called Ergot, or horn seed." The latter name, a translation of "bled cornu," does not seem ever to have come into use. Two years later Thomas Beddoes, more capable as a linguist than as a physiologist, wrote: "The disease of rye called *ergot* is exactly analogous to the scurvy in animals." He based this strange view on observations by Saillant and Tessier, and does not seem to have had first-hand knowledge of the subject. Such names as horned rye, spiked rye, spurred rye and the spur were used in the earlier part of last century, but would appear to

be mere translations of French names. At the time when ergot was being introduced into official medicine in the United States, the information given about it in the *Edinburgh Medical and Physical Dictionary* [1807], (by R. Morris, J. Kendrick *et alii*) was contained in a single sentence: "Ergot, a name by which the French call rye that is diseased in a particular manner, from its grains assuming somewhat of the form of a cock's-spur." Parr's *London Medical Dictionary* of 1809 even states that it is a human disease, involving mortification of the extremities. Indeed, no Anglo-Saxon name for the fungus exists.[1]

French names.—The word *ergot* is defined as "petit ongle pointu derrière le pied du coq, du chien," etc. It is probably derived from *articulus*, through *artiglio* and O.F. *argot*. This name was applied by the peasants of the Sologne to the sclerotium, on account of its resemblance to a cock's-spur; other French names are or were: blé or bled cornu (Gâtinais), chambucle (Lyonnais), mane (Maine), ébrun, bled avorté, bled ergoté, bled farouche, bleds fourchus, bled hâve, bled rachitique, faux seigle, seigle cornu, seigle corrompu, seigle à l'éperon, seigle ivre, seigle noir. Clou de seigle and mère de seigle I suspect of being translations from the German or Latin. The common name seigle ergoté applies, strictly speaking, only to a mixture of sound rye and ergot, although most French authors have used it as a synonym for the latter.

Latin names are: Calcar, Clavus, Clavus secalinus, Clavus siliginis (Lonicer), Grana secalis degenerata (Brunner), Secalis mater (Thalius), Orga, Secale cornutum (Baldinger; still much used on the continent), Secale luxurians (C. Bauhin) and a number of names such as Spermœdia clavus (Fries), Sphacelia segetum (Léveillé) applied by mycologists to stages in the life cycle until the latter was elucidated by Tulasne, who definitely named the fungus *Claviceps*.

Italian names are: grano allogliato, grano cornuto, grano sprone, grano speronato, segala allogliata, segala cornuta, sperone di gallo, chiodo segalino. **Spanish**, cornezuelo de centeno. **Portuguese**, cravagem de centeio. **Rumanian**, secara cornuta. **Danish**, meldrøje. **Norwegian**, meldrøie. **Swedish**, mjöldryga, mjölöka. **Dutch**, moederkoorn. **Russian**, sporynia.

[1] Tschirch [1923] gives "Bunt" as a synonym of ergot, but this is *Tilletia caries*, a form of smut.

German names.—Although we cannot agree with Tschirch, "that ergot started its triumphal career from Germany"—it was first introduced into official medicine in America and France—we may recognise with him that it is a German drug; the beginnings of its history are in German folk-lore. The association of theriomorphic and anthropomorphic demons with corn has been studied by Mannhardt in his *Roggenwolf und Roggenhund* [1865] and *Korndämonen* [1868]; when the corn waved in the wind, the corn mother was said to pass through the field; her children were the rye wolves and ergot was of her making. In Bavarian folk-lore there was a male spirit of the corn, "Kornvater," and in Austria this name is applied to ergot itself (Daubrawa). According to *Nature*, 8th September 1928, p. 385, this spirit of the corn is known in England as "corn" or "kern baby," "corn maiden," "corn mother," "corn dolly," "hare" and so forth.

In Germany ergot seems at first to have been identified with the corn mother, as the old name Rockenmutter implies [Thalius 1588; Schwenckfelt 1600; Stocker 1634]. The term Mutterkorn seems to be of somewhat later date [M. Hoffmann 1662]; according to Mannhardt it most probably involves a connexion with the corn mother, rather than an allusion to the action of ergot on the womb. The same idea is contained in Kornmutter, Kornmuhme, Roggenmuhme, Meelmutter, Mütterlein, Rockenmütterle, and in Mutterkörnlein, Stiefmutterkorn, and a similar one in Kornvater and Kornmänner. Further names connected with folk-lore seem to be: Hasenbrod (*cf.* English "hare" above), Krähenkorn (Austria), Rezroggen (*Secale murinum*), Rezkorn, Hahnenbrod, Martinskorn (Harz Mountains, Brunner). Wolfzähne was reported by Mannhardt to be in use near Crefeld, on the lower Rhine, and already by Lang near Lucerne. According to Hartwich [1911] this name is still in use in Switzerland (along with Roggenbrand and Turf). The shape and other properties of ergot have given rise to the following: Kornzapfen [Lonicer 1582], Hahnensporn, Horn, Vogelsporn, Bockshorn, Dürrkorn, Taubkorn, der taube Rocken (these three because it appeared to be sterile), Rankkorn (compare *Secale luxurians*), Schwarzkorn, Tollkorn (compare bled farouche). Yet other names are: Achterkorn, Afterkorn, Brandkorn, Brandrocken, Erdenkopf, Faulkörner, Hungerkorn, Klaap (Mecklenburg), Kummerkorn, Mehldrine,

Moderkorn, Mühldrie, Mutterzapfen [Frank 1783], Rundrie, Todtenkopf, Todtenkorn.

Earliest references.—This great wealth of names implies an early German familiarity with ergot, in contrast to the ignorance concerning it in England. It is not surprising that the first unmistakable mention of the drug itself (as distinct from its toxic effects in epidemics) was in a German book, the 1582 edition of Adam Lonicer's *Kreuterbuch*, where in cap. ccclxx., p. 285, an appendix was added to the description of rye or corn (*siligo*), as follows:—

Nota: Von den Kornzapffen/ Latinè, Claui Siliginis: Man findet offtmals an den ähren deß Rockens oder Korns lange ſchwartze harte ſchmale Zapffen/ſo beneben vnnd zwiſchen dem Korn/ſo in den ähren iſt/herauß wachſen/vñ ſich lang herauß thun/wie lange Neglin anzuſehen/ſeind innwendig weiß/wie das Korn/vnd ſeind dem Korn gar vnſchädlich.

Solche Kornzapffen werden von den Weibern für ein ſonderliche Hülffe vnd bewerte Artzney für das auffſteigen vnd wehethumb der Mutter gehalten/ſo man derſelbigen drey etlich mal einnimpt vnd iſſet.

FIG. 1.—First mention of Ergot, by A. Lonicer, 1582.

These "long black hard narrow corn pegs, internally white, often protruding like long nails from between the grains in the ear," must undoubtedly be identified as ergot. Their use by women as a proved means of inducing pains of the womb is at once mentioned and the dosage (three sclerotia (=about 0·5 gram) repeated several times) accords with modern practice.

I have been at some pains to ascertain whether this is really

the oldest reference, particularly since some modern writers on ergot have mentioned earlier editions of the same herbal. The history of the latter is as follows (G. A. Pritzel, E. H. F. Meyer): The Frankfurt publisher Egenolph used the same figures over and over again with a text originally based on that of Rhodion's (Roesslin's) *Kreutterbuch*, but modified by various editors. The chief of these was his son-in-law Adam Lonicer [1528-1586] who was responsible for a Latin edition, *Naturalis historiæ, opus novum*, 1551-1555 (not so new as the publisher would make his customers believe; Sir Joseph Banks's copy is in the British Museum). Practically the same text and figures were issued in 1565 under a new title, *Botanicon: Plantarum historiæ*, etc., and according to Bonjean [1845] ergot is first mentioned in this edition; this error is repeated by Atanasoff [1920]. The *Botanicon* is rare and the only copy which I have been able to trace is in the Conservatoire Botanique of the city of Geneva; it belonged to de Candolle. I am indebted to Dr J. Briquet, Director of the Conservatoire, for an opportunity to consult this copy, which contains no mention of ergot. According to Meyer there were, during the lifetime of Lonicer, six German editions of the same work, which were gradually enlarged. The German text first appeared in 1557; this edition has not been accessible to me, but I have seen those of 1560, 1564, 1569, 1573, 1577 and 1582. Only the last (published four years before Lonicer's death) mentions ergot; the passage reproduced was photographed from Linnæus's copy now in the possession of the Linnean Society. This 1582 edition is evidently rare for it is not mentioned by Pritzel, nor is it in the British Museum. In particular the edition immediately preceding [1577] which I have seen in the Bibliothèque Nationale, has no mention of ergot, despite Kobert's statement to the contrary. All the later editions of the herbal, such as those published in the seventeenth century by Uffelmann, contain the note in question. I am at a loss to suggest how Lonicer came to include ergot in 1582. In that year he produced an edition of Eucharius Roesslin's treatise on midwifery (translated into English as "Birth of Mankynde"), but here there is no mention of ergot. Nor is there any indication in other herbals published a few years before 1582, in particular not in M. de Lobel's *Plantarum historia* [Antwerp 1576], nor in H. Bock's *Kreutter-*

buch [Strassburg 1577], nor in R. Dodoens' *Herbal*, translated by H. Lyte [London 1578]. These botanists either did not know ergot, or did not think it worthy of mention. Joannes Thalius, however, included it a few years later in his *Sylva*

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vbi defloruerit, frumenti alicuius genus imitatur, vtpote Secalen, vel aliud simile. Frequens est in mõtibus aridioribus passim, ac secus vias. Videtur vero hoc genus vitium esse secalis. Ac, sicuti sæpissime in Secale nostra accidit, vt aristæ quædam, postquam flores deciderunt, ac semina iam augmenta suscipere incipiunt, vitium aliquod in granis cõtrahant: forte maior succi copia, quã ad grani iustũ alimentum opus est, attrahitur, vt ita necesse sit, corticem adhuc tenerum rumpi, & ita internam substantiam in maiorem molem augeri, ac à feruore solis & ambiente in circumferentia sua affici. Tunc enim videmus quædam semina longius ex suis vtriculis seu glumis protendi, ac in mediocrem etiam crassitiem excrescere, nigrumq; colorem foris contrahere, intus candida farina densioris materiæ constantia. In Thuringia vulgo vocatur vitij hoc genus mater Secalis, Rockenmuter. [Vtuntur etiã eo ad sistendũ sanguinem.] Eodem inquã modo vitij id, anno LXXV. in hac festuca Secalina obseruaui. Reperi enim in montibus quibusdã Stolbergæ huius plures spicas, non vnũ ciusmodi vitiosum granum oblongum, nigrum, continentes, sed plura, eaq; maxima ex parte in corniculi modũ recurua. Verum tempore floreſcentiæ ipsius anno illo copiosæ erant pluuiæ & postea succedebat calor solis feruidior. Porro si quis singula velit ad amussim examinare, facilime differentia maioris & minoris esset reperiri, solummodo discrimir ein spica vel longiore vel breuiori constituto.

FIG. 2.—Second mention of Ergot, by Thalius.

Hercynia, a description of plants growing in the Harz Mountains, and one of the earliest of good local floras. The first edition of this work was published somewhere about 1585; I have only seen the second edition [1588] edited by Camerarius, which contains a lengthy reference to ergot, reproduced in Fig. 2.

From this it appears that Thalius had himself observed ergot [in 1575] in a hot summer after a wet spring, optimal conditions for its production. The reference to its obstetric use, in square brackets, was probably added in 1588 by Joachim Camerarius.[1] It is perhaps significant that his edition of the *Sylva Hercynia* appeared at Frankfurt, where also Lonicer's *Kreuterbuch* was published.

The next reference is in Caspar Bauhin's *Phytopinax* [Basle, 1596, p. 50] under the name *Secale luxurians*. He mentions Lonicer and almost quotes Thalius (copiosæ pluviæ . . . calor solis fervidior . . . ad sistendum sanguinem utuntur). A later edition of this work by the author's son, under the title *Theatrum Botanicum* [Basle, 1658, p. 434], has a woodcut (Fig. 3), the first illustration which I have been able to trace. Schwenckfelt [1600] in his list of Silesian plants, mentions: "*Secale luxurians, Mater secalis* (Thal.), *Clavi siliginis* (Lonic.), Rockenmutter, Meelmutter. Ex succi abundantia fortè nascitur. Sanguinem sistere vulgus credit."

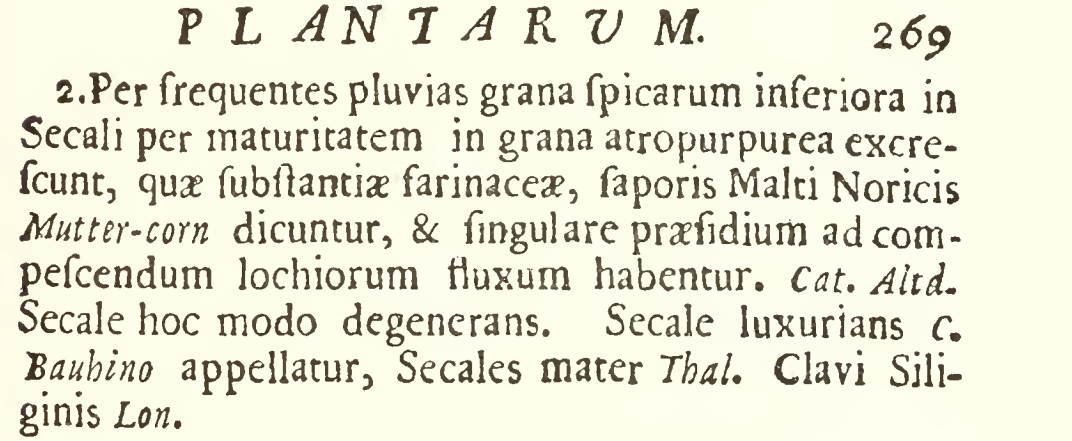
Caspar Bauhin and Schwenckfelt, who evidently knew ergot at first hand, thought it worth while to follow Lonicer and Thalius in mentioning it, but Gerarde's *Herbal* [1597] even when much enlarged by Johnson [1633], and John Parkinson's *Theater of Plantes* [1640] say nothing about ergot, although they discuss rye at some length. Ergot does not appear in an English book until 1677, in the second edition of John Ray's *Catalogus Plantarum Angliæ* (p. 269).

This note is practically identical with one in M. Hoffmann's *Flora Altdorffina* [1662] to which reference is made (Fig. 4, p. 11); it does not occur in Ray's first edition of 1670.

[1] Some modern writers have fallen into a curious error in referring the first mention of the obstetrical use of ergot to a much later date, to a dissertation *De Ustilagine frumenti* [Tübingen 1709] by J. A. Planer, the pupil of quite another Camerarius (Rudolphus Jacobus, famous for his discovery of sex in plants). In this dissertation (p. 13) it is indeed stated: "clavos autem secalis plerique in usum medicum admittunt," but R. J. Camerarius denies the efficacy of ergot. "Errare igitur illas obstetrices oportet, quæ clavos illos exhibent fœminis ægrè parientibus, sub vano fortè prætexte, quod vocantur mater secalis, mutterkorn." Likewise the same Camerarius [1717] in discussing gangrene, wrote: "clavi referuntur ab obstetricibus rockenmütterle, ut oxytocion dantur pauperculis: adeo incertæ et suspectæ sunt muliercularum traditiones!" Evidently this author did not believe in old wives' tales!

FIG. 3.—First illustration of Ergot. (From C. Bauhin's *Theatrum Botanicum*, ed. 1658.)

By a coincidence the first French publication on ergot preceded its first mention in England by one year only. Dodart [1676] reported on a disease of rye (called "ergot" in Sologne and "bled cornu" in Gâtinais) which had already been recognised some years before as the cause of gangrene in those districts. Attention was thus directed to the toxic, instead of to the therapeutic effect of ergot, and Brunner [1695] recognised that it was also the cause of convulsive ergotism in Germany. In the eighteenth century the interest in ergot was therefore almost entirely toxicological. Zorn [1714] in his *Botanologia Medica* indeed still mentions its obstetric use (evidently from Lonicerus), but his contemporary R. J. Camerarius was already



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2. Per frequentes pluvias grana ſpicarum inferiora in Secali per maturitatem in grana atropurpurea excreſcunt, quæ ſubſtantiæ farinaceæ, ſaporis Malti Noricis *Mutter-corn* dicuntur, & ſingulare præſidium ad compeſcendum lochiorum fluxum habentur. *Cat. Altd.* Secale hoc modo degenerans. Secale luxurians *C. Bauhino* appellatur, Secales mater *Thal.* Clavi Siliginis *Lon.*

FIG. 4.—First mention of Ergot in an English book.

derisive (see footnote, p. 10), and the *Materia Medica* of P. J. Bergius [1782] refers only to the causation of convulsions and gangrene. The latter effect led to the more accurate study of ergot by Tessier [1776, iii; 1783] and Tillet [1755] in France, by Ginanni [1759] and Sangiorgio [1772] in Italy; and Münchhausen [1764] in Germany first recognised it as a fungus. (For contemporary views see Béguillet and Rozier.)

Obstetrical use of ergot in the eighteenth century.—Although the learned did not recognise the obstetrical advantages of ergot already mentioned by Lonicerus, Thalius, and others, there is evidence that it was used in the eighteenth century by midwives in France, Germany and Italy. Paulizky reported in 1787 (in *Neues Magazin für Aerzte*) that some thirty years previously powdered ergot had been introduced

into (Marburg?) pharmacies by an empiricist from the Netherlands. It was called *pulvis ad partum* and was not only administered by midwives but also prescribed by a number of physicians. Its action was considered to be more rapid and more powerful than any other similar agent, but it lost its action on keeping. This would seem to be the first recognition of the oxytocic action of ergot in a medical journal. Much later Osiander, in his handbook of Midwifery of 1830, in discussing the new drug ergot, says that it had long been known, particularly in Swabia, and that nearly forty years earlier (therefore about 1790) the use of ergot had been forbidden to the midwives of the Palatinate. Richter states that a similar prohibition was made in Hanover in 1778. Balardini, in reporting early experiments with ergot [1826], mentioned that midwives had used it in Italy for generations.

In 1774 the Parisian apothecary Parmentier published a letter which he had received from a certain Madame Dupille of Chaumont in the Vexin district (35 miles north-west of Paris) stating that she, and her mother, had frequently administered a thimbleful of ergot powder to hasten labour. It was only given in favourable presentations and acted within a quarter of an hour; no ill effects had been observed.

In 1777 Desgranges, a young physician at Lyons, met a midwife who was in the habit of giving a pinch of ergot, ground in a coffee-mill, as decoction. Both the liquid and marc were administered. Desgranges himself used the drug on various occasions, as did some of his colleagues, but he did not publish his observations until much later [1818], after Stearns and Prescott had published theirs, in America. Desgranges already observed that the decoction, given without the marc, was much less active. He gives the dose as 60 to 80 grains and points out the precautions to be taken. He states that in the neighbourhood of Lyons ergot seemed to have been used popularly from time immemorial, and that a dose of 4 oz. boiled with water was given to cows. Desgranges further suspected that ergot (which he called *poudre obstétricale*) was the secret medicament of the Dutch accoucheur Rathlauw [1747], for which the latter claimed that in his experience a second dose had never failed to excite true labour pains, and that he had

thus successfully terminated most difficult labour without instruments.[1]

Introduction into official medicine.—It is thus clear that ergot was used by European midwives in various countries in the eighteenth century. Yet its real entry into official medicine took place in the United States, early in the nineteenth. In the *Medical Repository of New York* there appeared in 1808 an "Account of the *Pulvis parturiens*, a Remedy for quickening Child-birth," in the form of a letter from Dr John Stearns, of Saratoga county, to Mr S. Akerly. "In compliance with your request I herewith transmit you a sample of the *Pulvis parturiens*, which I have been in the habit of using for several years, with the most complete success. It expedites lingering parturition, and saves to the accoucheur a considerable portion of time, without producing any bad effects on the patient. . . . Previous to its exhibition it is of the utmost consequence to ascertain the presentation . . . as the violent and almost incessant action which it induces in the uterus precludes the possibility of *turning*. . . . My method of administering it is either in decoction or in powder. Boil half a drachm of the powder in half a pint of water, and give one-third every twenty minutes till the pain commences. In powder I give from five to ten grains; some patients require larger doses, though I have generally found these sufficient.

"If the dose is large it will produce nausea and vomiting. In most cases you will be surprised with the suddenness of its operation; it is, therefore, necessary to be completely ready before you give the medicine. . . . Since I have adopted the use of this powder I have seldom found a case that detained me more than three hours. Other physicians who have administered it concur with me in the success of its operation. . . ."

[1] Kobert and others mention "Rathlaw" without indicating the source. J. P. Rathlauw practised midwifery in Friesland until 1741, when he moved to Amsterdam. He wrote [1747]: "The notorious secret in midwifery of Rogier Roonhuyzen discovered, and published by authority." In addition to the knowledge of this secret (relating to forceps, and sold by Chamberlen to certain Dutch accoucheurs) Rathlauw claimed to have an unknown drug (ergot?). During his extensive travels he attempted to sell the secret and visited Paris, where he doubtless made the acquaintance of Levret, who in 1751 accurately quoted (in translation) the title of Rathlauw's publication, but misspelt his name. Evidently Desgranges and later writers did not know the original source.

"It is a vegetable, and appears to be a spurious growth of rye. On examining a granary where rye is stored, you will be able to procure a sufficient quantity from among that grain. Rye which grows in low, wet ground yields it in greatest abundance."

Stearns enjoyed the esteem of his colleagues who in 1808 elected him secretary of the State Medical Society of New York; he settled later in Albany. The recipient of Stearns' letter, Dr Samuel Akerly, was physician to the New York City Dispensary, and in 1809 himself published a letter (on "Ergot or Spurred Rye") addressed to his former teacher, W. P. Dewees of Philadelphia, at that time the largest town in the United States. Akerly remarks that ergot "is known to but few regular practitioners, though it has long been used in Europe and this country by old women and others as a secret. . . . The medicine in question was made known to me by my friend Dr John Stearns . . . pulvis ad partum accelerandum. . . . The prejudice which you observe exists in Europe against the use of the ergot, as being injurious or contemptible for its active qualities, I know to be totally unfounded. I have administered it to more than one hundred parturient patients and I have never given it except in cases that threatened a difficult and lingering labour. . .

"It is much to be regretted that scientific physicians have generally held in contempt every medicine that quacks have been in the habit of administering. When we reflect that accident has given origin to the use of our most active medicines, and that we are indebted to empiricism for a knowledge of their most useful qualities, we certainly should neglect no opportunity of deriving aid to science from this source." (Akerly also mentions that his colleague Beekman had used it in amenorrhœa and that he had heard of a case of abortion.) "I have also been informed that it has long been known in some parts of Connecticut and this State [New York] and really been used by women themselves for this purpose" [of procuring abortion].

Akerly's letter establishes the fact that the popular knowledge of the properties of ergot had spread to America, and in a later publication Stearns mentions that his attention had been directed to the drug by an old woman immigrant from Germany who lived in isolation and was unlikely to have

acquired the knowledge in America. Thus ergot, like digitalis, was introduced into medicine from a popular source in Europe; it was, however, only in the New World that freedom from prejudice secured the recognition of ergot; perhaps the Old World had suffered too much from its poisonous properties.

A great impetus to the use of the drug was supplied four years later by Oliver Prescott, who read a "Dissertation on the natural history and medicinal effects of the *Secale cornutum*, or ergot," at the annual meeting of the Massachusetts Medical Society at Boston, on 2nd June 1813, and published it in that year in pamphlet form. The meeting was more fully attended than any previous meeting and upwards of one hundred members were present. (Boston had then about 35,000 inhabitants.) A copy of this rare pamphlet, in the New York Public Library, has written on it: "This Dissertation was very favourably received by the profession. It was reprinted in Philadelphia and London, and was translated into the French and German languages, and was published in full, so far as relates to the medicinal properties of ergot, in the article Ergot, in the 13th volume of the *French Dictionaire des Sciences Médicales*." It was indeed Prescott's publication which aroused interest among European physicians in the obstetrical use of ergot; its title-page is reproduced on the following page (Fig. 5).

In 1816 Jacob Bigelow, a medical botanist of Boston, published an article "on the Clavus or ergot of rye." Referring to the controversy in Europe, due to the Linnæan name *raphania*, he remarks, that since *Raphanus* was absent from New England "we may, without impropriety, set aside what has been said upon this subject in Europe and attend only to the observations and inquiries into the properties of spurred grain, which has been found in our own country. Since its medicinal qualities began to excite notice, the ergot of rye has been continually observed in various parts of the northern and middle States. Wheat appears to be affected by the same circumstances as rye, and considerable quantities of that grain, brought from Vermont, have been offered for sale at the druggists' stores in Boston. . . . Its character [of the spurred rye] as a medicine is so well established, that a majority of practitioners in Boston, and probably throughout the State, are in the habit of employing it in cases, where a medicine of this sort is indicated."

A

DISSERTATION

ON THE

NATURAL HISTORY

AND

MEDICINAL EFFECTS

OF THE

SECALE CORNUTUM, OR ERGOT.

BY OLIVER PRESCOTT, A. M.

FELLOW OF THE MASSACHUSETTS MEDICAL SOCIETY.

Read at the annual meeting of the Massachusetts Medical Society, June 2, 1813.

BOSTON:

PUBLISHED BY CUMMINGS AND HILLIARD NO. 1, CORNHILL.

Andover.....Printed by Flagg & Gould.

1813.

Bigelow also discusses the contra-indications; the first hint of harm done by the new drug was contained in a note "On the occasional bad effects of Ergot" in the *New England Journal of Medicine and Surgery*, 1813. The same journal, in 1818, in an editorial on Spurred Rye remarks: "This article, the effects of which seem to us as undoubted as those of most other agents in the materia medica, appears to be coming into use in Europe. A late number of the *Continental Medical Repository* states that it has been employed by several practitioners on the continent with unequivocal effect in quickening the uterine efforts and hastening the birth of the child." Again in the same journal there was published a letter by Dr L. Spalding [1818] complaining that the "tea" from a quarter of a pound of ergot was without effect. This led to a controversy with Stearns; the letter is, however, chiefly remarkable for the statement by Spalding, that when a boy he heard from the farmers that ergot would "make the mare slink her foal and the cow her calf." He had also "seen the farmer when winnowing his rye, drive the mares and cows from this refuse part of his grain." Evidently the effect of ergot on cattle was known in the United States as it was in France (Desgranges).

This same year [1818] saw indeed the first publications by European physicians on the subject, notably that by Desgranges, referred to above, who related his experiences with ergot since 1777. Partly owing to his influence, the drug was introduced in France more rapidly than in other European countries, and in 1827 Villeneuve, in his valuable account of the use of ergot in hastening labour, could quote 91 publications on the subject, of which number 58 were French, 15 were American and only 4 were British. The first of the latter is in a book by Merriman [1820], who could not get ergot in Britain and used a supply from America. Villeneuve collected in a statistical table all the published clinical results which had come to his knowledge. By 1827 forty authors had reported on 720 cases; of these 200 were due to Stearns, 200 to Chapman and Dewees of Philadelphia and 57 to Prescott; thus the American material constituted nearly two-thirds of the total. Of these only Prescott recorded cases in which the ergot failed to act. Yet in France Madame Lachapelle could not confirm the ancient experience of less highly trained midwives; in her *Pratique des accouchemens* [1825] she recorded 52 failures in 54 trials!

Fortunately her countrymen Desgranges, Bordot [1826], Chevreul and Goupil were more successful, as were Davies and Clark in England.[1] Yet in 1832 a punning sceptic wrote in a Parisian medical journal: "même les . . . écrits des *ergotistes* n'avaient rien moins que contribué à faire de moi un apôtre de leur prétendu remède obstétrical et hémostatique." (*ergoter* = to argue falsely, from *ergo*). The accidents (résultats facheux) numbered only 12 in the total of 720. In 1822 Hosack, however, already wrote that since the introduction of ergot the number of still-born children had increased so much, that the medical society of New York had instituted an inquiry. "The ergot has been called . . . *pulvis ad partum*; as it regards the child, it may with almost equal truth be denominated the *pulvis ad mortem*." Hosack, however, approved of its use to stop post-partum hæmorrhage, to which ergot was later almost entirely restricted.

The first mention of ergot in a textbook of materia medica seems to have been due to Chapman [1817] of Philadelphia. Dewees of the same city, in his *Compendious System of Midwifery*, in 1825, suggested its use to assist the delivery of the placenta, and in his edition of 1832 wrote that it "has obtained throughout this country, as well as in Europe, a high reputation."

Villeneuve's work was largely utilised and condensed by Adam Neale [1828] in what appears to be the only British book entirely devoted to ergot. Indicating the rarity of the drug at that time, Neale mentions two commercial sources of supply in London; his historical data are scanty and inaccurate. In the same year [1828] there also appeared a book on difficult parturition and the use of ergot by Michell, a Cornish physician, who stated that the drug was then only obtainable in one pharmacy of his county. Michell was extremely enthusiastic about the new drug and published 31 cases. "I am of opinion that as soon as it is generally known in female

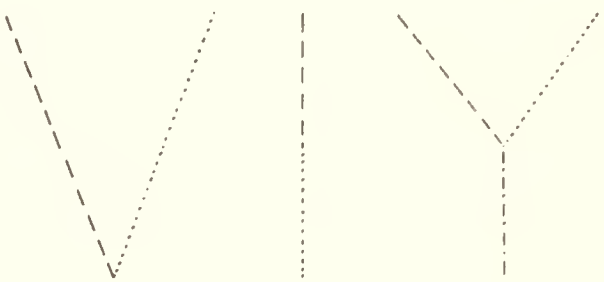
[1] Davies had been an army surgeon in America "during the late war" [1812-1814?]; "frequent mention was made by the American practitioners of the effects of ergot." After his return to England he procured some from New York, and after Merriman, was the next in England to report on its effects [1825]. Clark, a Bristol surgeon, did likewise in 1826. In the *Lancet* of 1827 and 1828 there are notes on single trials by various practitioners; in 1828 two books on the subject were published in London (see below).

practice, it will supersede the necessity for male practitioners, except in a very few cases." Had the action of ergot been known earlier, lever and forceps would never have been invented; its benefits were not more generally acknowledged, because its use would bring about a falling off of fees! The therapeutic history of ergot is fully dealt with by Galama [1834] and by Bayle [1835]. The United States Pharmacopœia was quite fittingly the first official publication to admit ergot, which was included in the original edition [1820] among "such substances, as were deemed of secondary or doubtful efficiency"; to this day the U.S.P. leads in the quality of its fluid extract of ergot. On the other hand, the drug was only admitted to the Pharmacopœia of the London College of Physicians in 1836. The French Codex of 1839 required ergot to be kept in all pharmacies, and Jourdan in his *Pharmacopée universelle* [1840] mentions that, besides being official in America, England and France, it had been included in the pharmacopœias of Schleswig-Holstein [Kiel 1831], Turin [1833] and Greece [1837]. From the date of Stearns' first publication [1808] it took about thirty years for ergot to become thoroughly established in Europe. Its introduction into scientific medicine led to prize dissertations, to a crop of academic theses, often of little value, and to Bonjean's ergotine [1842]. Of the prize dissertations that by Wiggers [1831] is chiefly chemical, that by Diez [1832] chiefly pharmacological; that by Galama [1834] is a remarkably full compilation of the literature on ergot and ergotism, with over 400 references often at second hand; this book is hardly ever mentioned, perhaps because it is in Dutch, and scarce. In 1845 Bonjean published a monograph on ergot, which is chiefly valuable on account of his own observations and experiments; his references are scanty and not always accurate. Other compilations of this time are by Ritter [1841] and by Parola [1844], by Arnal [1849] and by Millet [1854].

CHAPTER II

ERGOTISM

Relation between the two types.—It is a coincidence that the earliest detailed descriptions of ergotism appeared within a few years of the first unmistakable references to ergot itself, towards the close of the sixteenth century, at a time when the connection between the two had not yet been recognised. Before that we have only very doubtful references by Greek and Roman authors, to what may or may not have been ergot and its effects (p. 41), and the brief but unmistakable references to severe epidemics of ergotism, in the chronicles of the Middle Ages (p. 43). The vast literature of modern times clearly shows the existence of two distinct types of ergot poisoning, the convulsive and the gangrenous, respectively east and west of the Rhine. Many authors have regarded these varieties as two distinct diseases. If we represent symptoms of gangrenous ergotism by dashes and those of the convulsive type by dots, this view may be represented diagrammatically by the letter **V**; the two diseases have merely a common starting point in ergot.



Others again have not sufficiently insisted on the difference between the two types, for instance, in treating of them in a common chronological account (Ehlers, Heusinger). It has even been suggested that a gangrenous epidemic is merely the severe outcome of a convulsive one, badly observed. Such

a view is represented above by the letter I. It also is far from satisfactory; there are records of carefully observed epidemics [*e.g.* that of 1709 near Lucerne] in which the convulsive symptoms were very much in the background, in any case by no means so severe or characteristic as in German epidemics. In the latter formication was very common, not so in the gangrenous type. Cataract and severe mental derangements were entirely limited to the convulsive type. If gangrenous ergotism were merely a severer form of the convulsive variety, mixed epidemics should have been much more common, whereas they were almost restricted to a geographical border land. Hence we will here adopt an intermediate position (Y); the two varieties have a common cause and share a number of milder symptoms in their earlier stages: on these are superimposed, on the one hand gangrene, on the other severe nervous symptoms. Frank [1821] regarded the gangrenous form as the acute, and convulsive ergotism as the chronic variety of the same disease. Yet in particularly severe cases there were no premonitory signs and either gangrene or convulsions were the first symptoms of the disease. As is pointed out by Desnos in the article "Ergotisme" in the *Nouveau Dictionnaire de médecine et de chirurgie pratiques* [1870], the descriptions of gangrenous ergotism are apt to be by surgeons called upon to treat only the severest and most advanced cases when brought into hospital (in the eighteenth century at Orleans, in the nineteenth at Lyons, by Janson and Barrier). These surgeons did not themselves observe the minor symptoms preceding gangrene and either passed them over in silence or were dependent on hearsay. Where, on the other hand, we have descriptions by physicians who treated an epidemic on the spot [Lang 1717; Boucher 1749; Courhaut 1814 and 1816] we find mention of lassitude, formication, præcordial anguish, livid colour of the skin, painful contractures and even convulsions, symptoms constantly mentioned in the German accounts. Other symptoms common to both types are vomiting, a feeling of intense heat or cold, pain in the muscles of the calf, the yellow colour of the face, the formation of vesicles on the hands and feet (due to trophic disturbance of a nervous kind, as in herpes zoster?), severe diarrhœa (often a precursor of death) and some impairment of mental function. Desnos seems to regard convulsive ergotism as the earlier stage

of the disease, which, in the severest cases, may be continued to the production of gangrene (letter I of diagram). This view is not satisfactory, however. The severer symptoms of convulsive ergotism, unaccompanied by gangrene, are so pronounced and characteristic that they could not have escaped the notice of laymen, witness the large number of popular German names for the disease. Yet there is no mention of them in the French accounts, and it has long been a problem why the severer manifestations of the same poison should be so different in the two countries. Attempts have been made to explain the diversity by assuming a difference in chemical composition of the ergot.

Kobert distinguished two active principles; one (sphacelinic acid) was supposed to cause gangrene, the other (cornutine) was considered to be the cause of convulsions; he further assumed that French ergot was richer in the former and German in the latter principle; there might even be two races of ergot. More precise investigation showed, however, that both Kobert's principles are impure forms of the alkaloid ergotoxine, and that with the latter gangrene can be produced in animals.[1] Gangrenous ergotism must therefore result from poisoning by a specific alkaloid. If an additional factor is to be invoked, to differentiate the two forms, it must be in convulsive ergotism. The case of the gangrenous form is relatively simple: it appeared on a large scale in the Middle Ages, it remained for some centuries common in particular districts of France, where it was almost endemic. The problem of convulsive ergotism is more complicated; the disease was at one time rarer than the gangrenous type, local in each epidemic, appearing in fitful fashion in many parts of Central Europe, and persisting till a much later date. The French disease was recognised in the Middle Ages as "holy fire" and was known continuously to French physicians from the seventeenth century onwards, since when its cause was never called into question. In Germany the disease was at first generally described as "unusual," "unheard of," and "unknown";

[1] Yet Tschirch writes in his *Handbuch der Pharmakognosie* (vol. iii., 1923): "Als Erzeuger des convulsiven Ergotismus wird das sehr giftige Alkaloid Cornutin betrachtet; als Träger der Gangränwirkung d.h. als Erzeuger der Kriebelkrankheit (sic), des Ergotismus gangraenosus, gilt (*sic*) besonders die Sphacelinsäure und das Ergotoxin."

it occurred locally, at long intervals, often on a restricted scale, and until late in the eighteenth century its causation by ergot was in dispute. This would indicate that in addition to ergot a second factor was involved, already surmised by one or two of the older observers.

Deficiency of vitamin-A—a probable factor in convulsive ergotism.—It seems from the work of E. Mellanby [1930]

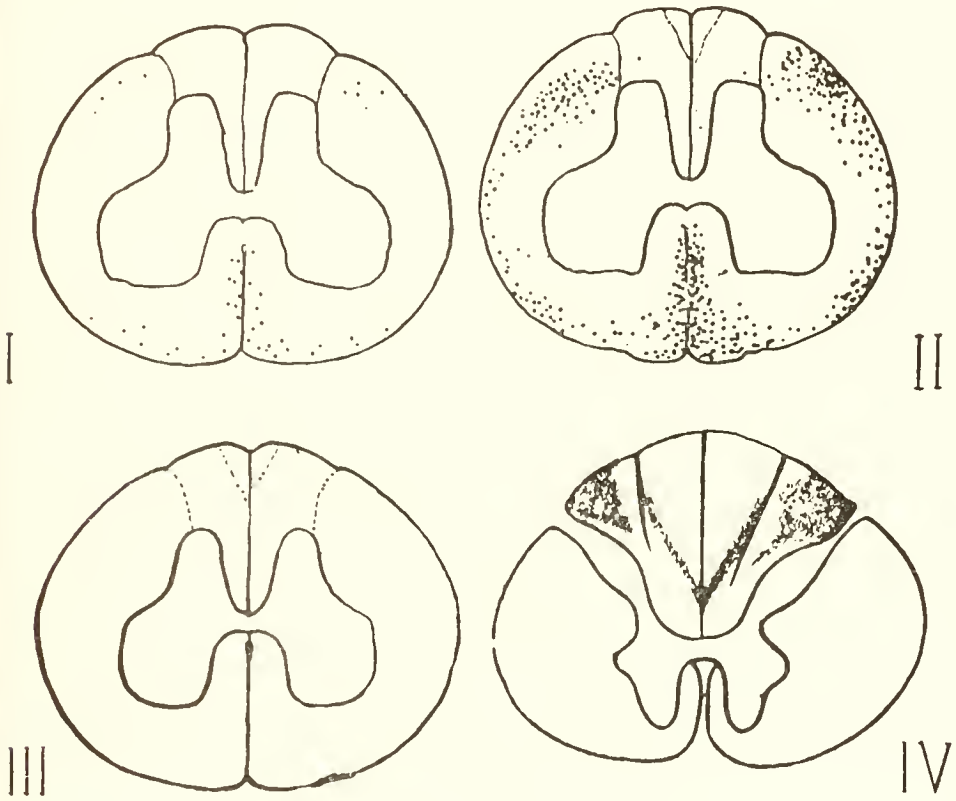


FIG. 6.—Lesions of the Spinal Cord.

The degenerated tracts are shaded; all sections are from the middle cervical region; the posterior side of the cord is uppermost. I. Dog on a basal diet deficient in Vitamin-A; II. Dog on basal diet + 2 to 3 grams of ergot per day; III. Dog on basal diet + 2 to 3 grams of ergot per day + Vitamin-A (mammalian liver oil); IV. Convulsive ergotism in man. I.-III. after E. Mellanby (private communication); IV. after Tuczek [1882]. The degenerated areas in man and in the dog are not identical.

that this other factor is a deficiency of vitamin-A. He finds that in dogs, deprived of this vitamin, ergot and to a lesser extent wheat germs, produce lesions in the spinal cord (Fig. 6) which may occasion the symptoms of convulsive ergotism in man. The constituent of ergot which brings this about is unknown; it is not the alkaloid, but probably a simpler substance. A deficiency of vitamin-A is liable to occur in the diet of institutions, which would explain the repeated outbreaks

of convulsive ergotism in orphanages; Heidelberg [1589? Brendelius], Turin [1789] and Milan [1795, Moscati], Braunsdorf in Saxony [1832], as well as in prisons: Treves [1801], New York [1825] (these three quoted from Hirsch), and in Belgium [1844, Vleminckx].

In order to support this hypothesis further, it will be necessary to show that the German sufferers from the disease, in comparison with the French, received little vitamin-A, and further to compare the quantities of ergot consumed by both. The chief source of the vitamin to be considered is dairy produce, and with this even the poor peasantry of the Sologne seem to have been well supplied. Tessier who visited this district on account of the prevalent ergotism, states that it was well supplied with cattle [*Sur les bestiaux de la Sologne*, 1776]. The reverse was the case in those German districts which were subject to convulsive ergotism. Wichmann, in describing the state of the country round Celle, in Hanover, after the epidemic of 1770-71, states that the affected districts were barren sandy heaths, to which he applies the lines of Ovid (*Metamorphoses*, viii, 789-791)—

> Triste solum, sterilis, sine fruge, sine arbore tellus :
> Frigus iners illic habitant Pallorque Tremorque
> Et ieiuna Fames.

Apart from buckwheat, honey and *very little milk*, or *none at all*, the sole food of the peasants was rye. Buckwheat grows on poor sandy soils, and according to Tessier, was also cultivated in the Sologne, where it was not harvested until late October or early November. Since the food supplies of the previous year were often exhausted at the time of the rye harvest (late July or early August), the grain which fell out during harvesting (Krümmelkorn in Germany) was milled immediately; it was especially rich in ergot, since the ergot becomes detached more readily than the rye grains. "Since the buckwheat had not yet been harvested, there remained, besides some fruit and vegetables, nothing, absolutely nothing, with which to maintain life, except rye, although the various foods made from it bore different names" (Wichmann). Besides being baked into bread, it was made into dumplings, pancakes, porridge, soup, etc. This almost exclusive use of the new rye explains the sudden outbreaks of ergotism immediately after the harvest. Ignorance and obstinacy played a part, but the main factor was dire

necessity. Ergotism was a disease of the poor peasantry, hence the name Bauernkrankheit, and probably also Schwere-Nothskrankheit. The well-to-do could separate the ergot, but the poor could not afford to waste anything. In the later epidemics the Hanoverian and other German Governments supplied sound corn, but when this gave out, the peasants were again forced to use their own supplies, which resulted in a recrudescence of the disease. The French Government does not seem to have helped in the same way, although the need of the Sologne also was great.

A difference between the Sologne and Hanover was in the supply of dairy produce. As has been said above, there was little or no milk among Wichmann's patients; he further states that honey was used instead of butter. Milk and butter were repeatedly mentioned as remedies against the convulsive disease. Already the Marburg faculty [1597] advised the use of "good fresh eggs and butter" to ward off the disease (eggs are also rich in vitamin-A) and Grüner, in re-editing the Marburg account (*q.v.*), confirms this opinion in a footnote. Friedrich Hoffmann [1734], a celebrated physician of the eighteenth century, wrote "nihil enim certius et efficacius . . . quam opportunus lactis usus." The Royal College of Physicians of Copenhagen, in replying [1772] to the Schleswig-Holstein practitioners (*q.v.*), advised butter and bacon.

Even better evidence than that supplied by these opinions, is contained in an account of a Hanoverian epidemic by A. Hensler, printed by Taube (p. 860). In 1767 the author was called to a family of eight, all of whom were suffering from convulsive ergotism; there was much ergot in the rye from all the fields of the village, yet no other family was attacked. On inquiry, Hensler learned that his patients alone had been deprived of milk and butter, owing to their cows having died; the frugal housewife had not even supplied the small amount of bacon usual during the harvest. This observation is as good as a control experiment. In discussing the causes of ergotism, Hensler states that he never observed the disease in the fens (Marsch), a grazing country, but only on the higher ground (Geest). Here it was much rarer in the fertile districts than on sandy heaths, and in the latter much less common among farmers than among labourers and cottagers. The farmers, especially the "Marschbauer," were amply supplied with meat,

bacon and milk; not so the labourers, who could only buy bad rye from the miller. The epidemic near Lille in 1749 and 1750 was peculiar among French outbreaks for its manifestation of convulsive symptoms; this may have been connected with an epizootic disease of cattle, recorded some years previously.

Finally, it should be mentioned that Taube and Hensler laid great stress on the large numbers of round worms (*Ascaris*) in their patients. They both devoted a separate section to this subject (respectively pp. 131-141 and 874-875 in Taube's book). Mr Clifford Dobell and Dr H. H. Dale have called my attention to a recent paper by Hiraishi, who quite failed to infect young pigs with *Ascaris*, whether from man or from pigs, unless the animals were kept on a diet deficient in vitamin-A, when he succeeded in every case. It is also significant that Professor Mellanby has noted a large number of round worms in his dogs deprived of vitamin-A (private communication).

Amount of ergot required to produce the two types of ergotism.—Although it thus seems likely that the paucity of dairy produce in Germany was a contributory cause of convulsive ergotism, the question remains why gangrene was hardly ever observed there. We might incline towards the assumption that the convulsive type is produced by smaller doses of ergot than the gangrenous, and for this there is some, if not quite conclusive evidence. No precise data are available concerning the proportion of ergot in the Sologne. Noël [*Académie des Sciences*, 1709] mentions one-quarter; Read [2nd edition 1774, p. 82] considered that one-eighth would in the long run produce giddiness, nausea and spasmodic movements, whilst one-third, one-quarter or even less would produce gangrene. Janson states that in 1814 bread baked in Dauphiné and the Department of the Isère contained 33 to 50 per cent. of ergot.

In epidemics of convulsive ergotism the amount was generally less; Wichmann, Heusinger, Spoof, place it as a rule at 10 to 12 per cent. Hussa reported 17, Wagner 20, Lorinser [Silesia 1821] 33 per cent. In Finland, according to Spoof, it was occasionally as high as 33, and as low as 4 or 5 per cent. Griepenkerl [1854-56 in Brunswick] found 3 to 4·5 per cent. by accurate weighing, Siemens [Hessen 1879] mentions 9 per cent. Flinzer [Saxony 1867] records two deaths from convulsive ergotism, after eating bread from grain

containing 6 to 7 per cent. of ergot, during five days. Both patients were 16 years of age; adults survived. In the extensive epidemic of 1879, in Hessen, there was only 2 per cent. of ergot in the rye. By far the most accurate data have been supplied by Bonjean, and relate to sporadic cases of both forms of ergotism. He reported that a family in Haute Savoie consisting of father, mother and seven children ate within three days (16th to 18th November 1843) 18 livres = 8600 grams of bread, containing 14 per cent. of ergot. On the average each member therefore consumed 133 grams of ergot. All suffered from severe convulsions, lasting a month; Bonjean also investigated gangrenous ergotism in a family near Chambéry in November 1844. He calculated that the eight members together consumed 960 grams of ergot in three weeks. A boy of 10 years of age had both legs amputated and died; another child (one of twins) lost one leg; the others were but little affected. Bonjean estimated that the dead child had consumed 125 grams of ergot, much the same amount therefore as that which had produced convulsive ergotism a year previously in another district of Savoy. The juxtaposition of these two cases shows some puzzling features. Although the total amount of ergot was about the same, the daily dose was much greater in the convulsive case, the effect more sudden and more uniform, extending to all the members of the family. The slower intoxication in the other case was not followed by uniformly serious results, since only two children suffered from gangrene. The individual susceptibility to gangrene seems to vary greatly; I have not seen any records of whole families being attacked by it; even in the very severe Wattisham case the father escaped. On the other hand it was common for all the members of a family to be attacked by convulsive ergotism —at first the disease was considered to be infectious—and cases are even on record of whole families dying from it (Scrinc). In convulsive ergotism there were many intermediate stages from mere formication to epileptiform convulsions, in the gangrenous form the symptoms were mild, unless the critical limit was exceeded, when gangrene set in.

Mixed epidemics.—If two factors were necessary to produce convulsive ergotism (avitaminosis and an ergot constituent) it is possible to understand why convulsions hardly occurred in France, but it is not so intelligible why gangrene was not more

frequently superimposed on severe convulsions, for instance in Finland, where the rye seems to have not infrequently contained one-third of ergot. The only records which I have been able to trace of both forms occurring in the same individual are: first that of Brunner [1695] who in the Harz Mountains saw a woman with daily recurrent convulsions, who had previously lost a foot from gangrene, and secondly that of Boucher [1749] who near Lille commonly saw spasmodic contractions of the limbs, which were later followed by gangrene. If we adopt the view, put forward above, that the two forms of ergotism have more in common than is often supposed, these cases are quite intelligible; it is only surprising that they were not more numerous. This also applies to the mixed epidemics which were observed in Lorraine [*e.g.* 1085] and in Russia [1722, 1824 near Dünaburg, 1832, 1863, 1881 near Pultawa; Kobert, Hirsch, Grünfeld].[1] It does not appear that in these the same patients were attacked by both varieties of the disease. Of the Lorraine epidemics, the chronicle states that *some* were twisted by nervous contractions, whilst *others* were consumed by the "holy fire." The Lorraine epidemics occurred on the border-line separating two regions, each having its own type of disease. East of this line the only gangrenous epidemics on record seem to have been one in 1486 near Meissen in Saxony (G. Fabricius) and a small one in 1855-56 near Brünn in Bohemia (Hirsch), together with a few of the many Russian epidemics.[2] West of the border-line typical convulsive ergotism was never recorded.

Effect of ergot from hosts, other than rye, and of other impurities in corn.—The only English cases of gangrenous ergotism [Wattisham 1762] seem to have been due to ergotised wheat. In Sweden ergotised barley (and oats?) apparently caused the disease, rather than rye which was not much cultivated there. The epidemic of 1855-56 in Hessen was attributed by Heusinger not so much to ergot of rye, as to

[1] A perusal of the original descriptions of the 1709 epidemic near Lucerne, and of an outbreak in Belgian prisons in 1844 has convinced me that the former was purely gangrenous, the latter almost purely convulsive and that neither was of the mixed type, as tabulated by Hirsch. Colin writes of the Lucerne outbreak: "Cette épidémie a été considérée, *trop facilement peut être*, comme une épidémie mixte."

[2] Kobert was in error in describing Hussa's sporadic cases [Bohemia 1856] as gangrenous; they were convulsive.

ergot of *Bromus secalinus* (German: Trespe), a wild grass, particularly abundant among the rye in those villages where slovenly agriculture was associated with ergotism. According to Maurizio this weed was so abundant among rye that it was sometimes regarded as arising from the latter by metamorphosis. Griepenkerl devoted a paper to the ergot of "Trespe" in the same epidemic in Brunswick; in 1879 in Hessen some samples of rye contained one-third of this grass seed; it is also mentioned by Scrinc. This plant, *Bromus secalinus*, seems also to have been abundant in Sweden. Wahlberg [1843] found it to constitute one-quarter of a sample of rye and both grasses were heavily ergotised. An epidemic at Leksand in 1813 was due to oats containing 22 per cent. of *Bromus secalinus*. The ergot on the latter grass deserves investigation. The Swedish epidemic of 1765 was attributed by Wåhlin to oats.

The ergot of maize produces neither gangrene nor convulsions, but causes baldness in man, and is hence termed *maïs peladero* in Columbia, according to Roullin. He states that it has a narcotic effect on monkeys and parrots in the fields; mules lose their coat and hoofs and hens lay eggs without shells.

Before ergot was definitely recognised as the cause of the convulsive disease, the latter was attributed to a variety of other impurities in corn. Thus in Sweden Linnæus considered that charlock, *Raphanus Raphanistrum*, was the cause; although there was not the slightest foundation for this, the name *raphania* was at one time used, on the authority of Linnæus, to designate convulsive ergotism. In Germany and elsewhere the darnel (*Lolium temulentum*, zizania, the tares of Scripture?) was considered by some to be the cause of the Kriebelkrankheit and more plausibly, since this grass does indeed contain a narcotic poison. Hussa observed a number of cases of actual poisoning by rye containing 16 to 20 per cent. of darnel seeds; the symptoms were frontal headache, giddiness, rumbling in the ears, gastric pains, twitching of the tongue, difficulty in swallowing and in speech, vomiting, diarrhœa, fatigue, cold sweat, and trembling of the limbs. The patients declared that they felt completely intoxicated. There is here a slight resemblance to some of the symptoms of ergotism, but various observers agree that the effects of *Lolium* poisoning are of

short duration; after a sound sleep Hussa's patients were practically normal next day. Compare also Kircheisen's experiment on himself (p. 77).

Whether the disease in a prison in Lombardy in 1769 which Sangiorgio attributed to corn mixed with "covetta" (a grass = *Cynosurus?*) was in reality due to ergot, as has been supposed by many authors, seems to me doubtful. In any case Sangiorgio makes no mention of ergot.

Description of gangrenous ergotism.—The patient often began by complaining of a general lassitude, vague lumbar pains, or pains in a limb, particularly in the calf. The pulse and appetite remained at first normal; sometimes there was slight vomiting. The intellect was dulled. In the course of a few weeks the part affected (more often a foot than a hand) became somewhat swollen and inflamed, and was attacked by violent burning pains, as if "un fer ardent traversait le membre affecté." Hence the names fire (of St Anthony, St Martial), *mal des ardents*, *arsura*, *ignis sacer*, *feu sacré*, *pestis igniaria*. Other names were: *necrosis ustilaginea* and *convulsio Solonicnsis*. A feeling of intense heat alternated with one of icy cold. Not being able to bear the heat in their beds, the sufferers would seek relief in the open air, and then feel so cold that they immersed their limbs in hot water. Gradually the part affected became numbed; the pains sometimes stopped suddenly. The skin was cold, livid, rimpled, and sometimes covered with red or violet vesicles. Salerne mentions that the skin in general, and particularly of the face, including the white of the eyes, was yellow. Kobert [1884] mentions subcutaneous icterus in fatal attempts to procure abortion with ergot. Later the diseased part became black ("like charcoal," as the chronicles have it), often quite suddenly, and all sensation was lost. The gangrenous part shrank, became mummified and dry; the whole body was emaciated and the gangrene gradually spread upwards; sometimes there was putrefaction (moist gangrene).

In severe cases the course of the disease was much more rapid; with violent pains for twenty-four hours, as the only premonitory sign, gangrene might set in suddenly. The separation of the gangrenous part often took place spontaneously at a joint without pain or loss of blood. It is related that a woman was riding to the hospital on an ass, and was pushed against a shrub; her leg became detached at the knee, without

any bleeding, and she carried it to the hospital in her arms. Amputation was not always favoured by the surgeons, who often preferred to leave the separation to nature. In bleeding their patients they found it difficult to obtain a satisfactory flow of blood.

The extent of the gangrene varied from the mere shedding of nails, and the loss of fingers or toes (see Fig. 7), to that of whole limbs. It is related in the *Histoire de l'Académie* [see *Académie des Sciences*, 1710, p. 62] that a peasant near Blois lost both legs at the hip, and Boucher (p. 340) mentions a woman in whom both legs were attacked after both arms had been amputated; the loss of all four limbs is reported by du Hamel [1748]; such patients did not survive for long. After the loss of a single limb the patients often made a good recovery and lived for many years, sometimes being attacked again in a second epidemic. Noël, surgeon of the hospital at Orleans, reported [*Académie des Sciences*, 1710] that in fifty patients he had only seen one gangrenous hand. The much greater susceptibility of the lower limbs is also illustrated by Bones [1762] and others. It is not clear whether one sex was more susceptible than the other, but if there was a difference, it was to the advantage of the female. Noël was surprised that he had not a single adult woman among his patients. It was stated by Dodart [1676] that ergot stops the milk secretion in nursing mothers; this was not the case in convulsive ergotism, but Grünfeld abstracted modern Russian papers on the inhibition of milk secretion by ergot.

Description of convulsive ergotism. — The numerous synonyms for this disease may be arranged under the following heads:—

English: convulsive, spasmodic or nervous ergotism.

German authors of the latter part of the sixteenth and first half of the seventeenth centuries: Scharbock, Schorbock (=scurvy), affectus scorbutico-spasmodicus or scharbockische Kriebelkrankheit [Drawitz 1647], febris maligna cum spasmo (Sennert).

Names referring to the sensus formicationis: Kriebelkrankheit (the most common name), Kriebelsucht, Kribbel-, Krabel-, Gribbel-, Grübelkrankheit. Modern German: kribbeln = to crawl about, to swarm; to itch, to tingle, to prick; compare grübeln = to stir, to rummage. Myrmeciasis (from

the Greek for ant) is used in German dissertations of the nineteenth century.

Names referring to spasms and convulsions: morbus spasmodicus vagus, morbus epidemicus convulsivus, morbus rigidus; Krampfsucht, Krimpfsucht, Krampfseuche; das Kromme, krumme Krankheit, krumme Jammer, Krümmer; das Steiffe, Steifenuss, steiffe Krankheit, Steiffkrampf; ziehende Seuche (= Swedish Dragsjuka), ziehender Krampf, Ziehekrankheit, zusammenziehende Seuche, das Reiszen; Grimmsucht (in allusion to mental symptoms of fury?); Nervenkrankheit.

Names based on ætiology: Kornstaupe, convulsio cerealis, Schwerenotskrankheit, Bauernkrankheit [Holstein 1717], raphania.

Perhaps the best modern description of the symptoms of convulsive ergotism is that by Tuczek (in Penzoldt and Stintzing: *Handbuch der speziellen Therapie*), but we will begin here by quoting the oldest account of the disease in English, from the translation of Sennertus: *De Febribus* [*Of Agues and Fevers*, 1658].

"It seized upon men with a twitching and kind of benummedness in the hands and feet, sometimes on one side, sometimes on the other, and sometimes on both: Hence a Convulsion invaded men on a sudden when they were about their daylie employments, and first the fingers and toes were troubled, which Convulsion afterwards came to the arms, knees, shoulders, hips, and indeed the whole body, until the sick would lie down, and roul up their bodies round like a Ball, or else stretch out themselves straight at length: Terrible pains accompanied this evil, and great clamours and scrietchings did the sick make; some vomited when it first took them. This disease sometimes continued some days or weeks in the limbs, before it seized on the head, although fitting medicines were administered; which if they were neglected, the head was then presently troubled, and some had Epilepsies, after which fits some lay as it were dead six or eight hours, others were troubled with drowsiness, others with giddiness, which continued till the fourth day, and beyond with some, which either blindness or deafness ensued, or the Palsie: When the fit left them, men were exceeding hungry contrary to nature; afterwards for the most part a looseness followed, and in the most, the hands and feet swell'd or broke out with swellings full of waterish humours,

but sweat never ensued. This disease was infectious, and the infection would continue in the body being taken once, six, seven, or twelve moneths.

"This disease had its original from pestilential thin humours first invading the brain and all the nerves; but those malignant humours proceeded from bad diet when there was scarcity of provision.

"This disease was grievous, dangerous and hard to be cured, for such as were stricken with an Epilepsie, were scarce totally cured at all, but at intervals would have some fits, and such as were troubled with deliriums, became stupid. Others every yeer in the month of December and January, would be troubled with it."

This description by Sennertus closely follows the well-known account by the Marburg medical faculty [1597]. It applies to severe cases only. Later authors (Wichmann, Hecker) have distinguished a milder form, which might pass off in a few weeks without preventing the patients from following their ordinary occupations. It was characterised by a feeling of fatigue, heaviness in the head and limbs, giddiness, pressure and pain in the chest. This was sometimes accompanied by mild diarrhœa, with or without vomiting, and lasting for several weeks. A very common, early symptom, often persisting throughout the disease, was "the kind of benummedness" in the hands and feet, and a tingling sensation "as if ants were running about under the skin," hence formication. (Hussa's description speaks of mice, instead of ants.) In well-marked epidemics this sensation of "pins and needles" is said to have been experienced by all the inhabitants of a village. It gave the most common German name to the disease: Kriebelkrankheit.

Waldtschmiedt and Wichmann state that (in the later stages) formication can be seen objectively as due to twitching of small muscle-fibres, or even of entire muscles (*orbicularis oris*). The *sensus formicationis* was most common in the fingers, but sometimes extended over the arms and the whole body, and became most painful when it affected the tongue, These common milder symptoms did not greatly attract the attention of the earlier physicians, and often passed off; they might, however, be followed after a few weeks by more pronounced nervous symptoms, convulsive clonic muscular

twitchings (von Leyden) and tonic spasms of the limbs. Often the thighs were drawn forwards, the leg below the knee bent backwards, the feet again forwards, the toes backwards. Similarly the arms were strongly flexed, with the fingers bent to a fist, or giving to the hand the characteristic appearance of an eagle's beak (von Leyden; see Fig. 8, after Heusinger, reproduced in Kobert's *Lehrbuch der Intoxicationen*). Several of the older accounts emphasise the force of these contractions: often a strong man could not extend the limbs, yet their extension gave some measure of relief to the sufferers, who often begged for this service to be performed. The flexure was sometimes so extreme that it interfered with the circulation and made the lower part of the limb purple. The patients were apt to complain of an icy cold, and also of burning heat. When a spasm was confined to the fingers the patients, unable to work, would walk about until their feet became affected in the same manner. The spasms might begin in the toes and then gradually extend upwards. Apart from the limbs, other groups of muscles might also be affected (see Figs. 9 and 10), resulting in spasms of the face, the vocal cords, the œsophagus (simulating hydrophobia) and the diaphragm. In severe cases the tongue was often lacerated and occasionally bitten off (Taube, Rothman, Scrinc, Wagner, Walker). (See Figs. 7-9.)

In severer cases, the whole body was attacked by general convulsions, often so suddenly "that some at table dropped knife or spoon and sank to the floor, and others fell down in the fields while ploughing" (Marburg). These convulsions returned at intervals of a few days, or daily, often at the same hour, most frequently in the forenoon; or even at hourly intervals (Steffens, Wagner). If not confined to bed, the sufferers "tumbled about as if drunk." When the flexor muscles remained the most strongly affected, "the sick would roul up their bodies round like a Ball"; under the more powerful action of the extensors, they were stretched stiff "like a piece of wood" (Marburg) or "like a statue" (Nebel; Taube did not observe this, but Hussa saw violent opisthotonus). These paroxysms lasted from a few minutes to several hours and were extremely painful. The loud cries of the sufferers are often referred to in a graphic manner. A cold sweat covered the whole body and the spasm of the abdominal muscles caused violent retching. Occasionally the disease first

showed itself by convulsions, two or three days after eating the poisonous bread. Hussa described a particularly severe attack in a boy who had not eaten bread for six months and then consumed a large quantity containing 17 per cent. of ergot. Two days later he was seized by violent convulsions.

In the intervals between the convulsions many patients suffered little discomfort and clamoured for food; there would be an alarm in a village one day, and on the next the patient might be working in the fields. Ravenous hunger was a most characteristic symptom in severe cases, but "digestion did not keep pace with this excitation of the abdominal nerves" (Hirsch). Taube (p. 110) gives somes remarkable examples of this voracious appetite. After finishing a meal, with which they declared themselves satisfied, two of his patients each consumed 3 lbs. of bread within seven minutes, in Taube's presence. He also reports the eating of garments and a case of scatophagy by a demented patient. Dr H. H. Dale has suggested to me that the severe hunger was the result of hypoglycæmia due to ergotoxine poisoning (see p. 160), and intensified by the disappearance of glycogen from the muscles during convulsions. (Hunger commonly occurs after a somewhat high dose of insulin.) Taube and Hensler considered that the convulsive attacks were aggravated by the enormous number of round worms (*Ascaris*) frequently infesting their patients, and observed improvement when these had been eliminated by vermifuges. Taube considered the possibility that the growth of these worms might be favoured by the great production of mucilage in the intestine. Their abundance was, however, more probably the result of shortage of vitamin-A (see p. 26).

Several descriptions mention severe insomnia. In extreme cases the patients would lie for six or eight hours as if dead; in the 1597 epidemic some narrowly escaped being buried alive (Marburg). In such cases there followed a pronounced anæsthesia of the skin, the lower limbs became paralysed, and the arms subject to violent jerky movements; epileptiform convulsions, delirium, imbecility, and loss of speech were apt to occur in such patients, who became unconscious and generally died on the third day after the onset of the first symptoms.

In severe but non-fatal cases, the disease might last for six to eight weeks, and convalescence took several months. Convalescents apparently remained very sensitive to ergot, for

Hussa recorded the deaths, due to a single meal of dumplings in February, of two patients who had more or less recovered from an attack in the previous August. Relapses were frequent (see for instance the enumeration of 39 deaths in a single village during the five years following the epidemic, Taube pp. 810-812). These relapses were accompanied by epilepsy, hemiplegia and paraplegia (von Leyden). Among the after-effects of a severe attack may be mentioned: general weakness, trembling of the limbs, gastric pains, chronic giddiness, permanent contractures of the hands and feet, anæsthesia of fingers and toes, impairment of hearing and of sight, and various mental derangements. In illustration of the anæsthesia of the fingers, Taube relates the case of a woman who while sewing, perforated her finger without knowing it; others picked up red-hot charcoal. The effect on the eyes consisted in an enlarged pupil, amblyopia, the seeing of small objects double, more rarely cataract, glaucoma and degeneration of the optic nerve. Cataract developed several months after the beginning of the disease. Taube describes a number of cases; Meier [1862] and Orlow [1905], both ophthalmologists, devoted special papers to the subject. Bechterew observed 7 cases of nystagmus and 8 of cataract among 89 patients; one-quarter had impaired vision. Orlow states that the cataract results from defective nutrition, due to a specific change in the epithelial lining of the ciliary body and of the posterior surface of the iris (*cf.* Peters). The functional troubles in the retina are not due to vaso-constriction, but to the direct action of the poison. The effects on the mind consisted of dullness and stupidity, even in less severe cases (this also in the gangrenous type); the more general disturbance in severe cases was dementia. ("The patient did not give sensible answers to questions.") Rarely maniacal excitement was the result; some of Taube's patients were secured by chains. Siemens relates that 11 victims of ergotism were received in an asylum in 1880. Tuczek [1882, 1887] and Walker [1893] report conversations with patients, and describe histologically the permanent injury to the posterior columns of the spinal cord (shaded in Fig. 6, IV.). The knee-jerk is abolished in all moderately severe cases within a few weeks of the onset of the disease, and is only restored in a few after the lapse of years. Walker describes patients who suffered from ergotism

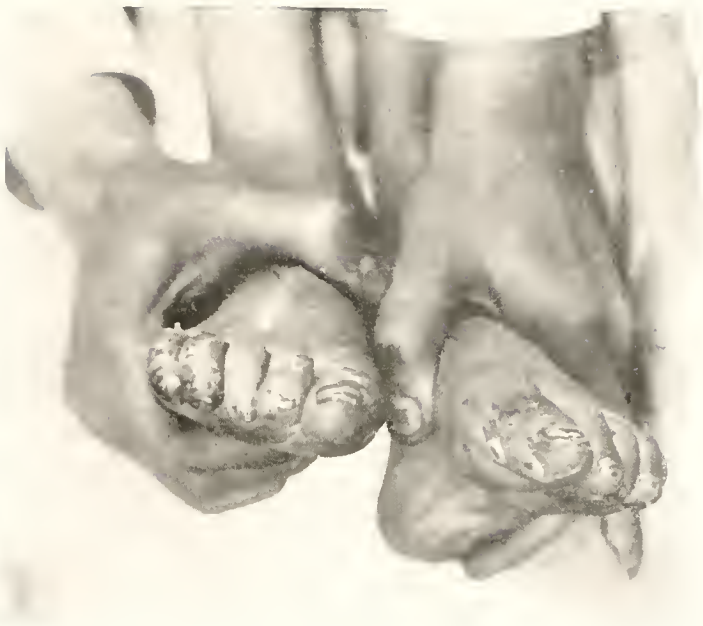


FIG. 7.—Gangrenous Ergotism, Hungary, early 20th century. (Observed by Dr K. Chyzer. From a photograph lent by Prof. G. Mansfeld, Pécs.)

FIG. 8.—Convulsive Ergotism. (Heusinger, 1850.)

in early childhood and remained normal, or were at most intellectually backward, until the onset of puberty, when epileptic convulsions, dementia, and after some years death supervened. Minor nervous defects, spasms and a dull intellect may persist for a long time in the adult, and serious relapses occurred years after the first attack. In one patient formication recurred annually in March for twelve years. Kolossow [1914] found mental disturbances in 27 per cent. of his patients (in Russia). Psychoses due to ergot have been especially studied by Gurewitsch [1911] and von Bechterew [1892]. A graphic early description of a patient with delusional insanity, seven months after the harvest, was already given by Hoffmeyer [1742]; the constant movements of the hands and feet were only interrupted by tetanic convulsions.

The "looseness," mentioned in the English description quoted above, followed frequently, but not invariably, after severe convulsions; this severe diarrhœa often persisted for months and was apt to prove fatal; it also preceded death in gangrenous ergotism. The "swellings full of waterish humours" were rare in the German epidemic of 1770. They were, however, commonly observed by the Marburg physicians and by Scrinc. Boucher [1749, near Lille] described them as precursors of gangrene; but in the purely convulsive ergotism true gangrene was never seen; Taube emphasises this, and figures the cast-off skin of fingers and toes in a single curious case, doubtless the result of trophic disturbance. The shedding of the epidermis of the trunk was also observed by Hussa, of nails by Heusinger (both in convulsive ergotism).

The belief that the disease was infectious is already contained in the title of the Marburg account, and was maintained for a long time; it no doubt orginated in the circumstance that all members of a family, living on the same diet, were often taken ill at the same time. Hoffmann's statement that relapses were most frequent in December and January, as were fresh cases, is amply confirmed by Taube.

Whatever may have happened in gangrenous ergotism, there is no evidence that the chronic convulsive type ever produced abortion (Wagner); in spite of the special attention paid by Taube to this point, he was unable to find any influence of the disease on the course of pregnancy. The same is found in almost all attempts to procure abortion (see p. 179 and p. 229).

Several of Taube's patients bore living children at term, after months of convulsions and dementia (compare also Menche). In these cases the children soon died from convulsions; the poison had evidently been communicated to the fœtus. On the other hand, the disease was never communicated to breast-fed infants; quite a number of cases have been recorded where all the other members of a family were attacked (Rosenblad mentions a case in which they all died, except an infant); the disease developed as soon as the child was weaned, and during the epidemic Taube advised mothers to continue the nursing of their children as long as possible. The secretion of milk was not affected either; cases are on record of a child having been suckled by its mother shortly before the latter's death from severest convulsions. Here there seems to be a distinct difference from gangrenous ergotism [this point is discussed by Krohl, 1894]. Dodart already remarked that ergot may stop the secretion of milk, an effect which has been confirmed by Janson clinically and especially by modern Russian authors, who also showed it experimentally in bitches (Grünfeld). Both forms of ergotism produce amenorrhœa (Lentin, Janson, etc.). Most information regarding the *post-mortem* findings in acute ergotism is to be obtained from modern attempts to procure abortion (see p. 230). The examination in chronic convulsive ergotism does not seem to have revealed any significant changes, except lesions in the posterior horns of the spinal cord [Vleminckx 1846; Tuczek 1887; Walker 1893] and bleeding and softening in the brain [Bechterew 1892]. Taube and others state that putrefaction sets in very rapidly. In chronic cases the patients usually suffer from defective nutrition and become emaciated. (See Fig. 9.) In order to give an idea of the mortality, I quote what I believe to be some of the most significant statistics:—

	Cases.	Deaths.	Per cent.	Authority.
Bohemia, 1736-37 . .	500	100	20	Serine
Hanover, 1770-71 . .	600	97	16·2	Taube
Finland, 1840 41 . . .	1800	220	12·2	Haartmann
Hessen, 1855-56 . . .	102	19	18·6	Jahrmærker
Siebenbürgen, 1857 . .	283	98	34·6	Meier
Finland, 1862-63 . . .	1429	...	about 10	Spoof
Hessen, 1879-81 . . .	500	...	„ 5	Menche

Brückmann [1741, Brandenburg] gives 26·7 per cent.; von Leyden [1867-68, East Prussia] 6 to 9 per cent.; Grünfeld (Russia, nineteenth century) 11 to 66 per cent.; Poehl [Russia, 1832, 1837] 25 to 55 per cent. Apart from these latter figures, the mortality is thus seen to be generally between 10 and 20 per cent. The high percentage given by Meier is probably due to the fact that he, as an ophthalmologist, failed to include a number of milder cases. For the same reason Brückmann's and many Russian figures may be too high. Taube on the other hand personally treated very nearly all the six hundred cases in the district under his charge.

All accounts of convulsive ergotism agree that children were more liable to convulsive ergotism than adults; thus 56 per cent. in the Finnish epidemic of 1862 were under 10 years of age; 60 per cent. of Scrinc's cases were under 15 years of age; the mortality of children under 10 years of age in the Hessen epidemic of 1855-56 was about 50 per cent. Hoffmann stated that females were more liable to the disease than males, and this seems to have been true in some epidemics; on the other hand, Taube and Spoof reported a preponderance of males (60 per cent.) so that there seems to be no definite influence of sex (this is also Wagner's view).

Bibliography of the history of ergotism.—The first histories are due to physicians who observed the last great epidemics of the eighteenth century. Read [1771] gave a sketch of the gangrenous variety and identified it with the St Anthony's fire of the Middle Ages, as Sauvages first did three years earlier in his *Nosologia Methodica*. De Jussieu, Paulet, Saillant and Tessier [1776] published a much more comprehensive history of this disease, with quotations from the chronicles, and Saillant at the same time contributed a (less detailed) account of convulsive ergotism, which he recognised as a separate disease. The history of the latter was treated very fully by Taube [1782], and Baldinger [1793] contributed its first accurate bibliography. Later writers on the history of ergotism did not have similar opportunities of observing an epidemic themselves. Thus in the epidemiologies of Foderé, Ozanam and Schnurrer [all three published about 1823] there is considerable mention of ergotism, but also some confusion. Ozanam, for instance, has a chapter on ergot, *convulsio cerealis*, *ustilago*, *raphania*, *mal de Sologne*, and one on *feu sacré*, *feu de St Antoine*, *mal des ardens*, *feu*

persique. Thus he did not recognise the identity of the modern disease of the Sologne with the holy fire of the Middle Ages, as his countrymen had already done half a century earlier. The true nature of *ignis sacer* was, however, elucidated by Sprengel in a short paper, and particularly by Fuchs in an admirable monograph on gangrenous ergotism [1834]. Fuchs gives most complete references to chronicles and other sources with copious quotations; his enthusiasm has made him include a few epidemics of very doubtful nature. A full description and history, more especially of the convulsive type, was supplied by Hecker [1839]. The brief account by Hirsch, in his handbook of geographical and historical pathology [English translation, 1885], is chiefly of value for its very full chronological table of epidemics, in each case with references to the original authorities. Kobert's historical study [1889] is mainly important for his attempt to show that ergotism occurred among the Ancients, a view not shared by Husemann in Neuburger and Pagel [1903]. Kobert and his pupil Grünfeld have also made information about Russian epidemics available. Ergotism in the first half of the nineteenth century was specially dealt with by Heusinger [1856] who refused to recognise two distinct diseases. Leteurtre's "Documents" [1871] is mostly concerned with the disease in France, and much less accurate than its title would imply.[1] Ehlers [1894] devoted a small book entirely to the history of ergotism. Translated into French, this work is the most readily available comprehensive account; unfortunately the author did not differentiate sufficiently between the two varieties of the disease, and seems to have relied mainly on previous compilations; he has, however, collected some information about early Scandinavian epidemics.

In England and Ireland only sporadic cases of ergotism have become known, and there is no full account of the disease in the English language; the best is that by Christison. Allbutt and Dixon [1906] state that epidemic gangrene = Kriebelkrankheit (!) and have relied almost entirely on Ehlers' book, criticised above.

Supposed references to ergot and ergotism by the Ancients.—Kobert [1889], in a learned article, collected a large

[1] On the other hand, there is a full and careful account of convulsive ergotism under the ætiologically unsound title raphanie, in the *Dictionnaire encyclopédique des sciences médicales* (1874 [iii.], 2, pp. 297-323), by Léon Colin.

number of passages from Greek and Roman authors, referring, as he supposed, to ergot and its effects, but it would seem that he was carried away by enthusiasm for his subject. Husemann (in Neuburger und Pagel, *q.v.*) could not agree that ergot was known to the Greeks and Romans, already for the simple reason that rye was hardly grown round the Mediterranean in classical times (see the section on Rye, chapter I.). This does not indeed dispose of the possibility that other cereals, or even fodder grasses, were occasionally ergotised, but a scrutiny of the passages mentioned by Kobert would seem to leave little doubt that ergot was unknown to classical writers. Passages in Pliny's *Natural History*, and particularly his mention of the Rubigalia (lib. xviii., cap. 69), have often been cited by writers on ergot. This festival was instituted to ward off a disease of corn, which was in all probability not ergot, but rust, as the name would indeed indicate; nor is there anything in Pliny's descriptions of barley, wheat and rye (xviii. 18, 20, 40), which to my mind suggests a reference to ergot. The same applies to the noxious wheat mentioned by Columella (*de re rustica*, ii. 9). Kobert even quotes a passage from Plautus (*Miles Gloriosus*, act ii., scene 3, line 50; mirumst lolio victitare te tam vili tritico), and suggests quite gratuitously that in this case instead of darnel (*lolium*), ergot was meant. Perhaps the least improbable reference to ergot itself is by Galen (2nd century A.D.) in *de alimentorum facultatibus* (lib. i., cap. 37; in Kühn's edition, vol. vi., p. 553, Leipzig, 1823). In discussing seeds which are apt to be present in corn as impurities, Galen mentions a black wheat (μελάμπυρον) which is formed by a change (ἐκ μεταβολῆς) from wheat, but is much less harmful than darnel or tares. It is not clear whether the "black wheat" was formed by an actual transformation of the seed on a wheat plant, or whether it was an entirely different species, assumed to be formed from sown wheat by a kind of mutation, in which classical writers were apt to believe (compare for instance, Columella). That "black wheat" was an entirely different plant is the view of modern writers. But if the wheat grain itself was transformed, the reference might still refer both to smut and to ergot. In the same chapter Galen discusses symptoms due to a heavy contamination of corn with darnel in a year when, owing to scarcity, the farmers and bakers did not clean the corn with the sieves intended for the

purpose; the symptoms (headache, and afterwards ulcers) were not exactly those of ergotism. This passage has been dealt with at length, because it illustrates the difficulties of identifying ergot in classical writings; it also shows that Galen was fully aware of the dangers of poisonous corn, and of the need of cleaning it.

Most of Kobert's passages are not supposed references to ergot itself, but to its effects. He [1899] attempted to show that the plague at Athens in the Peloponnesian War was an epidemic of smallpox in a population suffering from latent ergotism. Thucydides (ii. 47) states that the mortality was highest among the physicians, which points to an infectious disease (plague?). Kobert quoted modern Russian cases in support of his view that intercurrent infections of typhoid, pneumonia, etc., may cause latent ergotism to develop into gangrene. He further assumed that the Athenians lived on ergotised grain imported from what is now Southern Russia, and that the home-grown grain of the Spartans was not ergotised. Kobert's theories have been adversely criticised.

Cæsar, in the *Civil War* (ii. 22) mentions a grave pestilence at the siege of Marseilles, due to poisonous grain, but here there is no mention of the symptoms. The *ignis sacer* of Lucretius (*De Rerum Natura*, vi. 1166) was not ergotism, to which this term was only applied in the later Middle Ages.

Kobert cites a number of isolated references to gangrene and other possible effects of ergot in the writings of Hippocrates, Dioscorides and Galen. Single cases of gangrene may well have been due to other causes. Hippocrates' mentions abortion in certain women after a wet winter and dry spring (favouring the growth of ergot?), and elsewhere he attributes an oxytocic action to barley (assumed by Kobert to be ergotised). The disease, resulting in the loss of hoofs in cattle, mentioned by Aristotle (*Historia Animalium*, viii. 23, 24) was foot-and-mouth disease, according to Aubert and Wimmer (*q.v.*); yet even had it been due to ergotised fodder grass, the main question must be answered in the negative: there is no evidence that ergotised cereals were known to the Greeks and Romans; nor were there outbreaks of ergotism, such as those caused by ergot of rye in the Middle Ages.

According to Schelenz ergot seems to have been used in Chinese midwifery at a very early date. Leclerc considers that

ergot was known to the Moorish physician Avicenna (980-1037); for other references to its supposed use in Arabian medicine, see also Schelenz and a paper by Achundow.

Ergotism in the Middle Ages.—The chronicles of the eleventh and twelfth centuries, particularly in France, mention epidemics of a disease which they call fire, often "holy fire" or *ignis sacer*, and sometimes *arsura*, *clades* or *pestis igniaria*, *feu sacré* or *mal des ardens*. In the thirteenth century this fire became associated with St Anthony and St Martial, and was also known as *ignis Beatæ Virginis*, *invisibilis* or *infernalis*. References to it became rarer and ceased in the fourteenth century, until it was identified in the eighteenth as gangrenous ergotism. The name *ignis sacer* had already been used by ancient writers (*e.g.* Lucretius) for an entirely different disorder, a chronic skin disease or erysipelas, and was also used in the fourteenth and subsequent centuries as a synonym for *ignis persicus* or anthrax. These and various other sources of confusion in the *nomenclature* misled some epidemiologists, until Fuchs [1834] cleared up the matter by basing his inquiry on the *symptoms* mentioned in the chronicles.

He found the earliest reference to ergotism in the *Annales Xantenses* for the year 857. (1) A great plague of swollen blisters consumed the people by a loathsome rot, so that their limbs were loosened and fell off before death.

(1) Plaga magna vesicarum turgentium grassatur in populo et detestabili eos putredine consumpsit, ita ut membra dissoluta ante mortem deciderent (Pertz, ii. 230). These annals are so called because they describe in detail the sack of the church of Xanten, near the lower Rhine, in 863 by the Norsemen. Exactly where and by whom they were written is not known; there is only one copy, discovered in 1827. (See Map, Fig. 15, p. 67.)

The falling-off of limbs is the most characteristic indication of gangrenous ergotism. The gangrene was often dry and not putrefactive; the vesicles are a less prominent symptom. It is stated elsewhere (Bouquet, vii. 71) that the winter of 856-857 was very severe and dry, and that there was a great pestilence.

A plague of "fire" is first mentioned in 945, in and around Paris. Limbs were burnt up and gradually consumed, until death ended the torment. As many as could reach the church of St Mary in Paris were saved, and Duke Hugh fed them with

daily rations. When some of the patients went home, the quenched fire was rekindled, but returning to the church, they again recovered. The duke was Hugh the Great, Count of Paris and father of Hugh Capet, the founder of the royal dynasty. Evidently he had a store of sound grain, and relapses occurred when the patients fell back on their own supplies.

(2) In pago Parisiacensi, necnon etiam per divisos circumquaque pagos, hominum diversa membra ignis plagâ pervaduntur; quæque sensim exusta consumebantur, donec mors tandem finiret supplicia: quorum quidam, nonnulla Sanctorum loca petentes, evasere tormenta. Plures tamen Parisius in Ecclesia sanctæ Dei genetricis Mariæ sanati sunt, adeò ut quotquot illò pervenire poverint, asserantur ab hac peste salvati: quos Hugo quoque Dux stipendiis aluit quotidianis. Horum dum quidam vellent ad propria redire, extincto refervescunt incendio, regressique ad Ecclesiam liberantur. (Chronicle of Flodoard, archivist of Rheims, who was fifty-one when the epidemic took place. Pertz, iii. 393; Bouquet, viii. 199.)

In 994 there was a violent epidemic in Aquitaine and Limousin (see Fig. 11). It is mentioned in half a dozen chronicles one of which (3) states that over 40,000 persons died by this pestilence. (Perhaps the writer confused it with bubonic plague.) After an extremely severe winter there followed a great drought and scarcity (10). The end of the millennium was approaching and when a plague of invisible fire broke out, cutting off limbs from the body and consuming many in a single night (9), the sufferers thronged to the churches and invoked the help of the Saints (8). The cries of those in pain and the shedding of burned up limbs alike excited pity; the stench of rotten flesh was unbearable; many were however cooled by the sprinkling of holy water and snatched from mortal peril (8). The bishops of Aquitaine assembled at Limoges (Lemovica) and the bones of St Martial, a bishop of that town in the third century and patron of Gaul, were shown to the people (3-6). These relics were restored to their grave on 7th December and the pestilence ceased (3). It is evident that the epidemic occurred during several months following the harvest.

(3) . . . plaga ignis super corpora Aquitanorum desævit, et mortui sunt plus 40 millia hominum ab eadem pestilentia. Ideò . . . Episcopi Aquitaniæ adunati Lemovicas, levaverunt corpus S. Martialis Apostoli, et in Montem-gaudii transtulerunt; et exinde pridie Nonas Decembris

FIG. 9.—Fatal case of Convulsive Ergotism, 1909, in Bihar (S.E. Hungary, now Rumania). (Photograph due to Prof. I. v. Magyary-Kossa, Budapest.)

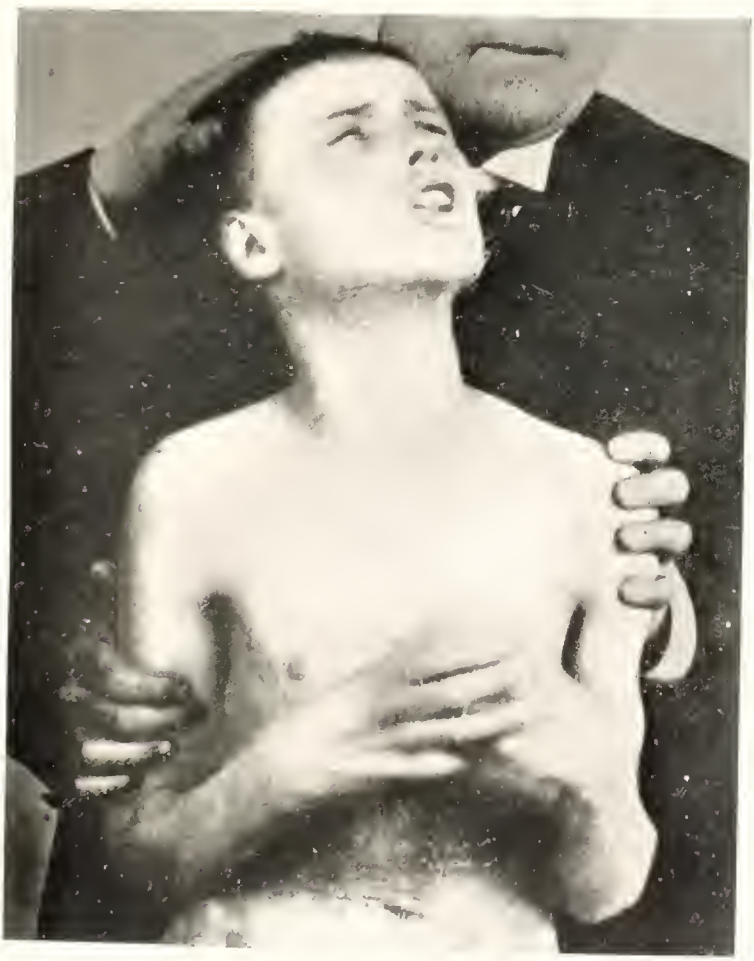


FIG. 10.—Convulsive Ergotism, Hungary, early 20th century. (Observed by Dr K. Chyzer. Photograph due to Prof. G. Mansfeld, Pécs.)

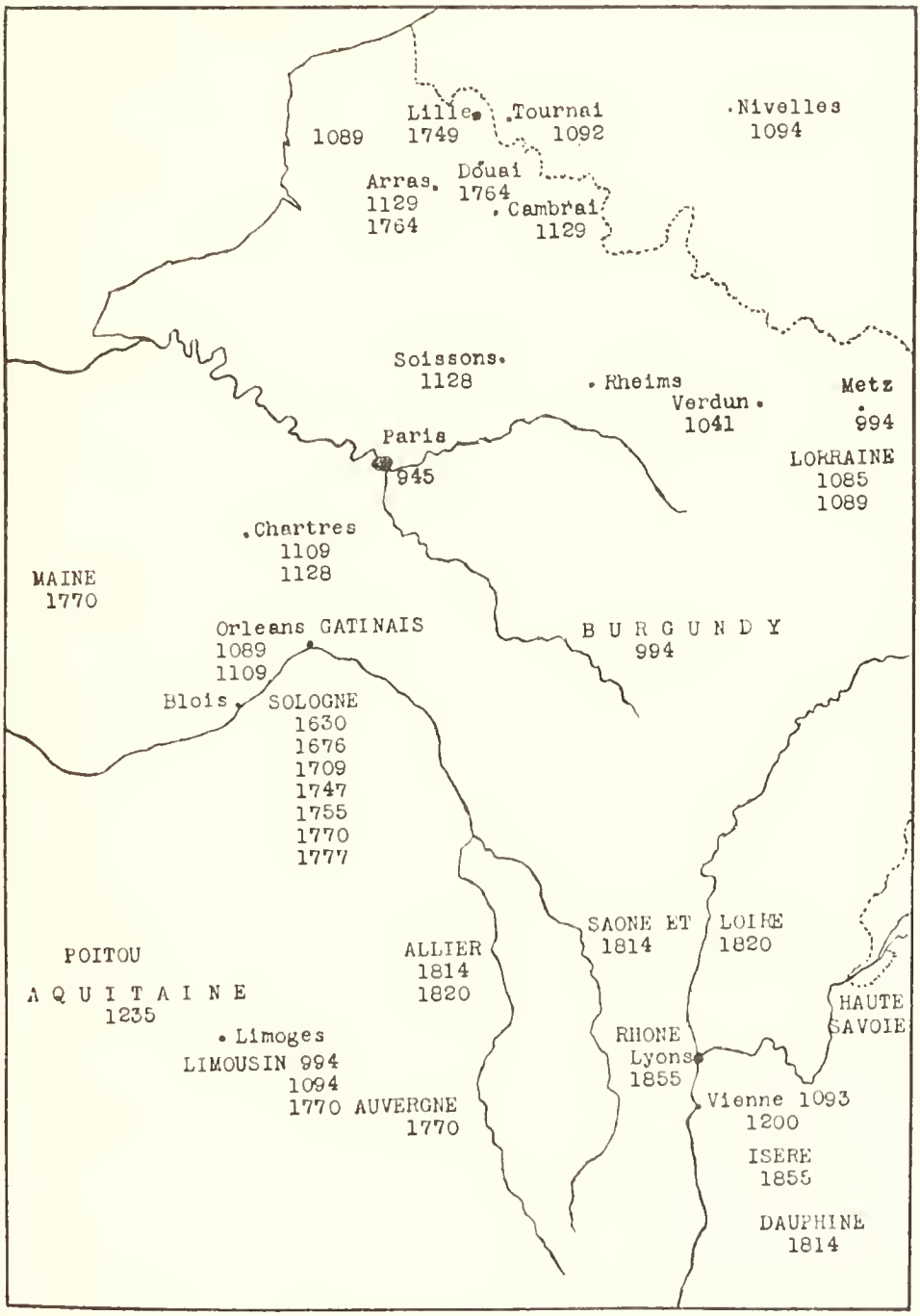


FIG. 11.—Ergotism in France.

tumulo suo restituerunt, et cessavit pestilentia ignis (Commemoratio abbatum S. Martialis, by Adémar de Chabannes, circa 988-1034; Bouquet, x. 318).

(4) His temporibus pestilentiæ ignis super Lemovicinos exarsit: corpora enim virorum et mulierum supra numerum invisibili igne depascebantur; et ubique planctus terram replebat. . . . Tunc omnes Aquitaniæ Episcopi in unum Lemovicæ congregati sunt: corpora quoque et reliquiæ Sanctorum undecumque solemniter advectæ sunt ibi; et corpus S. Martialis Patroni Galliæ de sepulchro sublatum est (chronicle of Adémar de Chabannes, Bouquet, x. 147).

(5) His diebus lues gravissima Lemovicinos devoravit, incendens corpora, et exardescendo devorans, donec omnes Aquitaniæ Episcopi Lemovicæ congregati, corpus B. Martialis ab imo sublatum sepulchro mortalium visibus ostenderunt, et mox pestis ipsa cessavit (Fragmenta Historiæ Aquitaniæ, Bouquet, x. 147 footnote).

(6) Notandum . . . corpus S. Martialis, anno scilicet 994 fuisse cum magna processione in Montem Gaudii-Jovis reverenter deportatum propter gravissimam plagam ignis . . . extinguendam (Gesta Lemovicensium Episcoporum, Bouquet, x. 147 footnote).

(7) Mirum in modum ardenti igne cruciantur et perimuntur Aquitani (MS. Sangerm., Bouquet, x. 318).

(8) Contigit aliquando judicio Dei, quodam carnis incendio multos periclitari mortalium ex populo Christianorum: quorum multitudines ob sui remedia deposcenda, Sanctorum expetere loca certantes. Huc etiam quàm plurimi tunc fidelium miseratione subsidioque delati sunt; qui secus Ecclesiæ fusi jacentes introitum ob intolerabilem passionem, die noctuque magnis clamoribus Salvatoris mundi clementiam, Sancti Præsulis Genulfi suffragia proclamabant. Erat autem non solùm audire stridores eorum præ dolore, vel exustas à corporibus effluere partes videre miseria; verum etiam ex putræ carnis fœtore res intoleranda, qua clade multi eorum consumpti sunt: multi etiam aquis aspersi sacratis, rore misericordiæ Dei per gloriosa Confessoris Christi Genulfi merita refrigerati sunt, et ab illo mortis erepti periculo (History of the Translation of St Genulfus, Bouquet, x. 361).

(9) Desæviebat eodem tempore clades pessima in hominibus, ignis scilicet occultus, qui quodcumque membrorum arripuisset, exurendo truncabat à corpore: plerosque etiam in spacio unius noctis hujus ignis consumpsit exustio (Glabri Rodulphi Historiarum liber ii., cap. vii., de incendiis, Bouquet, x. 20; Raoul Glaber was a monk at Cluny 1031-33, where this was probably written.)

(10) Anno Dom. Incarn. DCCCCXCIII. Hiems durissima . . . ad ultimum Non. Julii [7th July] grande factum est gelu; tantaque siccitas . . . ut pisces morerentur . . . et fruges perirent. . . . Subsecuta quoque

est grandis pestilentia. (Ex Chronico Saxonico, 994, Bouquet, x. 228-229.)

A circumstantial account of what must have been the same epidemic occurs in the life of Adalbero II. (Bishop of Metz from 984 to 1005) written about 1012 by his friend and admirer Constantine, abbot of St Symphorian of that town. The author relates how, when there was a great pestilence in Burgundy and all the neighbouring countries, many sufferers, having heard the fame of the pious prelate, flocked to his palace, and were fed and washed by him personally, to the number of eighty or one hundred each day. The disease showed itself by a burning in the hands and feet and the patients, sometimes having lost one foot, sometimes both, arrived leaning on sticks or carried on carts. The biographer mentions that he himself took part in the care of the sick and washed their wounds with his own hands. The stench was unbearable.

(11) . . . in Burgundiæ cunctis finibus cladis pessima multitudinem magnam populorum invasit, qua manibus pedibusque ardentes miserabili pœna, hic perdito uno, hic utroque truncatus pede, hic medio adustus, aliquis tunc primum incipiens, non multum sero veniens, audito sancto pontificis rumore, innitentes baculis aut carriotis devecti, undecumque confluebant. . . . Vere loquar, septem diebus huic divino servitio cooperator interfui, et propriis manibus aut lavabam aut detergebam, dum non minus centum aut octoginta, ut diximus, cotidie lavaret et cibo recrearet . . . fetor etiam intolerabilis. Pertz, iv. 658.

That in these times of famine the poor consumed ergot is not surprising, since even cannibalism was reported in 996.

(12) . . . tanta penuria bladi [of grain] et aliorum alimentorum omnium invaluit, ut, quod auditu est horribile, homo homine vesci cogebatur (Richerius, Chronicon monasterii senonensis, in Calmet, Histoire de Lorraine III., cli.)

In 1039, or perhaps a few years later, a "deadly burning" consumed many of all classes (13). It was regarded as a sign of the divine wrath for the breaking of the truce of God (which, *inter alia*, restricted fighting to Mondays, Tuesdays, and Wednesdays). The sins of the princes were visited on their peoples; some patients survived in a mutilated condition as an example to those coming after. The Verdun Chronicle (14) mentions a fire which "twisted" the people; the nervous

symptoms seem indeed to have been prominent, for the effects of gangrene are not alluded to. (In other Lorraine epidemics both sets of symptoms are mentioned, see below.) There was a remarkable remedy for the disease: relics of the Saints were sprinkled with holy water and then washed with wine; the wine was besprinkled with a powder, scraped from the stones of the Holy Sepulchre, and was given to the sick, after they had sworn to maintain the peace. So great was the number of the sufferers, that it was found expedient to have a vessel of this potion in readiness for those who did not come at the usual time for the ablution of bones, after Mass.

(13) Deinde quoque occulto Dei judicio cœpit desævire in ipsorum plebibus divina ultio: consumpsit enim quidam mortifer ardor multos tam de magnatibus, quàm de mediocribus atque infimis populi; quosdam verò truncatis membrorum partibus reservavit ad futurorum exemplum. Tunc etiam penè gens totius Orbis sustinuit penuriam pro raritate vini et tritici (Glabri Rodulphi Historiarum liber v., Bouquet, x. 59-60).

(14) A.D. 1041 . . . divino judicio cœpit desævire ignis qui eos torquebat: et eo anno ferè totus orbis penuriam passus est. . . . Sequuta est è vestigio mortalitas hominum præmaxima anno ab Incarn. Dom. MXLII. Multi eorum, qui torquebantur ab igne, venientes ad virum Dei . . . curabantur. . . . Videres Monasterium eximii Patris, ardentium turmis refertum; quos ipse Sanctorum reliquis, aquâ benedictâ respersis et vino lotis, et pulvere qui de petra sepulchri Domini radebatur vino ipso consperso et ad potandum miseris dato, pace firmata et jurata pristinæ sanitati reddebat. Pro innumeris autem turbis confluentium infirmorum vas potui illi paratum erat, ut si advenirent ægroti, potus salutaris non deesset; ne fallerentur, si horâ incompetenti venissent; neve tunc foret necessitas recurrendi ad ablutionem Reliquiarum; quod post expletionem Missæ impleri mos erat. (Chronicon Virdunense, Bouquet, xi. 145.)

Both the convulsive and the gangrenous symptoms are explicitly mentioned in the next account. [Lorraine, 1085] (15).

"Many were tortured and twisted by a contraction of the nerves; others died miserably, their limbs eaten up by the holy fire and blackened like charcoal." Here for the first time the fire is called "holy."

(15) Anno Henrici Imp. xxix. (the German Emperor Henry IV., 1056-1106; hence A.D. 1085) factus est terræ motus magnus, et in Occidentali parte Lotharingiæ pestilentia magna, ita quòd multi nervorum contractione distorti cruciabantur; alii, sacro igne membris

exesis, ad instar carbonum nigrescentibus, miserabiliter moriebantur (Chronicon Turonense, by a canon of St Martin of Tours, Bouquet, xii. 465).

There are several accounts of an epidemic in 1089 (one places it in 1088, another in 1090). It started near Orleans (20) in the middle of August, in Flanders a fortnight later (17), evidently immediately after the harvest in both regions; it also visited Lorraine. The account of the disease in the latter province is similar to that of 1085 and is alone in mentioning nervous contractions as well as (moist) gangrene (16). Those suffering from the latter either died miserably, or deprived of hands and feet, they were condemned to an "even more miserable life." Bones were cut off with a knife, when the fire had eaten up their flesh (20). Most writers called the disease *ignis sacer* (16-19) or *arsura* (21); one (Adalgisus) considered it identical with the Greek erysipelas (19). He evidently clearly recognised the difference between the holy fire and bubonic plague, for he described an outbreak of the latter disease (at Chalons in 1111) in very different terms, mentioning its rapid course and high mortality, and the flight from plague spots.

(16) Anno MLXXXIX. . . . Annus pestilens, maximè in occidentali parte Lotharingiæ, ubi multi sacro igne interiora consumente computreseentes, exesis membris instar carbonum nigreseentibus, aut miserabiliter moriuntur, aut manibus ac pedibus putrefactis truncati, miserabiliori vitæ reservantur, multi verò nervorum contractione distorti tormentantur (Chronographia Sigeberti Gemblaecncis, Bouquet, xiii. 259. Sigebert, a monk at Gembloux in Brabant, was one of the most famous of medieval chroniclers; he died in 1112).

(17) [1088] . . . Tertio Calend. Septembris visus est igneus draco volare per medium cœli . . . statimque subsecutus est pestilens ille morbus, qui Ignis sacer vocatur, quam tum arsuram appellabant quidam (J. Meyer, Annales rerum Flandriearum, liber iii., p. 31 a).

(18) [1089]. Quo anno sæviit vehementer in Flandria sacer ignis, quam ignariam vocabant pestem (*ibid.*, p. 31 a).

(19) Sacer ignis, quem Græei heresipilam dieunt. . . . Flandriæ incubuerat partibus, christicolarum quamplurimâ multitudine tam horribilis cladis verbere grassante partim prostratâ, partim gemente, et præ doloris immanitate dentibus stridente, partim morte jam multatâ (Miraeles of St Theoderic of Reims, by Adalgisus, soon after 1123; Bouquet, xiv. 142).

(20) Medio ferè mense augusto [incerti anni], ingens lues populum Aurelianensem [of Orleans] devastare cœpit. . . . Deinde plurimorum ossa ferro recidebantur acuto, quorum carnes exederat ignis (Bouquet, xiv. 142, footnote).

(21) [1090]. Hoc anno orta est pestis in hominibus, quæ Arsura dicitur, quâ etiam multi perierunt (Chronicon Lobiense, Bouquet, xiii. 581).

(22) [1089]. Pestilentia terribilis. . . . Ardentium (Chronicon S. Jacobi Leodiensis, Bouquet, xiii. 600).

There were bad harvests and neglect of agriculture in these troublous times preceding the Crusades. Famine, wars and disease carried off many in Germany, France and Italy; in several places the cemeteries were filled, and great pits were dug to serve as a common grave (23). De Jussieu *e.a.* considered that among the evils of this time the holy fire may even have been a minor one; yet one of the accounts (25) says the number of its victims was incredibly great, when recording that the Bishop of Tournai instituted a day of prayer against the disease in 1092, on the Feast of the Elevation of the Cross, 14th September.

Another account (26) mentions that the relics of the Saints were translated at Limoges about the Feast of the Nativity of the Virgin (8th September), so that there and at Tournai the epidemic was at its height within a few weeks of the harvest.

(23) A.D. 1094. Ipsa quoque cœmiteria Ecclesiarum adeò sepulturis impleta sunt, ut homines ibi mortuos suos sepelire non potuerint. Unde in pluribus locis factâ prægrandi fossâ extra cœmiterium, omnes suos mortuos in illam conjecerunt. Hæc autem mortalitas non solùm Teutonicos, sed et Franciam, Burgundiam, Italiam usque vexabat. . . . Superstites à secularibus vanitatibus, id est à jocis, tabernis et aliis hujusmodi superfluis abstinere studuerent, et ad Confessionem et pœnitentiam currere, seque Sacerdotibus commendare non cessaverunt (Chronicon Bertoldi Constantiensis, Bouquet, xi. 27).

(24) Nam Gallias per aliquot annos nunc seditio civilis, nunc fames, nunc mortalitas nimis afflixerat, postremò plaga illa quæ circa Nivalensem [Nivelles, Belgium] S. Gertrudis Ecclesiam orta est, usque ad vitæ desperationem terruerat; tactus enim quisquam igne invisibili quâcumque corporis parte, tamdiu sensibili tormento incomparabiliter et irremediabiliter ardebat, quousque vel spiritum cum cruciatu, vel cruciatum cum ipso tacto membro amitteret. Testantur hoc nonnulli manibus vel pedibus hâc pœnâ truncati (Chronicon Saxonicum Ekkehardi monachi Sangallensis, Bouquet, xiii. 716).

(25) [1092]. Tornaci religiosa instituta supplicatio ab Rabodone episcopo die exaltationis sanctæ Crucis ob pestem quam vocabant igniariam, hoc est sacrum ignem. . . . Nam alii instar carbonum nigrescentes, alii exesis morbo visceribus tabescentes, pars truncati miserabiliter membris, incredibile est dictu quam multi mortales sacro illo igni sunt absumpti (J. Meyer, Annales rerum Flandricarum, liber iii., p. 31 b).

(26) A.D. MXCIV iterata lues subcutanei ignis plebem Aquitanicam atrocissimè torrebat. . . . De toto . . . Lemovicino ad sanctissimum Martialem delata sunt sancta Sanctorum corpora. . . . Facta est hæc translatio Sanctorum circa festivitatem Nativitatis perpetuæ Virginis Mariæ. (Chronicon Gaufredi Vosiensis, not written till about 1170; Bouquet, xii. 427.)

(27) Anno MXCV. Fames diu concepta gravissimè ingravatur, et fit annus calamitosus. . . . Hoc anno, sacro igne multi accenduntur, membris instar carbonum nigrescentibus (Chronographia Sigeberti Gemblacensis, Bouquet, xiii. 260).

About this time (1093) the Order of St Anthony was founded near Vienne,[1] in Dauphiné, by one Gaston, a nobleman who built a hospital near the church containing the relics of the Saint, brought in 1070 from Constantinople. Pope Urban II. recognised the Order in 1095 at the Council of Clermont-Ferrand (which gave the impulse to the Crusades). In 1297 Pope Boniface VIII. raised the priory to the dignity of an abbey (see *Histoire du clergé séculier et régulier*, i. 192, where, however, there is no mention of the holy fire). During the twelfth century the holy fire became associated with St Anthony, and many suffering from the disease began to visit the Saint's relics. Of these pilgrims there is an interesting account (28) from an English source, in the life of St Hugh of Avalon, Bishop of Lincoln (1186-1200) and chief builder of its cathedral. Hugh was a member of the Carthusian Order (founded about the same time and in the same region as that of St Anthony) and was called to England by Henry II. about 1174. During the last year of his life (1200), the bishop visited the Grande Chartreuse and also the shrine of St Anthony; on this journey his biographer and private chaplain accompanied him, and so described at first hand the effects of the holy fire. The sick either died within seven days of their arrival, or were "miraculously" restored to health, notwithstanding the loss

[1] A recent writer makes it Vienna!

of their limbs. Such recovery was, however, also observed in modern times; the chief virtue of the hospital must have consisted in wholesome food.

(28) Vidimus enim juvenes et virgines, senes cum junioribus, per sanctum Dei Antonium salvatos ab igne sacro, semiustis carnibus, consumptisque ossibus, variisque mutilatos artuum compagibus, ita in dimidiis viventes corporibus, ut quasi integra viderentur incolumitate gaudentes. Concurritur siquidem a totis mundi finibus . . . qui omnes fere infra diem septimam divinitus curantur. Nam si quis sub hoc dierum spatio corporis sanitatem non recepit, . . . morte intercedente confestim excedit. . . .

Est autem in ipsis miraculis hoc insignius miraculum. Igne namque restincto in membris patientium, caro et cutis, vel artus quisque, quos morbus vorax sensim depascendo exederit, minime quidem restaurantur. Verum, quod est mirabilius, nudatis ossibus quae truci incendio superfuerint, sanitas et soliditas cicatricibus ipsis residui corporis tanta confertur, ut videas plurimos in omni ætate et sexu utroque, brachiis jam usque ad cubitos, aut lacertis usque ad humeros absumptis, similiter et tibiis usque ad genua, vel cruribus usque ad renes aut inguina exustis funditus et abrasis, tanquam sanissimos multa alacritate pollere (Magna vita S. Hugonis episcopi Lincolniensis, ed. Rev. J. F. Dimock, Rolls Series, No. 37, p. 308).

According to de Jussieu, *c.a.* there were several houses of the Order of St Anthony in France for the care of sufferers from the holy fire; one at Lyons was called *Domus Contractoria*, and the walls of these hospitals were painted a symbolic red. Thus in Rabelais' *Pantagruel*, chapter xxx.: "Une muraille, en laquelle estoit painct le feu de St Antoine," and Satyre Ménippée, vertu du catholicon, art. viii., "faites peindre à l'entour de votre maison, non du feu de St Antoine, mais. . . ." According to Ozanam and Bacquias mummified cast-off limbs were still preserved in the Abbey of St Anthony in 1702. Durrer states that at one time there were 390 houses of the Order in various countries; of the four Swiss the oldest was founded at Basle in 1304.

In 1109 (or 1108) a (not very severe) epidemic occurred near Chartres and Orleans (the disease remained almost endemic near the latter town until the eighteenth century). The summer was very wet (29). Ives, Bishop of Chartres, in a letter to Pope Paschal II., saw in it a punishment for the iniquity of the people (30). Another author (31) remarks that

famine, holy fire and leprosy were respectively peculiar to England, France and Normandy. (In England, and probably also in Normandy, less rye was cultivated than in France.)

(29) A.D. MCIX. . . . In Gallia, maximè in Aurelianensi et Carnotensi provincia [Orleans and Chartres] clades ignifera multos invasit, debilitavit, et quosdam occidit. Nimietas pluviarum fructus terræ suffocavit . . . valida fames terrigenas passim maceravit in mundo. (Historiæ ecclesiasticæ of Orderic, born in 1075 in Shropshire; became a monk of the Monastery of Uticum = St Evroul en Ouche in Normandy and received the name Vitalis; the epidemic therefore happened in his life-time. Bouquet, xii. 708.)

(30) In tantum enim apud nos in majoribus populi abundavit iniquitas, ut nec paternis admonitionibus obediant, nec Deum terrentem timeant; cùm et ex sterilitate terræ fame pauperes eorum afficiat, et morbo qui dicitur sacer-ignis multorum membra ad præcisionem, multorum corpora ducat ad mortem (Epistolæ Ivonis Carnotensis episcopi; ad Paschalem II. Papam; Bouquet, xv. 148).

(31) Anno MCIX . . . multi sacro igne accenduntur, membris instar carbonum nigrescentibus. Tres plagæ tribus regionibus appropriari solent, Anglorum fames, Gallorum ignis, Normannorum lepra (Chronicon Alberici, Bouquet, xiii. 690; this author copied other chronicles. The first sentence occurs also in Sigebert of Gembloux, Bouquet, xiii. 264; the second is from Elinandus).

Fuchs states that according to Short (of the air, weather, etc., p. 108) in the year 1110 "the people over all England were afflicted with sore diseases, especially an epidemic Erysipelas, where of many died; the Parts being black and shrivelled up." I have neither been able to trace this book, nor to find any evidence on which the statement and others referring to the years 1182 and 1196, are based. In France there was an unusually severe epidemic in 1128 and 1129 after a succession of several years of famine (Chronicon Lamberti Waterlosii for 1124 and 1126, Bouquet, xiii. 498; J. Meyer, *Annales rerum Flandricarum*, liber iv.; Mézeray, *Histoire de France*, mentions two consecutive years of famine caused by rain).

Among the many accounts, the most detailed description of the disease is contained in a book on the miracles of St Mary of Soissons, *de curatione ardentium*, by a contemporary, Hugh Farsit (32). He calls the disease a wasting one (*tabificus*; another account (33) speaks of *quædam pestilentia flegmatica*; it was not acute, like bubonic plague or anthrax). Under the

stretched and livid skin the flesh was separated from the bones and consumed (32). Death was denied to the sufferers until the fire invaded the vital organs. Most strangely this fire could consume without heat, and poured over the sufferers such an icy cold, that they could not be warmed by any means; and what was no less strange, if by divine grace, the fire had been extinguished, so great a heat pervaded the limbs of the sick, that it was often accompanied by cancer (gangrene?) unless treated by medicaments. These details, as to the colour of the skin, and the feeling of great heat and cold, are repeated in modern descriptions of convulsive ergotism, *e.g.* by Lang, and leave no doubt at all as to the identity of the disease. In 1129 the divine fire raged in Chartres, Paris, Soissons, Cambrai and many other places (33-36). It attacked not only the limbs, but also the breasts and the face (35). The Blessed Virgin appeared in September with a host of angels and in Notre Dame of Soissons 103 persons were cured of the holy fire within a fortnight, and also three girls whose limbs were twisted (34); convulsive symptoms were evidently rare.

(32) Anno ad incarnat. Domini MCXXVIII . . . concessa est potestas adversæ virtuti plagâ invisibili percutere homines diversæ ætatis et sexûs in pago Suessionensi; ita ut semel succensa corpora eorum cum intolerabili cruciatu arderent usque ad exclusionem animæ, nisi sola Dei misericordia occurreret. Est autem morbus hic tabificus, sub extenta liventi cute carnem ab ossibus separans et consumens, et morâ temporis augmenta doloris et ardoris capiens, per singula momenta cogit miseros mori, et tamen desiderantibus mortem tantum remedium denegatur: donec, prioribus depastis artubus, celer ignis invadat membra vitalia; et, quod mirum est, ignis hic sine calore validus ad consumendum, tanto frigore velut glaciali perfundit miserabiles, ut nullis remediis possint calefieri. Item quod non minùs est mirabile, ex quo divinâ gratiâ restinctus fuerit, fugato mortali frigore, tantus calor in eisdem partibus ægros pervadit, ut morbus cancri eidem fervori persæpè se societ, nisi medicamentis occurratur. Horror est et infirmantes et recèns sanatos intueri, et vestigio mortis evasæ in corporibus eorum et faciebus exterminatis oculis pererrare (Hugo Farsitus: De miraculis B. Mariæ Suessionensis, de curatione Ardentium, Bouquet, xiv. 234; quoted by Alberic in a slightly different form; Bouquet, xiii. 697).

(33) A.D. MCXXVIII. . . . Magnam multitudinem virorum et mulierum mortalitas, sacer ignis, quædam pestilentia flegmatica, maximè in pago Carnotensi [Chartres] prostravit. (Chronicle of the

Monastery of St Stephen at Caen, written about 1143; Bouquet, xii. 780.)

(34) Anno MCXXVIII . . . multi de pago Suessonico sacro igne accensi, ad Ecclesiam beatæ Dei genitricis Mariæ . . . convenerunt; . . . ita ut intra quindecim dies centum et tres nominatim ab hoc igne restinguerentur, et tres puellæ distortæ sanitati redderentur (Alterius Roberti appendix ad Sigebertum, Bouquet, xiii. 328; Pertz, vi. 475; Howlett, Rolls Series, No. 82; possibly by Robert du Mont, 1128-1186, Abbot of Mont St Michel).

(35) A.D. 1129. Hoc anno plaga ignis divini Carnotum, Parisios, Suessionem, Cameracum, Atrebatum, et alia multa loca mirabiliter pervadit; . . . Juvenes etenim, senes cum junioribus, virgines etiam teneræ, in pedibus, in manibus, in mamillis, et quod graviùs est, in genis exuruntur, et celeriter exstinguuntur (Anselmi Gemblacensis appendix ad Sigebertum, Bouquet, xiii. 269).

(36) A.D. 1129 (*circa*) En cel tamps la maladie du fu qui vient de Dieu, fu moult griefs à Chartres, à Paris, à Soissons, à Cambray, à Arras et par moult d'aultres lieux. (Chronique de Cambrai, Bouquet, xiii. 495; this seems to be the oldest mention in French.)

(37) A.D. 1128 . . . invisibilis ignis plurimos depastus est in regno Francorum (Chronicon S. Petri Vivi Senonensis, Bouquet, xii. 283; this chronicle relates to Sens in Burgundy, whither the epidemic evidently did not extend. The same sentence occurs in Chronicon Turonense, Tours, Bouquet, xii. 470, and the epidemic is further mentioned (for the year 1129) in Chronicon Lobiense, Bouquet, xiii. 582, and in Anonymi Blandiniensis appendicula, St Pierre, near Gent, Bouquet, xiv. 18).

(38) Morbus igneus . . . quem physici sacrum ignem appellant, eâ nominum institutione quâ nomen unius contrarii alterius significationem sortitur (Liber miraculorum B. Genovefæ virginis; Paris, Bouquet, xiv. 235).

For 1141 an epidemic is briefly mentioned in Anonymi Blandiniensis appendicula, Bouquet, xiv. 20; in Chronicon Lobiense, Bouquet, xiii. 582; and by Waterlos in the Cambrai Chronicle, Bouquet, xiii. 501. For the year 1151 there is a single reference to holy fire by Robert of Mont St Michel in his appendix to Sigebert's Chronicle, Bouquet, xiii. 293, and in this year it is said to have rained from midsummer to the middle of August (Bouquet, xiii. 275).

After the middle of the twelfth century contemporary references to ergotism become much rarer, and we may safely conclude that there were few epidemics important enough to be

mentioned by chroniclers. One in 1235 was, however, repeatedly referred to:

(39) 1230 (1235?). Fames magna . . . Sequitur tanta mortalitas quod tam igne sacro quam pestilentia multa millia hominum moriuntur (Chronicon Girardi de Fracheto, Bouquet, xxi. 3-4).

(40) 1235 . . . facta est magna valde fames in Francia, maximè in Aquitania, ita ut homines herbas campestres sicut animalia comederent. . . . Ibidem quoque facta est magna pestilentia, qua multa pauperes, magni et parvi, sacro igne accendebantur. (Speculo historiali Vincentii Bellovacensis, Bouquet, xxi. 72. Almost identical with chronicon Guillelmi de Nangiaco (Guillaume de Nangio) in Bouquet, xx. 547.)

(41) 1235. Pestilentia etiam sacri ignis tanta fuit, tunc in Lemovicinio et in Pictavia [Limousin and Poitou], quod divites et pauperes et pueros et senes ignis accendebat. (Majus chronicon Lemovicense, Bouquet, xxi. 764.)

For the fourteenth century Fuchs only mentions an outbreak of "Infirmitas Sancti Antonii" in Brittany in 1347 (Chronicon Briocense, a bad compilation, written about fifty years later). This, the last, appears to be the sole reference in the chronicles, in which the fire is named after the Saint, and the association of the two must be inferred chiefly from what is known of the Abbey of St Anthony, especially from the description of the visit of Hugh, Bishop of Lincoln in 1200, quoted above. Another contemporary record of this association has been preserved in the fifteenth-century frescoes of the Chapel of St Anthony at Waltalingen, north of Zürich; two of these are reproduced from Durrer. Fig. 12 shows the Saint blessing the victims of gangrenous ergotism; one on the right has lost a foot (and a hand?); in Fig. 13 an appeal is made to him by sufferers whose limbs have been twisted by the convulsive variety of the disease (compare the left hand of the man on the right with Figs. 8 and 9). There is indeed not infrequent mention of St Anthony's fire in early printed books, down to the first half of the sixteenth century, but such simple allusion does not include any symptoms which would permit of certain identification with the holy fire. One passage from Rabelais was quoted above which, according to his modern editor refers to ergotism, but in others it is more probable that Rabelais meant syphilis. Fuchs and Ehlers have collected a number of such later doubtful printed references. They include an interesting one in a book on military surgery by Gerssdorff,

FIG. 12.

FIG. 13.

Frescoes in the Chapel of St Anthony at Waltalingen, near Zürich (15th century), showing Gangrenous and Convulsive Ergotism.

first published at Strassburg in 1535. The section "von dem kalten Brandt" has a woodcut (Fig. 14) representing the appeal to St Anthony by a peasant who has lost his right foot, and holds up his left hand enveloped in symbolic flames. Ehlers seems to suggest that this illustration refers to gangrenous ergotism; perhaps it does, but the text of Gerssdorff's book brings no certainty on this point. It identifies the cold fire with "estiomenum," the fire of St Anthony and St Martial and "cancrena" of the Greeks. It identifies the hot fire with *ignis persicus* (=anthrax), and with pruna; it is also called St Anthony's fire and *ignis sacer*. Evidently Gerssdorff had no clear conception of St Anthony's fire, and when other authors identify it with smallpox and even with syphilis, the confusion towards the end of the Middle Ages is seen to be complete. Incidentally Gerssdorff was one of the last writers to employ the term *ignis sacer*, which along with St Anthony's fire, fell out of use. Fuchs cites a few epidemics of alleged ergotism in southern Europe, taken from Villalba's *Epidemiologia Española* and from Portuguese writers. They do not refer to contemporary sources and such of these passages as I have been able to trace have not convinced me that they deal with ergotism. The most likely is perhaps an outbreak at the siege of Majorca in 1230, mentioned by Villalba (p. 57). De Jussieu *c.a.* quote the description by an Italian writer of the fifteenth century, Petrus Parisus, of a disease in Sicily, in which large livid and dark patches were formed under the knee and extended to the calf. The leg was shortened and convulsed. The patches seemed dried up, as if burned in a fire or dried for a long time in the sun. They were swollen, devoid of sensation and mortified, as is apt to happen in confirmed gangrene. ("Prive di senso et mortificate, come suole accedere nelle cancrene confirmate.")

Since very little rye was grown in Italy (*cf.* p. 3) it is not surprising that the Italian chronicles, in contrast to the French, do not mention the holy fire. It is all the more remarkable that it is so rarely mentioned in Germany, where much rye was grown and convulsive ergotism was common in modern times. This problem is referred to in the discussion on the relationship of the two types. Some mention of gangrenous ergotism may yet be discovered in Pertz's collection of German chronicles, for the most part published after Fuchs' monograph. The

Von dem kalten Brandt.

O Anthoni heiliger Man/
Warumb nimbst dich der Artzney an?
So Gott dem Herrn gebürt die Ehr/
Vnd keinem Menschen sonst nit mehr.

Fig. 14.

search is laborious because the indexes are apparently not detailed enough. I have found only one such reference (42) in the annals of Meissen (in Saxony) for the year 1486, which mention an outbreak of "scurvy," a name later applied in Germany to convulsive ergotism. This, together with the mention of gangrene and the separation of flesh from the bones, makes it very probable that the "new and unheard of disease" was gangrenous ergotism. The fact that it was described as contagious is not much opposed to this view; (convulsive) ergotism was later often so described, since several members of a family were mostly attacked at the same time.

(42) Grassatus est novus et inauditus in his terris morbus, quem nautæ Saxonici dicant, Den Schorbock: quae est inflammatio in membris partium carnosarumcui: quò celerius adhibetur medicina, eò citius malum restinguitur: Sin mora accedit paulo tardior, sequitur membri affecti mortificatio, quam siderationem nostri, Græci σφακελὸν dicunt, ultimum gangrænæ malum: nam caro de ossibus defluit, et continua quæque à lue corripiuntur. Fuit idem morbus contagiosus, multorum mortalium gravi periculo. (Annales urbis Misnæ 1486, in G. Fabricius, vol. ii., p. 71.)

Gangrenous ergotism in modern times. — The modern history of gangrenous ergotism starts with a letter written by Dodart [1676] to the French Academy of Sciences, which describes the disease in the Sologne, a marshy district south of Orleans. The attention of the Academy of Sciences had been directed to it and Dodart was asked to report. He ascertained from Tuillier (or Thuillier, a later spelling), a physician at Angers, that the latter's father had already observed the disease in 1630, knew that it was due to ergot, and had noticed the fatal effects of the latter on poultry. Thus in France the cause of the disease was established from the beginning, and was never in doubt among the educated; in Germany controversy about the cause of convulsive ergotism continued down to 1800. Dodart stated that the diseased rye was called ergot in the Sologne, on account of its resemblance to a cock's spur, and bled cornu in the Gâtinais district, respectively south and east of Orleans. Ergot was also found in Berry (south of the Sologne), and the country round Blois (south-west of Orleans), and occurred mostly on light sandy soils. In some years the ergot was not found to have any harmful effects;

these were chiefly observed when a hot summer followed a wet spring. Ergot was said to be most poisonous when fresh, and to lose its toxicity on keeping. Dodart gives a brief description of the gangrene, which could only be treated by amputation.

The publication of Dodart's letter did much to call attention to the harmful character of ergot, not only in France, but also in Germany [Brunner, 1695, and others]. The next French outbreak took place in 1709, and was recorded by the *Académie des Sciences* [1710]. According to Noël, physician of the Orleans hospital, the rye crop of the Sologne in 1709 contained nearly one-quarter of ergot, and after eating bread from the new harvest the peasants felt almost drunk. The disease also appeared in Languedoc and in Dauphiné; in the latter province it was identified at the Abbey of St Anthony as the mediæval fire of that Saint. A severe outbreak in 1747 was briefly recorded by du Hamel [1748].

An epidemic of gangrene occurred in the marshy country round Lille (but not in the town) in 1749 and 1750, immediately after the war of the Austrian Succession. It was described in considerable detail by Boucher [1762] and is remarkable in several respects. In the first place this author expressly excludes any "particular degeneration" of the food and does not make a single reference to ergot; he quotes the *Académie des Sciences* [1710] only in discussing the advisability of amputation; he attributes the disease to extremes of temperatures and to cold mists, to which the peasants working in the fields were exposed. The spring of 1749 was unusually wet and in the summer of that year great heat and rains alternated. All later French authors agree, however, in regarding this epidemic as also due to ergot. The second peculiar feature, rare in France, was the description of nervous symptoms in the early stages of the disease. "La maladie étoit ordinairement annoncée par des contractions spasmodiques violentes des muscles des jambes, ou du bras et de l'avant-bras, et par des douleurs vives." The contraction of the flexor muscles was sometimes so violent as to make the heels nearly touch the buttocks. This is characteristic of convulsive ergotism, but no mention is made of other symptoms of that disease, and the spasmodic contractions later gave way to gangrene. It may be that the nervous symptoms in Flanders were connected with a great mortality of cattle a year or two earlier, mentioned by

Boucher; it may be also that Boucher saw the earlier and milder manifestations of the disease. This was obviously not the case with Salerne, who in 1755 described another epidemic in the Sologne; patients began to arrive at Orleans in the middle of August, and among them the mortality was very high. Of 120 patients, whether operated or no, only five left the hospital. For three to four weeks before death there was generally a severe colic. In cases of recovery from the gangrene the patients remained dull and stupid for the rest of their lives (likewise in severe convulsive ergotism this, together with mania and other forms of insanity, was not uncommon).

Delarsé and Taranget [1765] and Read [1771] described an outbreak of gangrene observed by them in 1764 near Arras and Douai.

The year 1770 was marked by a great outbreak of ergotism in several countries of Europe. In France gangrene appeared in Sologne, Maine, Limousin and Auvergne. Vétillart [1770] reports that a peasant saw a farmer sifting his grain and begged the rejected portion, consisting largely of ergot. Being in great want he did not heed warnings, and made bread of the diseased grain. In the course of a month the man, his wife and two children died; a third, still breast fed, was given a porridge made from the flour; it alone escaped death, but became completely deaf and lost both legs.

In 1777, 8000 people are said to have died of gangrene within a short time in the Sologne district where, according to Tessier [1776, iii.], suitable sieves were not in use; in the same year le Brun described a rather mild epidemic in the Landes, where Raulin had earlier attributed gangrene to atmospheric conditions.

In the nineteenth century there were still several well-marked epidemics of gangrenous ergotism in France. The first followed the terrible winter of 1812-13, which defeated Napoleon in Russia. It continued in 1814, 1816 and 1820, particularly in the Departments of Saône-et-Loire and Allier; these epidemics were described by Bordot [1818], François, Orjollet [1818], Courhaut [1827] and Janson [1844]. Gangrene was preceded in many cases by contraction of the limbs and formication.

The last epidemic in France was described by Barrier, surgeon of the Hôtel-Dieu at Lyons, and occurred in 1855 in southern France (departments of Isère, Ardèche, Haute-Loire and Rhône, *i.e.*, those bordering on the Rhône river at and south

of Lyons). These epidemics of the nineteenth century yielded to medical treatment and the mortality was not so high as in the eighteenth. Apart from them only sporadic cases of ergotism were observed.

Few epidemics of gangrenous ergotism have been recorded outside France. The best known was in **Switzerland** in 1709 (at the same time as a French one); its notoriety is due to the accuracy of its description by C. N. Lang,[1] rather than to its severity or extent. In the canton of Lucerne there were in 1709, in the course of ten weeks, only fifty patients, most of whom suffered no permanent damage; some lost toes or finger, or a foot, a few lost a leg; only one man died. During a recurrence in 1716 there were only ten cases, and these yielded to treatment. In 1709 there were observed in Berne only six cases requiring amputation. When we compare these figures with those of Salerne, quoted above, it is evident that the latter, in contrast to Lang, saw only the severest and most advanced cases. Lang mentioned spasmodic movements ("gichterische Bewegungen") in some patients, who did not suffer from gangrene, "either on account of the smaller quantity of poison absorbed or on account of a more robust constitution." This has given rise to the statement that the Swiss epidemic was of a mixed type, but the severer manifestations of convulsive ergotism were entirely wanting. Lang attributed the disease to ergot, of which he gave a good description and a fairly good plate (*Spica secalis luxuriantis* C. B. *pin.* 23). He considered that ergot is toxic only in certain years, when attacked by honey-dew, from which the rye inside the ear is protected. "Just as a beneficent God did not create any poison, which is wholly useless to man, so the poisonous ergot grains have some good in them with which they may serve to comfort mankind." This sentence introduces a mention of the obstetrical use of ergot, recorded by Lonicerus; Lang thought, however, that so dangerous a drug should not be administered internally.

In a few epidemics in **Germany** and **Eastern Europe** cases of gangrene have been described, but here the convulsive

[1] Lang held a public medical office at Lucerne and was also a naturalist of some distinction. His book on ergot was already rare in the eighteenth century, and is not included in the British Museum and the national libraries of Berlin, Berne, Munich and Paris; there are two copies in the library of the University of Basle.

symptoms predominate, so that they are dealt with in a later section. The occurrence of gangrenous ergotism among a poor Kabyl population in **Algeria**, living on ergotised barley, was described as late as 1898 by Legrain (photograph of gangrenous feet).

In **England** there appears to have been only one occurrence of typical gangrenous ergotism, in the family of a poor agricultural labourer at Wattisham, near Bury St Edmunds, in 1762. This outbreak aroused much interest at the time; it was described by Wollaston and by Bones in the *Proceedings of the Royal Society*, and also in the parish register, of which Henslow (*q.v.*) has published an extract. There is a commemorative tablet on the church tower. On 10th January two children complained of pains in the calf of the leg; two days later all except the father were attacked. The pain became so violent that the neighbourhood was alarmed by the shrieks of the sufferers, and after about a week one or more legs were "sphacelated." The mortified parts were amputated at the ankle or knee, with little or no pain; the foot of one child was separated without the aid of the surgeon; the mother and five children all lost one or both feet or legs. The father escaped such dire calamity and suffered only from numbness of the hands and loss of finger nails. These cases of "mortification of the limbs" are very typical of severe gangrenous ergotism; the dry gangrene was rapid in its onset, so that the preliminary symptoms of cold and numbness were absent, or at least not prominent enough for mention, except in the much milder case of the father; apparently the gangrene was not fatal to life. There was no rye in the neighbourhood but apart from dried pease, pickled pork, bread, *cheese*, *milk* and small beer, the family lived on bread from "clog-wheat, or revets, or bearded wheat" (*Triticum turgidum*?) which had been laid, was discoloured, and had been kept separate by the farmer. Some other men who had eaten it also suffered from numbness in the hands and a feeling of cold, but the farmer's family who had used this wheat exclusively was not affected. It is not stated whether the wheat was ergotised, but this must almost certainly have been the case (*cf.* p. 99, as to the liability of this wheat to be ergotised). Its effect must, however, have been reinforced by poverty or some other factor, in the case of the mother and children. Their greater susceptibility is typical of convulsive, rather than of

gangrenous ergotism, which according to most authors attacked men more than women. The wide differences in the severity of the disease among members of the same family seems, however, not uncommon in the gangrenous type. According to Carbonneaux le Perdriel [1862] wheat ergot is medicinally more active than that of rye. The Wattisham outbreak was accepted by Tissot [1765] as undoubtedly one of ergotism, but this unique occurrence still presents many obscure features.

In the nineteenth century mild cases of ergotism in **Ireland** were described by Nuttall and by Colles in 1847. The only patient who came to the Dublin hospital was a young man from a farm in Co. Meath who had fed on bread from (ergotised) rye on marshy ground. In the year 1846 the rye crop was particularly bad and scanty (in the same year the potato crop failed entirely). This patient had in the following April a cold pricking sensation in his fingers, and cramp in the legs; he lost all nails of both hands and one toe by gangrene. His hair fell out and his pupils were dilated. He reported that he had also lost his nails three years before, and that a few relatives and neighbours were similarly affected. The disease seems to have been known in the district for a long time; its cause had, however, not been recognised.

An even milder but more extensive epidemic of ergotism was reported recently from **Manchester** by Robertson and Ashby [1928], and by Morgan [1929], among Jewish immigrants from Central Europe who lived on rye bread. The symptoms were coldness in the extremities, numbness and lack of sensation in the fingers (tailors pricked themselves without feeling it), sensation of an insect creeping under or over the skin, headache, depression, gastric disturbances, shooting pains and twitching in the limbs and a staggering gait. These symptoms are characteristic of mild ergotism of the nervous kind. (Strictly speaking this epidemic should therefore be discussed in the next section.) All the 200 patients complained of formication, and all were in the habit of eating bread made from one part of rye meal with four parts of wheaten flour. The epidemic started in October 1927 after a wet summer. The rye was grown in south Yorkshire, had been ground to meal in a stone mill and had probably not been cleaned or screened. It yielded 0·9 per cent. of ergot by hand-picking, and colorimetric analysis showed 1·5 per cent. (which

is perhaps nearer the mark). Gaddum found later 0·01 per cent. alkaloid in the ergot by pharmacological means. Something like 5 grams of ergot must have been contained in a half-pound loaf, and in October 1927 the alkaloidal content may have been higher than that found by Gaddum. Robertson and Ashby's publication induced Dilling and Kelly to communicate a case of gangrene of symmetrical toes which they had observed in 1923 in a patient at Liverpool who ate only rye bread. In two successive Novembers a toe was amputated. The rye had been grown in Lancashire in 1922, a wet year, and was suspect. The flour was later shown pharmacologically to contain at least 0·1 per cent. of ergot.

These sporadic cases of ergotism show how little is known about the subject in this country. English analysts do not seem to be aware of the many papers published in Germany, Austria and Russia on the detection and estimation of ergot in flour (see Chapter VI.). How the ergot content of 1 per cent. was deduced in the Manchester epidemic is by no means clear.

Convulsive ergotism in Germany and Bohemia.—A few authors mention that convulsive ergotism (as a result of the importation of diseased rye from Prussia into Brabant in 1556), was first referred to by Dodonæus, but his *Historia frumentorum* [1569] and his *Herbal*, even in its later editions (*e.g.* 1616, well after Lonicer and Schwenckfelt) merely contain the statement that bread made from bad and decayed rye (*malum et corruptum*) causes various wearisome diseases, in particular that known as Schorbock or Schoorbuyck (scurvy). As will be shown below, older German writers regarded convulsive ergotism as a variety of this disease. In his *Medical Observations* [1581] Dodonæus attributes scurvy to bad food, particularly to bad rye, such as that imported in 1556 from Prussia into Brabant, "when not a few began to suffer from scurvy; in most the effects of the evil only showed themselves in the gums." There is no mention of the striking symptoms of convulsive ergotism and although rye was incriminated, it seems most likely that Dodonæus refers only to an outbreak of true scurvy.

The first unmistakable description of convulsive ergotism is contained in the *Epistolæ Medicinales* of Balduinus Ronsseus [1590], a native of Ghent, who became physician to the Duke of Braunschweig-Lüneburg and later to the town of Gouda in

Holland. The author describes a "new and unheard-of" disease, which broke out in August 1581 in many villages of the Duchy of Lüneburg (Fig. 15); in two there were 123 deaths. It began with paralysis and convulsions of hands and feet "compressing and bending the fingers to a fist, so that the strongest man could not unbend them." He mentions the cries of the sufferers (*maximum et horrendissimum ululatum*), the intolerable feeling of heat and other symptoms which leave no doubt that he is referring to a severe epidemic of convulsive ergotism, which is, moreover, known to have visited the same district in later times. To Ronsseus the disease was unknown, and he does not mention the word Kriebelkrankheit, so that this epidemic escaped the attention of Taube who begins his detailed historical account with Caspar Schwenckfeld [1603]. This Silesian naturalist, in discussing the magpie, states that its flesh is an excellent remedy against convulsions and spasms, and then mentions a new disease which, some fifteen or ten years previously, had attacked the poor more especially.

The people called the spasm "das Kromme." The ripening grain had been infested by some baneful manna or poisonous dew (*manna quadam aerea maligna, seu rore venenato, siligo jam maturescens inficiebatur*), so that all who partook of the bread baked from this grain were attacked by the disease, particularly the old men, women and children. These details are entirely characteristic, and with the popular German name leave no doubt as to the identity of the disease. It is interesting to note that Schwenckfeld, in another work, had three years previously given one of the first descriptions of ergot itself, and mentioned its styptic properties (of course at that time it was not known that honey-dew and ergot are two stages in the life cycle of the same fungus). Taube assigns the outbreak to the years 1587 and 1592, but these dates can only be approximate. The district, on the northern slope of the Riesengebirge, was repeatedly visited in subsequent centuries by the same disease.

An epidemic which broke out in the orphanage at Heidelberg in October 1589 is less certainly identified; most modern writers (*e.g.* Kobert) seem not to have consulted the original, for they wrongly attribute it to Zarachias Brendelius; it was, however, in a collection by his namesake Johannes Philippus, that the report was published of the Heidelberg physicians, charged with

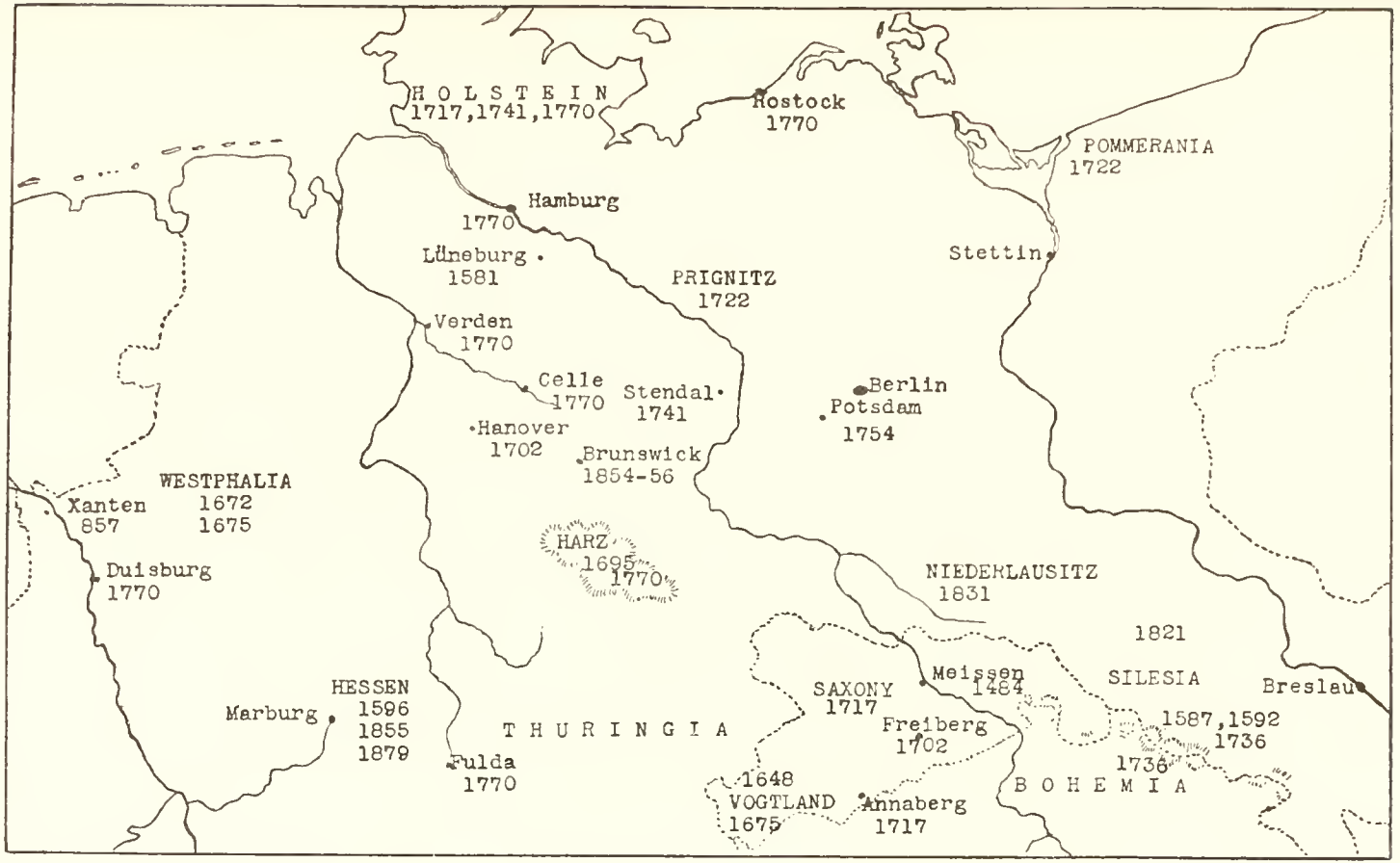


FIG. 15.—Ergotism in Germany.

investigating the outbreak. They wrote: "Adfectus iste . . . motus convulsivus præcipue diaphragmatis, oris ventriculi, œsophagi, nervorum recurrentium, quæ sunt vocis instrumenta, et musculorum thoracis et epigastrii." They attributed it to a wet season having spoilt the vegetables, which the orphans had consumed greedily, along with much milk. The symptoms were therefore not typical of convulsive ergotism, nor would there appear to have been a shortage of vitamin-A. The disease lasted for more than three months; two similar isolated cases were observed at Worms. It seems to me that the Heidelberg outbreak has been wrongly identified as ergotism. The next epidemic, in Hessen and Westphalia, during 1596 and 1597, was one of the most important in the history of the subject, for it led the Marburg medical faculty to publish their famous description and warning in the vernacular, for the benefit of the people [Marburg, 1597]. "Of an unusual, poisonous, infectious disease, hitherto unknown in these parts, which disease is called by the common people here in Hessen the tingling disease, the cramp or the spastic evil" (*die Kriebelkrankheit, Krimffsucht oder ziehende Seuche*). The original is now very rare. A Latin translation was published by Horst [1661]; it was freely retranslated into German by Leisner [1676], and the original text with valuable introduction and notes was reprinted by Grüner [see Marburg 1793]; considerable extracts were also reprinted by Wichmann [1799].

The Marburg faculty gave the first detailed description of convulsive ergotism. The cries of the sufferers could be heard in villages "beyond the eighth or the tenth house and quite far off in the fields." "Good fresh eggs and butter" are specially recommended as preventives; a purgative and a sudorific (Kribel Pulver) are prescribed for treatment, and were used throughout the seventeenth century; the beneficial effect of emetics was not discovered until later. The Marburg physicians were in error in considering the disease to be infectious, a belief shared by some later writers, no doubt because often in a family several members were attacked who would naturally live on the same diet. The exact cause of the disease remained as yet unknown and the Marburg faculty merely attributed it to bad food in general.

For a long time there were no further precise descriptions of convulsive ergotism. The disease was often regarded as

a variety of scurvy ("Schorbock" or "Scharbock"). In this connection Reusner [*De Scorbuto*, 1600] referred to the above-mentioned epidemic of 1596 - 97; Sennertus [in his *De Scorbuto tractatus*, 1624] reprinted the above-mentioned letter of Ronsseus. Drawitz [1647] in his *Unterricht von schmertz-machendem Scharbock* was the first to use the name Affectus scorbutico-spasmodicus or scharbockische Kriebelkrankheit; he considered the disease due to bad food in times of scarcity. He still regarded it as infectious. The sufferers often seemed to be bewitched, or possessed by demons; their cries could be heard four or five houses off. In the *Vielvergröster und heller polirter Schorbocks - Spiegel* of 1659 Horst discusses the question whether convulsive ergotism (Kriebelkrankheit) has anything in common with scurvy. Sennertus, in his book *De Febribus*, speaks of the Kriebelkrankheit as *febris maligna cum spasmo* ("malignant fever with the cramp," as the English edition of 1658 has it). New outbreaks occurred in Vogtland (the south-west corner of Saxony) in 1648 and 1649 (after the Thirty Years' War) and in 1675 (Leisner, F. Hoffmann). In 1672 and 1675 the disease occurred in Westphalia (Barbeck, May).

In France ergot was identified as the cause of gangrene by Dodart in 1676. That it was also the cause of the convulsive disease seems to have been first recognised (or at least published) by J. C. Brunner in 1695, a century after accurate descriptions of the Kriebelkrankheit had been available. During a visit to the Harz Mountains he observed the effects of the scarcity of food (*ex inordinata militum consumptione*: Peace of Ryswyk, 1697). He discusses the effects of darnel and of certain black grains in the rye, known locally as Martinskorn, of which he learned with surprise that the natives believed them to cause convulsions. Brunner was even more surprised to learn that the black grains also caused fatal gangrene. He saw a woman who suffered from daily recurring convulsions; her fingers were as if burnt at the tips, rigid, indurated, devoid of sensation and of movement. On questioning a surgeon he was told that rye was the cause; this surgeon had amputated one of her feet which had become gangrenous from the same cause. Brunner thus saw both kinds of ergotism in the same patient. Wepfer, in 1694, observed a single case of "Kriebelsucht" with violent convulsions, and

after nine months greatly diminished vision. This, like Brunner's cases, came from the Harz Mountains, where in one village there were 150 patients. The disease was attributed to black grains of rye, with a white interior, resulting from honey-dew in the previous summer. The poor did not separate these grains from sound corn, as was usual among the well-to-do.

About this time there are other less precise references to ergotism; Ramazzini attributed an epidemic of 1693 in Lombardy to *rubigo* (rust), Hoyer one of 1699-1700 near Mülhausen to honey-dew, which he considered identical with *rubigo*. Hoyer did not connect the epidemic with ergot, although he stated that in 1699 there was more "Mutterkorn" in Thuringia than had been observed in living memory (see also Sydenham). Later writers (Hoffmann, Taube, p. 31) identified outbreaks in 1702 near Freiberg in Saxony, and in Hanover with convulsive ergotism, but ergot was not indeed inculpated again until 1709, when there occurred in Switzerland an epidemic of gangrenous ergotism, described in detail by C. N. Lang; Scheuchzer also blamed ergot. The disease reappeared in a mild form in Switzerland in 1716, and in this and the following year an outbreak of the purely convulsive type occurred both in Holstein and in Saxony, giving rise to numerous publications (nearly a dozen in 1717). The Holstein "peasants' disease" was described in the *Breslauer Sammlung* and in a dissertation under Waldtschmiedt; although they refer to ergot as the cause of gangrene, these two accounts do not attribute the convulsive disease to it, but rather to a peculiar constituent of the air. In Saxony grain was, however, regarded as the cause of the convulsions; this was implied in the local name "Kornstaupe" (*Breslauer Sammlung*, Haberkorn, Longolius). Nevertheless most authors did not incriminate ergot; Longolius, for instance, attributed the disease to honey-dew. Budæus indeed regarded ergot as the primary cause, but honey-dew, poisonous vegetables and fungi as contributory; two-thirds of his book was devoted to promoting the sale of his own remedies, based on the prescriptions of the Marburg faculty 120 years before. The Saxon epidemic was also dealt with by Wedel and by Wilisch. The latter writes of the "rare disease" of which few have heard and still fewer have seen anything. Severe cases differed only from true epilepsy in that the patients were conscious. Often

three-quarters of the grain consisted of ergot and other impurities. It was even the subject of a printed sermon (Bruno) and of a theological thesis (Kunad); a belief in witchcraft was still prevalent and many believed the sufferers from convulsive ergotism to be possessed by demons. About this time some cases in St Annaberg in Saxony led to much controversy, as is reflected in such a title as *Opisthotonus daemoniacus deluce-datus et defensus.* Arnold in his translation [1726] of Bishop Hutchinson's *Historical Essay on Witchcraft*, discusses this controversy at length. Albrecht [1743] remarks that "through ignorance of natural causes" the common people were apt to "ascribe the symptoms of this peculiar disease to the action of spells" (*statim ad fascina refert*). Later in the eighteenth century the help of the clergy was enlisted in teaching the people the harmful effects of ergot.

After the many publications due to the epidemic of 1717 "the pens of the learned rested until 1723," when in a dissertation under Christian Vater the Silesian disease was again described and the harmful effects of ergot were insisted on. Poultry died from eating it; pregnant sows aborted; horses and cattle became ill; flies were killed after feeding on an infusion of ergot in milk.

In 1722 and in the spring of 1723 outbreaks occurred in Pommerania north of Stettin, and in the Prignitz district, north-east of Wittenberg [Müller and Glockengiesser in *Acta medicorum Berolinensium*, for 1726; Ludolff, 1727]. At first regarded as new (*autem adeo novus non est*), the disease cannot yet have been well known to the physicians of the time. Ergot was fully recognised as the cause, and the Prussian Government exchanged the bad rye for sound grain. Nevertheless Burghart questioned the poisonous nature of ergot in the next epidemic [1736, at the foot of the Sudeten Mountains, in Silesia]. The disease also occurred on the other side of this range, in northern Bohemia, where it was carefully described by J. A. Scrinc. Out of 500 patients more than 100 died between September 1736 and March 1737. About three-fifths of the patients were under 15 years of age. Two houses died out completely. The poor suffered from a very great and indescribable famine; only one of the well-to-do was attacked, and he also had ergot among his corn. There was not a single case in the town of Niemes, where the bread was of good quality. The people

believed the disease to be infectious, but Scrinc was convinced of the contrary and regarded the bad bread as the only cause. He considered that the toxicity of the latter was due to ergot and in part also to *Bromus secalinus* ("Trespe"; see also p. 29). Scrinc's publication in a Latin journal was provided with numerous footnotes in German, in order to avoid misunderstanding, and the author was emphatic that the disease was the real Kriebelkrankheit.

Henceforth convulsive ergotism became well known in Germany, and the celebrated Friedrich Hoffmann of Halle collected most of the available knowledge in his *Medicina rationalis systematica* [1738], although he did not himself observe any cases.[1] In 1741 and 1742 small but locally violent outbreaks occurred in Brandenburg, near Neu-Ruppin and Stendal. There are several descriptions: a dissertation by Müller under von Bergen; an account by Brückmann who reported that in one village 150 persons were attacked, of whom 40 died between September 1741 and April 1742; most of the patients were children; two cases of cataract were observed; there was also much ergotised barley. Hoffmeyer's account is interesting because of his conversation with a patient suffering from delusional insanity [March 1742]. The winter of 1740-41 had been excessively cold and the following spring was very wet. All these authors agree in attributing the disease to ergot; on the other hand Kannegieser, describing a simultaneous outbreak in Holstein, blames the cold air (*intemperies aëris, quæ toties nebulas fœtidas malignos rores et rubigenes effecit virosas*). According to him the urban population eat the same rye as the rural, yet did not suffer.

The next record related to a small epidemic near Potsdam which Cothenius ascribed to ergot; even the spirit made

[1] His confused ideas as to the origin of the disease are typical of the period; rust (*rubigo*) and honey-dew descended from the air, and produced darnel (*lolium*) and ergot: "causa est in aëre . . . aër suas exhalationes in forma rubiginis malignæ, vel frumentaceæ, vel mellitæ, in fruges campestres, maxime secale, eo cum florerent tempore deposuit; et hinc, non solum universum fere frumentum coinquinavit, verum etiam ad lolium præsertim frumentaceum, fatuum aut temulentum, quod Botanici vocant zizanium, nostri das Mutter-Brandtkorn, den tauben Rocken, generandum multum contribuit." Ergot was also confused with *Ustilago* = smut, *e.g.* necrosis ustilaginea of Sauvages [1768], and smutty rye in the English translation of Zimmermann's *Experience in Physic* [1782].

(distilled?) from ergotised rye was harmful. Unimportant dissertations (under Fabricius, Ludolff the younger, Detharding and particularly Linnæus, see below) created confusion concerning the cause of the poisonous properties of grain, until the great epidemic of 1770-71 which gave rise to so many publications and to such knowledge that since then few serious outbreaks have occurred in sufficiently civilised countries. In 1770, when gangrenous ergotism was observed in France, the convulsive type appeared extensively in northern Germany, Holstein and Sweden. Much the most important account is that by Johann Taube (1727-99), a Hanoverian court physician and corresponding member of the Gesellschaft der Wissenschaften of Göttingen. He indeed published a preliminary note in 1771, but his magnum opus of 920 pages appeared in 1782 (Fig. 16, p. 74). In the first 240 pages he abstracts nearly all German writers on the subject, and gives his own careful description of the disease, together with what was then known about ergot. The bulk of the work is taken up by numerous detailed reports on patients in hospital, and the last 132 pages form an appendix, consisting of eight accounts by neighbouring colleagues. Taube mentions that the winter of 1769-70 was not continuously severe; the spring was late, in June there was much cold and mist, particularly during the flowering of the rye, and then after heavy rains, followed a period of great heat and drought; much honey-dew was observed and was not washed off by rain, but dried up and harvested; even long before the harvest fears of disease were expressed. Taube states that the peasants in his district (Celle, 25 miles north of Hanover) were in the habit of collecting the so-called Krümmelkorn which falls out of the ears in harvesting, and baking bread from this before threshing the main harvest, partly from curiosity, partly from necessity. Since the larger grains of ergot fall out readily, Krümmelkorn is particularly rich in ergot, and several days after the new bread had been eaten the disease appeared; on 29th August 1770, Taube was called to his first four patients, two of whom soon died. Many more cases occurred in September and October and were often rapidly fatal; later, the disease took a less rapid course. Early in December a few cases occurred in the town of Celle as a result of importation of rye from some of the affected villages. As was generally observed in previous epidemics, only particular villages were attacked; in February

Die

Geſchichte

der

Kriebel-Krankheit

beſonders derjenigen

welche

in den Jahren 1770 und 1771

in

den Zelliſchen Gegenden

gewütet hat

beſchrieben

von

Johann Taube

Hofmedicus, Mitglied der Königlichen Landwirthſchaft Geſellſchaft zu Celle und Correſpondent der Königlichen Geſellſchaft der Wiſſenſchaften zu Göttingen.

Göttingen,

bey Johann Chriſtian Dieterich, 1782.

1771 a violent outbreak occurred in a village previously free from the disease, after the threshing of rye from an infected locality. The Hanoverian Government, acting on medical advice, gave warning to millers and bakers, and exchanged ergotised rye for sound grain in the villages, so that many patients recovered in the course of a week; yet others could not be convinced that the rye was poisonous and preferred to "eat death in their own harvest" rather than accept the exchange. Later, when the Government supplies gave out, absolute necessity caused a recrudescence of the disease in the spring of 1771; the last deaths occurred in September of that year. Taube gives a statistic of 600 cases from Celle and some forty villages. Of 505 patients who remained at home 91 died; of 95 patients removed to hospitals only 6 died, so that treatment was effective (emetics, purgatives, and better food! Shocks from a frictional electrical machine were tried extensively, but seem to have been useless). Of 91 dead, 56 were males, 35 females; 41 were between 2 and 10 years of age. Taube records several cases of insanity, and of cataract, but observed no gangrene of whole parts. He, however, figures a unique case in which the dried skin of fingers and toes was cast off in one piece. Hensler of Altona, in an appendix to Taube's treatise, gives a graphic picture of the misery of the peasants. "Many permanently retained stiff hands and bent fingers and toes. In all respects this is one of the severest plagues of the agricultural labourer. Even if he be not permanently deprived of the use of his hands, he is lamed in the best part of the year, the spring, when he should be obtaining a livelihood for himself and his children. . . . The misery of a labourer's family may be imagined, when some children lie in spasms on the floor and others cry for bread, while their parents are and long will be unable to help. Few scenes are more poignant."

Next in importance after Taube's book, is the account by his friend and colleague Wichmann, of the same epidemic near Celle. He distinguishes three stages of the disease, and gives interesting information as to the diet of the peasants. The widespread interest taken in convulsive ergotism at that time is proved by a collection of nineteen reports from physicians all over Schleswig-Holstein to the *Königl. deutsche Kammer* at Copenhagen. The Royal College of Physicians of that town in

reply advised the cleaning of grain and the plentiful use of bacon and butter in the diet. Rödder attributed the disease to ergot (*Secale cornicularc*) and to seeds of *Lolium*, etc.

The numerous other publications of the time are mainly of interest, because they show that even at this late period the belief in the poisonous qualities of ergot was far from universal. Indeed, temporarily the defenders of ergot were in the majority. Taube devotes a special section to them. Foremost among these was Schleger [1770], professor at Cassel, who attempted to prove the harmless nature of ergot by animal experiments, as did Model by chemical ones. When Nebel of Giessen described the 1770 epidemic in Hessen and gave very good evidence that ergot was the cause of the Kriebelkrankheit, Schleger [1772] replied, without adducing additional experiments; in any case his doses of ergot were far too small. Nebel's retort was virulent; *inter alia* he attacked his opponent's Latinity! Baldinger (Jena) also wrote against Schleger and translated Nebel's first paper into German, providing it with a preface of its own. Vogel (Göttingen) defended ergot in his *Schutzschrift für das Mutterkorn als einer angeblichen Ursache der sogenannt. Kriebelkrankheit* [1771], but next year, in his textbook of medicine, he was more cautious. With the exception of Nebel, none of these polemical writers appear to have seen many cases, but others who had to deal with local epidemics (Brawe of Verden, near Bremen, Herrmann in Hessen, Marcard of Stade near Hamburg) failed to recognise ergot as the cause. The same applies to Eschenbach (Rostock), Leidenfrost (Duisburg), Focke (Celle). (I have not seen the writings of Mücke, who observed the disease at Werningerode in the Harz Mountains, of Weickart who saw it near Fulda, of Smieder and of Richter.) Long after the epidemic of 1770 Lentin of Göttingen remained in doubt as to the effects of ergot, which he considered innocuous unless honey-dew descended on it. He even gives the peculiar advice to wash such contaminated ergot with dilute potash and then to feed it to cattle. Ergot itself could not be harmful since it was merely a stick of corn sap dried in the air!

The inability of many physicians of this time to see in ergot the cause of a disease is no less remarkable than the persistence of the peasants in eating bread made from ergotised rye. After the great epidemic of 1770-71 the harm done by ergot became generally recognised, although as late as 1800 there appeared a

pamphlet by Kircheisen exculpating it. This author ate, in the course of three days, bread containing a pound of darnel seeds and recovered, after taking an emetic, which hardly proved his contention that darnel was the cause of the Kriebelkrankheit. Grüner in a preface to this pamphlet writes: "Wofern meine Stimme etwas vermag, kann ich nicht umhin, die Unschädlichkeit des Mutterkorns aus Erfahrung zu vertheidigen." Fortunately convulsive ergotism had by then become rare in Germany.

The great diminution of ergotism after 1772 is due to various causes. In the first place the cleaning of the grain became general, partly through Governmental action. (For examples of official warnings, after 1770, see Marx; in Austria after 1812 insufficiently cleaned rye was confiscated.) Further, owing to improvements in agriculture, particularly by drainage, ergot became less common. Another important factor, as Hecker points out, was the great increase in the cultivation of the potato, much stimulated by Frederick the Great. According to Hecker it already had an influence on the Silesian campaign during the Seven Years' War. The great extension of potato growing, however, only resulted in Germany from the famine of 1770-71, when the advantage of a subsidiary food supply became evident in certain villages. In the south maize later fulfilled the same function (Meier).

Nevertheless convulsive ergotism continued in Germany, as did the gangrenous type in France; indeed there is a dissertation by Heusinger [1856, i.] specially devoted to the nineteenth century. Sporadic German cases from 1805-21 are most fully dealt with by Lorinser (pp. 49-66). In the latter year, which was very wet, the rye harvest in some parts of lower Silesia contained over one-third of ergot. It is related that the father of a family separated the ergot from several bushels of rye, but later, persuaded by his wife, added it all again to the first bushel to be milled. Thus the percentage of ergot in the flour was multiplied, and within six days the father and three children died; the mother alone survived. A more extensive outbreak occurred in 1831 and 1832, in a swampy district of the Nieder Lausitz in Saxony; the descriptions of this outbreak by Wagner, a local physician, and by his nephew and namesake, are among the most useful in the literature. An epidemic of 1855-56, in Upper Hessen, was described and illustrated by Heusinger

[1856, ii.] of Marburg. He records 102 cases with 12 deaths (11 children and 1 adult). Jahrmaerker traced the records of many patients and examined a few survivors as late as 1911. Of Heusinger's cases at least 19 ultimately died of ergotism; of 35 children under 10 years of age 18 died. At least half the patients never recovered completely. The year 1854 produced sporadic fatal cases in Bohemia, described in considerable detail by Hussa. In 1867-68 several cases from East Prussia in the hospital at Königsberg came to the notice of von Leyden who afterwards dealt with them somewhat briefly in his textbook of diseases of the spinal cord. The same year 1867 (with a cold spring after a mild winter) produced two other small outbreaks in Germany. Flinzer observed one on a farm near Annaberg in Saxony; he picked out 10 to 12 per cent. of ergot from a rye of which three parts had been mixed with one each of oats and barley; the meal must therefore have contained at least 6 to 7 per cent. of ergot. The bread baked from this was almost black, and had a sweetish, not unpleasant taste. The bread was eaten only from 6th to 11th October; on the 10th a boy of sixteen became ill; he died next day. A girl of the same age became ill on the 12th and died on the 22nd. Several adults were severely attacked, but survived. A less severe outbreak near Roding in Bavaria was described by J. Mayer (19 non-fatal cases; up to 1·5 per cent. ergot in the flour.)

The last German epidemic of any considerable extent occurred near Frankenburg in Upper Hessen in the autumn of 1879, with further outbreaks in the spring of 1880 and 1881. According to Menche the summer of 1879 had been very wet, and a warning appeared in the local paper even before the disease declared itself. After the first cases in September, the grain was confiscated and the millers were fined. Nevertheless, 200 cases of ergotism were notified to the police and the physicians calculated that there were in all about 500 cases in fifteen villages. The mortality was about 5 per cent.; eight samples of confiscated rye contained on the average 2 per cent. of ergot (hand picked); in some samples there was one-third of *Bromus secalinus;* the bread was dark with a bluish tinge and a sweetish taste. This epidemic is of importance because over sixty patients were observed at intervals over a period of twenty years by neurologists and psychiatrists (Siemens, Tuczek, Walker, Jahrmaerker [1902]), who also observed

lesions in the posterior columns of the spinal cord. Only about one-quarter of this group of patients were completely cured. A small epidemic near Breslau was described by Tuczek [1884].

Convulsive ergotism in Sweden, Norway and Finland.— After Germany these three countries rank next in interest, not so much because the disease was common (there was much more in Russia), but because it was exclusively convulsive in type (Dragsjuka = ziehende Seuche) and led to several important accounts. The first of these is in a dissertation by Heiligtag, a pupil of Rosén of Lund, and refers to an epidemic of 1746-47. An epidemic of 1755-56 is referred to by Bergius. Much confusion was created by a dissertation of Linné's pupil Rothman [1763], in which the disease was wrongly attributed to charlock (*Raphanus Raphanistrum*). It occurred in the province of Kronoberg and near Carlskrona in southern Sweden. Little or no rye was grown; the real cause seems to have been ergotised barley (*cf.* also Brückmann, in Germany, 1741-42). Since the fields were heavily infested with charlock, Rothman, without direct experiment, quite illogically considered this weed to be the cause of the disease, which he termed *raphania*. It is a remarkable proof of the great authority possessed by Linnæus that the term raphania persisted for a long time, even long after Linné's countryman Wåhlin [1771] had proved its inapplicability. Wåhlin reported on epidemics in the provinces of Jönköping and Westergotland, principally in 1765, and recognised that ergot was (mostly on barley) their true cause. Bad cereals (rye, barley, oats) are also blamed by Rosenblad [1783] who relates how a whole family died after eating porridge, and only a breast-fed infant escaped.

Hirsch mentions altogether ten Swedish epidemics from 1745-1867, nearly all in the south; how heavily rye was still ergotised at a late date, results from a report by Wahlberg, who in 1843 found a sample from Calmar to consist of rye $\frac{1}{2}$; ergot of rye $\frac{1}{4}$; *Bromus secalinus*, also heavily ergotised, $\frac{1}{4}$; this rye had actually killed a woman. For further details of the history of ergotism in Sweden, see Hedbom [1890].

The only Norwegian epidemic on record is said to have occurred in 1851, in the Smaalehnene province, south of Oslo, near the Swedish frontier. The discussion in the Medical Society of Christiania, *q.v.*, as to whether ergot was the cause, is not wholly convincing.

In Finland, probably owing to the many lakes and backward condition of agriculture, convulsive ergotism still occurred very frequently in the nineteenth century. Spoof [1872] devoted a monograph (with map) to this subject; from 1836-71 the disease occurred sporadically in thirty-three years, therefore almost annually; particularly severe epidemics occurred in 1840-44 and in 1862-63. The only cereal incriminated was rye, which in 1840 was often ergotised to the extent of one-eighth; in one district more than half the grain was ergot. The epidemic of 1862-63 extended over the whole of Finland. Spoof tabulates over 1400 cases, with a mortality of 2·7 to 22·7 per cent. according to the district.

Ergotism in Russia.—The disease was common down to recent times and apparently endemic in some districts; there was a very extensive epidemic as late as 1926-27. The first recorded outbreak was due to a bad harvest in 1722, chiefly between Moscow and the Volga and was investigated by command of Peter the Great by the German physician Schober who in 1723 published a brief account of it in the *Breslauer Sammlung* (*q.v.*). It is also referred to in a letter of the French ambassador Campredon, dated 29th January 1723, and published by the Imperial Historical Society of St Petersburg in 1885, here quoted from Kobert (*Historische Studien*, i., p. 41); it shows the influence of ergot on politics:—

"Je crois le Czar trop prudent pour s'engager dans une guerre qui diminuerait considérablement ses forces, quelque succès qu'elle pût avoir. Toute la cavalerie, qu'il avait menée à Astrakan, est ruinée, et ses finances sont en très mauvais état. La mauvaise récolte de l'année passée, la quantité prodigieuse des grains, qui ont péri sur la mer Caspienne, rendront la fourniture des magasins difficile, et il est déjà mort par la disette plus de vingt mille personnes aux environs de Nijny. On a cru d'abord que c'était la peste, mais les médecins qu'on a envoyés, après un examen fort exact ont rapporté que cette maladie n'était point contagieuse, qu'elle ne provenait que du mauvais grain, que les gens ont mangé. Il est rougeâtre et ressemble assez à l'yvraye, ayant été gâté, à ce qu'on juge par les brouillards envenimés. Les personnes, au moment qu'elles ont mangé de ce pain, sont devenues étourdies, avec de grandes contractions de nerfs, en sorte que ceux, qui ne sont pas morts ce jour, ont perdu les mains et les pieds, qui leur sont tombés, comme il

arrive en ce pays-ci, lorsque ces membres ont été gelés. Aucun des remèdes, dont on se sert dans les maladies contagieuses, n'ont opéré sur les malades, et il n'y a que ceux qui ont pris de bonnes nourritures et mangé d'autre pain, qui ont échappé. La dissertation, que les médecins ont faite à cette occasion, est très curieuse, et si je puis en avoir une copie, j'aurai l'honneur de l'envoyer à votre éminence. Or comme cette maladie peut avoir de fâcheuses suites, par la difficulté de trouver de bon seigle pour la subsistance des habitants et d'une armée et par la quantité du mauvais, qu'on a ordonné de brûler et que d'ailleurs les événements d'une guerre contre les turcs pourraient affaiblir tout d'un coup et peut-être sans ressource les forces et la considération du Czar, il est apparent, au moins jusqu'à présent, que les mouvements, qu'il fait faire à ses troupes, n'ont pour premier motif que d'en faire montre à l'envoyé turc, qu'on fait marcher fort lentement."

It would seem that the epidemic was both convulsive and gangrenous. Such a mixture of the two types was again observed in Russia in 1824, 1832, 1863 and 1881, although the vast majority of epidemics in that country were purely of the convulsive type. This appears from a review of the Russian literature by Grünfeld [1889] dealing with epidemics from 1832-83. Those of 1832 and 1837 involved large tracts of country; at one time or another most parts of Russia were affected, but the principal region was a belt between latitudes 55° and 60° (embracing the provinces Novgorod, Kostroma, Viatka, Kazan, Simbirsk, the Ural Mountains) and the Volga basin southwards to the province of the Don Cossacks. The mortality was very high, in a number of the earlier epidemics over 50 per cent.; in 1832 and 1837 in the provinces Kazan, Kostroma and Viatka 25 to 57 per cent. [Poehl] (probably only severe cases were included in the statistics). Epidemics of 1832 in the Novgorod province, and of 1863 in that of Simbirsk were mixed; one in 1834 among the Don Cossacks (much further south) was predominantly gangrenous.

More recent epidemics are mentioned by Bechterew (Viatka province, 1889-91) and Kolossow (provinces of Kostroma 1904, Viatka 1905-06, Tver 1911, Vladimir 1911; all these are in the northerly agricultural region, latitude 57° to 58°. An extensive epidemic occurred in 1926-27 in the neighbourhood of Sarapoul (between Kazan and the Ural Mountains), in the Votyak region

and near Perm. It has been described by Maksudow, who was sent by the University of Kazan to investigate the epidemic on the spot, and by Rojdestvensky [1928]. From September 1926 to August 1927 inclusive 11,319 cases became known to the authorities; of these 1618 were treated in hospital, of whom 93 died. There were, however, many deaths outside the hospitals and many cases were not officially notified. The northern and north-eastern limits of the epidemic were not defined but the above figures refer to a total population of 506,000, of which therefore at least 2 per cent. were attacked.

The wet and cold summer of 1926 extended the flowering period of the rye to more than three weeks (*cf.* Chapter III.). In June, July and August the rainfall was double the normal. The rye was moreover injured by night frosts in May, so that in the whole district the crop amounted to two-thirds of the normal; in some places as much as 85 per cent. was lost. This led to great scarcity and the use of unsound grain (the price in 1926 was often double that of 1925). The proportion of rye in the ergot varied considerably in different districts, from 1 to 26·7 per cent. by weight. In winnowed grain the average was 1·12 per cent., in grain taken from mills 0·56 to 2·40 per cent. Of 37 samples of flour, 31 were found to contain an inadmissible amount of ergot. Freshly harvested rye was found to be the most toxic. The correlation of grain inspection and medical statistics show that the disease occurred when there was 1 per cent. of ergot in the rye; 7 per cent. caused fatal poisoning. In 30 per cent. of the cases the disease was acute, and passed off in three to four days; the chronic form lasted three to four months. The case mortality varied with the district from 0 to 9 per cent.; over the whole region it was 0·8 per cent. The symptoms were almost entirely nervous; formication only occurred occasionally (in contrast to the older German epidemics); there was often great hunger; psychoses and disturbance of vision are reported. There were also cases of gangrene, in which fingers and toes had to be amputated. Acute cases were treated with emetics and heart stimulants, the chronic with intravenous injections of 5 to 25 c.c. of 0·25 per cent. magnesium sulphate at intervals of one to two days. The removal of the ergot from the rye was attempted by means of sieves (which, however, only removed the large sclerotia) and more successfully by steeping the grain in 30

per cent. salt solution, when all the ergot and 10 per cent. of the grain rose to the surface. Occasionally cows, to whom the latter mixture was given, were poisoned. The ergot was bought up by the Government at 1·25 to 2·50 Rbs. (2s. 6d. to 5s.) per kilo, but nevertheless only 1600 kilos out of an estimated 4000 tons were offered for sale. The epidemic declined in March. In 1927 the rye was again ergotised, up to 1·5 per cent., and a small second outbreak occurred (42 cases were treated in September, 18 in October, 87 in November and 186 in December, mostly as out-patients). Epileptiform convulsions were still observed during this period.

Convulsive ergotism in other countries.—A recent very mild epidemic in *England* is mentioned in the section on gangrenous ergotism.[1] Some mystery is attached to an outbreak in three *Belgian* prisons, in October 1844, although it was reported on at great length by Vleminckx, in the Academy of Medicine. Hirsch is in error, when he refers this epidemic to the mixed type; there is no mention at all of gangrene; the symptoms were quite typical of convulsive ergotism; for a time there were at Brussels 100 to 160 cases in hospital; two post-mortem examinations showed lesions of the spinal cord. The element of mystery arises from the fact that at Brussels and at Namur little or no ergot was found in the rye, and this cereal, as well as wheat, was exculpated in the discussion in the Academy. The prison authorities at Ghent incriminated the rye and oats used for making soup.

Convulsive ergotism in *Bohemia* [1736, 1854] and in *Denmark* [Holstein 1770] has been included in the German chronology. In *Lombardy*, Ramazzini reported cases in 1693. Two extensive outbreaks occurred in 1789 at Turin, and in 1795 at Milan (Moskati), both times in the month of June and in a school or orphanage. The time of year is more characteristic of pellagra, with which some have identified the disease, but the symptoms were those of convulsive ergotism.

[1] Apart from this outbreak, there is no evidence of convulsive ergotism in England. Willis [1667] indeed refers to the description by Gregor Horstius of a convulsive disease in Hessen and Westphalia in the seventeenth century (which was undoubtedly ergotism), and then states that an epidemic in England in the spring of 1661 was certainly of a similar type. This has induced some later writers to infer that convulsant ergotism occurred in England in that year. Willis' description of the symptoms hardly warrants this view, which is also extremely improbable on other grounds.

A severe epidemic occurred in 1857 in *Transylvania* (Siebenbürgen, then part of Hungary) among a poor Rumanian population addicted to alcohol. It attracted the attention of Meier, an ophthalmologist, on account of the resultant cataract; he, however, supplies other details. There came to his knowledge 283 cases, 98 deaths and 23 cases of juvenile cataract.

Thieme mentions that extensive epidemics occurred in *Hungary* in 1786 and 1788, which were stopped by confiscation of the grain. Sporadic cases occurred as late as 1908 in Bihar, then in Hungary, now in Rumania. A convulsive one terminated fatally after three years. (See Figs. 7, 9 and 10). Sporadic cases have also been described of late years by Glaessner and A. Fuchs. The latter indeed believes that outbreaks of tetany in Austria in the spring are in reality cases of ergotism.

CHAPTER III

BOTANICAL

History

THE first description of ergot, in the herbals of Lonicer and others, is in the form of an appendix to that of rye, and for a long time botanists regarded ergot as a diseased rye grain. Thalius [1588] suggested that the grain was forced to grow out because of an excessive formation of sap (after much rain followed by hot weather): "forte major succi copia, quam ad grani justum alimentum opus est, attrahitur, ut ita necesse, corticem adhuc tenerum rumpi et ita internam substantiam in majorem molem augeri." Adopting this view, Caspar Bauhin used the name *Secale luxurians*. Others attributed the formation of ergot to fertilisation of the rye not having taken place, to excessive humidity of the air or the soil, or to the bite of an insect. The last view was in particular advocated by Tillet [1755] and as late as 1826 Martin Field considered that infection was favoured by the puncture of the ovary by a fly. The conception of ergot as a particular kind of rye survives to the present day in the name *Secale cornutum* [Baldinger 1771].

That ergot is a separate plant, and a fungus, was first hinted by Geoffroy [1711; "plûtot approchante du champignon, que d'un grain de Bled"] and definitely assumed by Münchhausen [1764] who wrote: "Ich trage daher kein Bedenken, jene Mutterkörner mit unter die Geschlechte der Schwämme zu rechnen." Von Schranck, Imhoff and other writers of the latter part of the eighteenth century shared this opinion; without referring to them De Candolle [1815] put forward this view as novel and assigned ergot to the genus *Sclerotium* (*S. clavus*, DC.).

The attempts to prove that ergot is a fungus were at first chemical, rather than morphological; indeed much of the earliest chemical work on ergot was undertaken with this

end in view; for instance powdered ergot, placed in water, was found to putrefy rapidly and in composition it was found to resemble fungi rather than rye. Germinated ergot sclerotia, with their characteristic fructifications, were observed, from 1801 onwards, by a number of mycologists, who however regarded these fructifications as consisting of a separate fungus saprophytic on rye grains or on ergot (*Sphæria* sp. Schumacher, Fries; *Cordyceps purpurea*, Fries; *Kentrosporium nitratum*, Wallroth; *Sphæropus fungorum*, Guibourt) just as the genus *Cordyceps* is saprophytic on insect larvæ, or even parasitic on other fungi. Tulasne, in a classical paper [1853], recognised that these fructifications are produced by the ergot sclerotium itself.

The first obvious effect of the infection of rye by *Claviceps* is often the so-called honey-dew, a sticky, yellow, concentrated sugar solution, drops of which, secreted by the infected ovary, may protrude from between the glumes. The first mention of honey-dew is by Schwenckfeld [1603], as a cause of ergotism; "Manna quadam aerea maligna, seu rore venenato, siligo jam maturescens . . . inficiebatur." The same author, in another book, had three years previously described the ergot sclerotium, but the connection between the two was only definitely established by Tulasne [1851, 1853]. For a long time honey-dew was regarded as a separate phenomenon, *e.g.* by Hoyer [1706: *De rore melleo vitioso;* Helscher, 1736], but Hellwig [1699] definitely recognised it as the cause of ergot. In 1827 Léveillé (the uncle) described a fungus *Sphacelia segetum*, growing on the infected ovaries and in the honey-dew; it multiplies by forming conidia. Léveillé considered it to be the cause of ergot, which latter he still regarded as part of the rye plant (a monstrosity of the ovule) and not as the resting stage of the fungus. Tulasne showed that the mycelium of the *Sphacelia* stage gradually transforms and pushes up the ovary, and itself gives rise to the sclerotium. Tulasne's work was confirmed and extended by Kühn [1865], and more recently by infection experiments with spores, and by the cultivation of the fungus on artificial media. The fungus *Ergotætia abortifaciens* of Quekett [1841] growing on "a diseased grain" (*cf.* also Smith's paper and that of Bauer, in the same year) is, according to Tulasne, not the *Sphacelia* stage of *Claviceps* but an intercurrent infection with one of the *Mucedineæ* (*v.* also Fée).

FIG. 17.—Ergot of Rye. (Natural size.)

(From a photograph by Dr M. Wilson.)

FIG. 18.—Ergot of *Lolium*. (Natural size.)

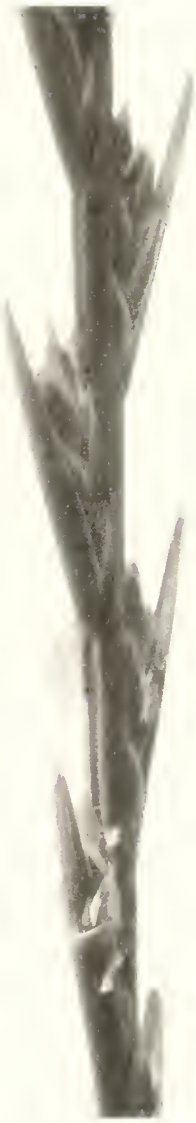


FIG. 19.—Drop of Honey-dew on *Lolium*. (× 3.)

(From photographs by Prof. F. T. McFarland.)

Characters of the Sclerotium.

The following description is quoted from *Botanical Pen Portraits* by Moll and Janssonius:—

Macroscopic characters.—Average length 14·6 mm., thick up to 6·5 mm., in the dry state brittle; cylindrical, at the same time tapering gradually towards apex and base. At the top sometimes a small greyish-white cap (*Sphacelia*). Surface longitudinally furrowed; generally two or three furrows much deeper than the rest; mostly showing also longitudinal and transverse fissures; dull greyish, sometimes purplish black, somewhat covered with bloom; transverse fracture smooth, dull pinkish white. Odour in somewhat large quantities disagreeable; taste feeble, sweetish, afterwards somewhat pungent (Figs. 17 and 40).

Micrography.—Pseudo-parenchyma; in the outer part the cells generally in longitudinal rows, showing their origin from hyphæ; the inner part consisting of two tissues, clearly to be distinguished; the central one being composed of smaller cells and having in transverse section the shape of an irregular star, sometimes showing large and irregular intercellular spaces in the middle part; the peripheral tissue composed of larger cells.

Cells of the outer part.—In radial and tangential directions 6 to 10 μ; length 7 to 20 μ; polygonal prisms with a longitudinally directed axis. Outer walls of the outmost layer of cells somewhat thickened; walls of the outmost layer or layers of cells deep brown to black, those of the rest pinkish white; walls containing no cellulose, but consisting of chitin. Cell contents: bodies with rounded edges, consisting of oil and protein.

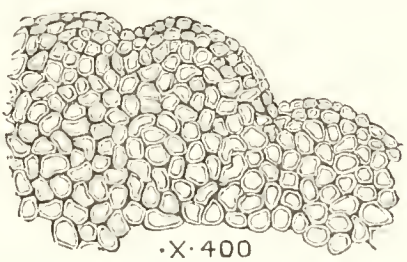


FIG. 20.—Fragment of a transverse section of the sclerotium, showing cortex (after Worthington Smith).

Peripheral cells of the inner part. — Somewhat more elongated and having rounded edges; walls pinkish white. See for the rest the cells of the outer part. *Sphacelia* consisting of colourless hyphæ; those united at the top of the sclerotium in a greyish-white cap and sometimes surrounding the lower part of the sclerotium in some flattened layers. Conidia

usually to be found. Some remains of the ovary, especially some epidermal cells often to be distinguished between the hyphæ of the cap, sometimes also in the lower parts.

With regard to the above description it should be noted that although we speak of a pseudo-parenchyma, because its cells are irregular and originate from hyphæ, there are nevertheless protoplasmic connections between them, the so-called plasmodesms, which are chiefly known in higher plants. Kienitz-Gerloff has, however, demonstrated them also in the sclerotium of *Claviceps*, where they are extremely thin. They doubtless make it possible for one cell to influence another, as when, after injury, fresh hyphæ are put out from sound cells a few layers lower down (P. Köhler). The stellate tissue in the centre of the sclerotium is dark and particularly well marked in *C. sesleriæ*.

Life Cycle.

Germination of the sclerotium.—Normally the sclerotia, which fall to the ground before or at the harvest, do not germinate until the following spring (much more rapidly in *C. cinerea*). For germination of *C. purpurea*, an exposure of several weeks to cold, followed by a similar period at a higher temperature is favourable, rather than a prolonged period of rest. According to Kirchhoff, who recently studied this question in detail, actual frost is not essential; an exposure to 2° to 3° C. during three to six weeks is quite as effective, probably more so, than actual frost; it caused 60 to 80 per cent. of the sclerotia to germinate after four to eight weeks at 15° C.: after an exposure to 8° to 10° C., only something like 10 per cent. ultimately germinated. The duration of the exposure to the low temperature is of importance; it must be at least fifteen to twenty days, and after such a brief period of cold, only a few sclerotia germinate, and that tardily, requiring about seven to nine weeks at 14° to 16° C. On the other hand, the great majority germinate, if kept sixty days in the cold, and then only require three to four weeks at the higher temperature. The sclerotia may be just covered with moderately moist sand; they do not germinate when dry. Their germination has been dealt with by Belzung, Granel, McFarland, Whetzel and Reddick. Klebahn recommends alternate drying and wetting.

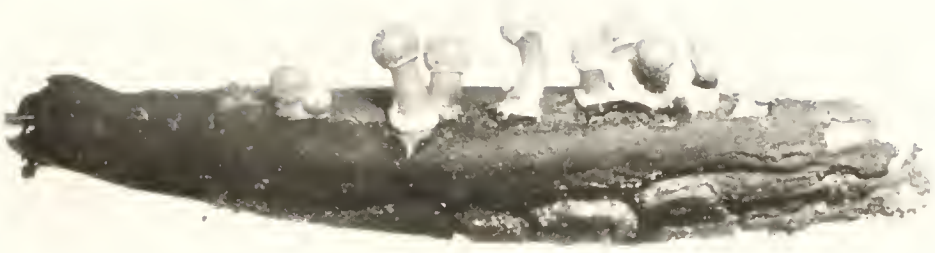


FIG. 21.—Germinating sclerotium of Ergot of Rye. (× 8.)

FIG. 22.—Later stage. (× 4.)

FIG. 23.—Fully-developed capitula. (× 7.)
(From photographs by Dr M. Wilson.)

According to Rostowzeff the power of germinating lasts only for one year; Lutz [1904] and Zimmermann [1906], however, observed germination after the second winter; even mouldy and broken sclerotia will germinate under favourable conditions. P. Köhler also studied the regeneration and germination of cut sclerotia.

Germination begins by the differentiation of elongated subcortical cells which multiply actively by division. They stand out so sharply by their dense protoplasmic contents that they have been likened to a parasite penetrating the tissue of the sclerotium. The outer envelope of the latter bulges and finally bursts under the pressure of the bundle of slender interwoven hyphæ which grow out into a stalk, from the apex of which thinner hyphæ radiate so as to form a knob (Killian, Fisch). In this way small white spherical heads (hence the name *Claviceps*) appear on the sclerotium; there are often about fifteen, sometimes as many as sixty (Figs. 21-23). Each head is pushed upwards, sometimes through a thin layer of soil, by the longitudinal growth of a stalk which, like the head, changes its colour through yellow and red to purple; the stalks (in *C. purpurea*) are generally about 15 to 25 mm. long, but are strongly phototropic and longer in the dark The base of the stalk is somewhat thicker and often surrounded by a feltwork of secondary mycelium. The hyphæ of the sclerotium near the base of the stalk gradually lose their oil and their cell walls become thin. The stalk is technically known as *stipe*, the terminal knob as *capitulum* or *spheridium;* both together constitute a *stroma.* When the knob is fully developed, its surface is covered by minute warts, each covering an elongated pear-shaped cavity called *perithecium.* The perithecia lie rather close to one another in a somewhat denser cortex composed of more or less radial septate hyphæ, which cortex surrounds the looser medulla of the head. The individual perithecium is surrounded by a dense mycelium of slender hyphæ, constituting its wall, and opens through a narrow channel at the apex of the wart. From the floor of the perithecium there

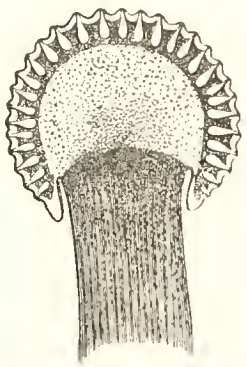


FIG. 24.—Section through capitulum showing perithecia (after Tulasne). (× 13.)

arise many tubes in the form of elongated clubs. These are the sporangia or *asci*, and each ascus contains eight filamentous *ascospores*. This determines the systematic position of *Claviceps*, in the large subdivision of fungi called *Ascomycetes;* since the asci are placed in a cup or perithecium, surrounded by

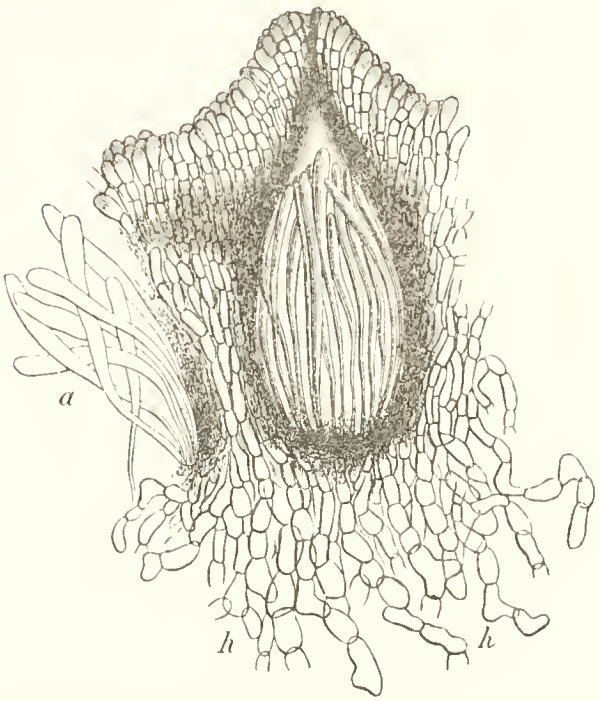


FIG. 25.—Section through perithecium. *h*, loose hyphae of the medulla; *a*, asci of a neighbouring perithecium (after Tulasne). (×170.)

FIG. 26.—Asci and spores of *Claviceps purpurea*. (×700.) (After Luerssen.)

mycelium, *Claviceps* further belongs to the order *Pyrenomycetes* (sub-order *Hypocreaceæ*). (See Figs. 24-26.)

The sexual process.—The systematic position of *Claviceps* would be further elucidated if a sexual process, which has been postulated in some other *Ascomycetes*, actually precedes the formation of asci. This sexual process was only described in *Claviceps* by Killian in 1919, after Fisch [1882] had denied its existence. The perithecia arise as loculi; inside and on the base of these are peculiar voluminous cells, which accumulate most of their protoplasm and their nuclei in their apical part. This portion widens and the nuclei in it become distributed in pairs. Soon two processes appear at the top of each cell, and grow out into branches. One of the branches (the antheridium)

twists round the other (the ascogonium). Inside the latter are six equidistant nuclei. At the point of contact between antheridium and ascogonium the cell walls disappear, the protoplasm of the two cells amalgamates, and the nuclei of the antheridium migrate to the ascogonium, in the lower part of which most of them collect. The apical part gradually dies off and its nuclei are resorbed; the basal portion elongates and becomes divided by transverse septa into cells each containing two nuclei. These cells are the primordia of the ascogenous hyphæ.

As an immediate sequel to the sexual process the perithecia are formed by the elongated cells adjoining the ascogonium separating from each other, and the space between them being filled up with hyphæ from the periphery of the loculus, which hyphæ intertwine and form the perithecial wall. The free ends of these hyphæ assume a clavate shape and become paraphyses. The ascogenous hyphæ lengthen along with the latter and recurve in the shape of a hook. Each of the two nuclei in them divides and the resulting four nuclei are distributed as follows: one passes to the apex, one to the base and two, probably male and female, remain in the bend. The portion of the hypha containing the two nuclei elongates, and the latter fuse, forming a single nucleus distinguished by its size, that of its nucleoli, and by its chromosomes. The elongated cell, containing this large nucleus, gives rise to the ascus.

The above sexual process is very primitive in that both the antheridium and ascogonium arise on the same branch. By this feature *Claviceps* is connected to some of the most primitive forms. On the other hand, it is complex as regards the development of the ascogenous hyphæ, and this complexity brings *Claviceps* close to the *Ascomycetes* proper (Rojdestvensky).

Dissemination and germination of ascospores. — The ascospores are set free by the rupture of the asci and the degeneration of the apical cells of the perithecium; as the result of a pressure set up in the perithecium through swelling of the surrounding mycelium, the ascospores are extruded on to the surface of the stroma and may be shot into the air to a height of several centimetres. Engelke placed sclerotia, which had germinated in a moist atmosphere, in the sun; on touching the perithecia with a needle, clouds of ascospores were expelled to a height of 6 cm. According to Rostowzew the ascospores

are always shot towards the light (2 to 8 cm.); the stalks of the stromata twist under the influence of light and thereby successively present different groups of perithecia, from which the spores are then released. The stromata are positively phototropic and negatively geotropic. According to Falck the ascospores are 50 μ to 75 μ long and 0·6 μ to 0·7 μ in diameter, so that their weight is about 14×10^{-9} mg.; when expelled a few centimetres into the air, they are readily carried by convection currents to the flowers, as Falck showed experimentally. On the other hand, Stäger found that the ascospores often emerged very slowly and stuck in a mucilaginous substance at the ostiole. He believes that insects are more important in distributing ascospores, a view adopted for *Paspalum* ergot by Rolfs and by Mitchell. It would seem that both means of distribution are possible; explosive ejection may occur after the ostiole has been sealed by drought, and a sufficient pressure arises in the perithecium. The ascospores are divided transversely by a number of septa. Under favourable conditions they may germinate within twenty-four hours, by putting out one or more germ-tubes of variable length. These grow out into the mycelium of the *Sphacelia* stage. Kühn, who first observed this, calculated that an average sclerotium may produce one million spores, each capable of starting the *Sphacelia* stage (Fig. 27).

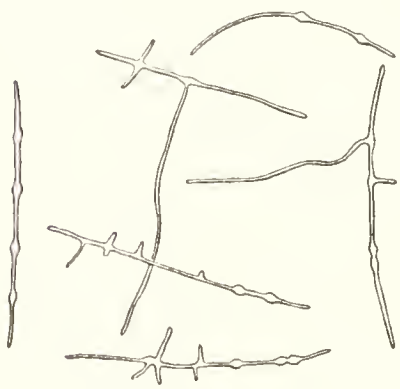


FIG. 27.—Germinating ascospores (after Kühn). (× 600.)

It would seem necessary that the germination of the sclerotia should coincide in point of time with the flowering of the rye; there is, however, considerable latitude, according to Kirchhoff, because the undeveloped apical flowers of the spike of rye are imperfectly enclosed by glumes and are thus apt to be infected well before the flowering period. The secretion of honey-dew, leading to secondary infection, does not begin until six to eight days after the primary infection with ascospores, and since the flowering period of the rye lasts only for about eight days, a general infection would hardly be possible, if the first attack could only take place on fully developed flowers, of which the glumes have separated.

The Sphacelia stage.—The infecting ascospores germinate on the moist stigmata of the flower to form the *Sphacelia* stage. According to Kirchhoff the hyphæ of the latter do not enter the ovary via the interior of the style (as do pollen-tubes) but grow down its outside and that of the ovary, until they enter the latter principally at its base; up till then the ovary is only surrounded by a superficial mycelium (Fig. 28). The growth of the *Sphacelia* brings about the secretion, by the host, of the honey-dew (Fig. 19), containing an enormous

FIG. 28.—*Claviceps purpurea*. *a*, very young ovary of Rye with the *Sphacelia* stage; *b*, older ovary, with the *Sphacelia* in its upper part, while the sclerotium is being formed in the lower; *c*, longitudinal section through the same stage as *b* (after Tulasne). (All the figures are enlarged—*a* about 8 times, *b* and *c* about 5 times.)

number of oval asexual spores or conidia, arising from the *Sphacelia* mycelium. This forms a soft, dirty white, slimy mass which in its lower portion contains canals and cavities. The whole surface of the mass, including the cavities, is lined with densely appressed elongated conidiophores, from which conidia are abstricted after a nucleus has passed into the apex of the conidiophore (Fig. 29). The honey-dew may cause secondary infection, by dropping from the upper flowers of a spike to the lower, but it is principally carried by insects. Mercier, for instance, found quantities of conidia on the skin and in the

intestine of a fly *Sciara Thomae*, L.; its faeces consisted almost entirely of these spores. Insects visit especially the periphery of a field and exceptionally tall plants of the interior, so that these are most liable to be ergotised. In undiluted honey-dew the conidia do not germinate, for the solution, containing reducing sugars, is about 2·33 molar (Kirchhoff). It is more-

FIG. 29.—Portion of Fig. 28 *c*, at the junction of *Sphacelia* (*s*) and sclerotium (*m*), showing the abstriction of conidia (*c*) (after Tulasne). (× 270-300.)

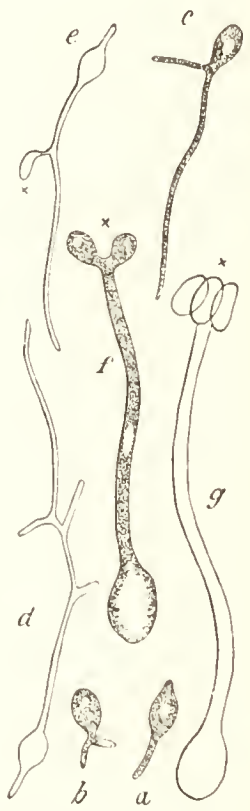


FIG. 30.—*a-d*, conidia in various stages of germination; *e-g*, germinated conidia producing secondary conidia (at *x*) (after Kühn.) (× 800).

over slightly acid, the acid being produced by the fungus. When the honey-dew is diluted (by rain under natural conditions) germination however takes place, in a tenfold dilution for instance, in ten to twelve hours. The conidia are somewhat shrunk in the strong solution (4 μ to 6 μ by 2 μ to 3 μ according to Tulasne) but expand after dilution to 7 μ by 4·5 μ (Kirchhoff). The conidia produce germ-tubes at one or both ends, and

the new mycelium very rapidly produces somewhat smaller secondary conidia (see Fig. 30).

The experimental infection of rye flowers with ascospores was first carried out by Durieu in 1856, that with conidia by Bonorden in 1858. Both with diluted honey-dew, and with a suspension of ascospores, Kirchhoff succeeded in 70 to 80 per cent. of the flowers. The infection with fragments of the sclerotium [Gibelli 1877] is much more difficult; Kirchhoff only succeeded with three flowers out of thirty-five. Under natural conditions infection by conidia is chiefly confined to the flowering period and the great susceptibility of rye, as compared with wheat, for instance, depends on the fact that the former grass, in contradistinction to the latter, depends mostly on cross-fertilisation, which requires the opening of the glumes and the exposure of the stigma to pollen. These same conditions simultaneously expose the stigma to ascospores and conidia of ergot. Immature rye flowers may, however, be readily infected five to six days before the opening of the glumes, if the latter are snipped off. During the first four days after fertilisation the great liability to infection is maintained, and then declines, disappearing altogether a fortnight after fertilisation, when the ovary has grown from 2 mm. to about 8 mm. These late infections give rise to "mixed" ergot grains, consisting of an upper pale portion of rye and a lower dark portion of fungus. The occurrence of such grains was used by Tulasne as an argument against the view that ergot is merely a transformed rye grain. Ordinarily the young ovary is invaded and destroyed by the *Sphacelia* mycelium, which forms a dirty white folded mass, containing irregular cavities and sometimes equalling the glumes in length. A transformation then begins at its lower end; numerous new branches insinuate themselves between the existing ones; all hyphæ become divided by transverse walls and increase in thickness, so that, as a result of mutual pressure, a hard pseudo-parenchyma is formed, the beginning of the sclerotium. As the process of transformation extends upwards, the production of honey-dew and of conidia ceases. At the same time a very thin cortex is formed, consisting of closely packed parallel hyphæ, which are violet or almost black, owing to the deposition of a colouring matter. Occasionally this is wanting, in an albino variety. The apex of the sclerotium may remain surmounted

by remnants of the *Sphacelia* stage, which may contain conidia still capable of germinating eleven months after the harvest (Stäger; *cf.* also B. Meyer).

Cultivation of the ergot fungus in pure culture as a saprophyte.—Brefeld already germinated ascospores on pieces of rye bread dipped in nutrient broth and so obtained the *Sphacelia* stage bearing conidia. B. Meyer [1888] started with conidia and obtained rapid growth on liquid media containing starch or glucose, albumen, peptone or asparagine, and the usual salts. Incidentally he noticed that conidia retain their power of germinating during several months; he had no indication of the formation of sclerotia. So-called microsclerotia were first obtained by Engelke [1902]. Rojdestvensky mentions experiments in A. A. Jaczewski's laboratory at St Petersburg in 1912, in which agar, malt extract and meat extract were used. Brown and Ranck [1915] cultivated *Claviceps paspali* on bean-pods.

Owing to the high price of ergot, then ruling, an attempt was made by Bonns [1922], in the laboratory of Eli Lilly & Co. of Indianapolis, to obtain sclerotia artificially. Starting from fragments cut aseptically from an almost mature sclerotium, he subcultured during many months on a variety of solid and liquid media. Cultures on rye meal yielded in six months a dense purple membrane covering a mycelial web, 2 to 3 mm. in thickness, consisting of cells which were a good deal larger than those of the natural sclerotium. The artificial sclerotium contained histamine but no trace of alkaloid, so that there was no promise of solving the economic problem in this fashion. Hecke [1921-22] grew the *Sphacelia* stage on malt extract, in an attempt to solve the same problem by artificial infection of rye in the field; his work is dealt with in a subsequent section. Kirchhoff [1929] made a detailed study of the nutritive requirements of the ergot fungus. He started mostly from fragments, taken from the inside of sclerotia which had been washed in corrosive sublimate, and generally used 2 per cent. agar slopes impregnated with salts and the carbon and nitrogen compounds to be investigated. Maltose, agar, cellulose, dextrin, starch, gum arabic, glycerol and the salts of a number of organic acids were not attacked. On the other hand, cane sugar, dextrose, levulose, galactose and mannitol were equally good sources of carbon, so that in practice 10 per cent. cane sugar was used. The fungus produces invertase, and the reducing sugars in

honey-dew either result from the cane-sugar of the rye or come as such directly from the host. Amylase and maltase are not produced by the fungus, nor is there apparently a ferment attacking mannitol. Although *Claviceps* is restricted to particular sources of carbon, it will take its nitrogen from almost any compound which is not poisonous: nitrates, ammonium salts, amino acids, amides, uric acid and proteins. The fungus produces proteolytic enzymes and a culture on gelatin rapidly sinks into the medium. In order to prevent an acid reaction and to induce the formation of sclerotia, Kirchhoff used 1 per cent. asparagine, to which an equivalent of alkali had been added. The peculiar odour of honey-dew he attributes to isobutyric acid. McCrae has also grown *Claviceps* saprophytically, chiefly on rye meal, and obtained microsclerotia; this author denies that Kirchhoff's sclerotia were comparable to natural ones, but nevertheless does not despair of completing the life cycle saprophytically. She finds that a current of oxygen greatly favours growth, and that sunlight favours the production of a red (not brown) colouring matter.[1] She claims that ergotoxine is produced in the mycelium, but the evidence for this is merely pharmacological and by no means conclusive; the cock's-comb tests were used, *inter alia*, but the vasomotor reversal was not.

The spreading of ergot.—As has been stated, the ascospores are chiefly distributed by air currents, and to a minor extent by insects, the conidia almost exclusively by insects, since they are embedded in honey-dew. Stäger [1903] has given a long list of insects visiting various hosts of *Claviceps;* they mostly suck honey-dew but occasionally also eat pollen; some of the commonest forms are *Melanostoma mellina*, *Rhagonycha fulva* and *Sciara Thomæ* (*cf.* also Mercier).

Neither ascospores nor conidia are likely to be carried very far, at most 50 to 100 yards, but the sclerotia may be carried through considerable distances. Although those on rye and other cultivated cereals, and on fodder grasses normally fall to the ground and germinate where they fall, many are harvested and may then be transported by human agency (for instance, *Paspalum* ergot to South Africa, ergot of rye and other ergots

[1] There is, however, but little that is new under the sun. Aymen in 1763 exposed the white cut surface of not quite ripe ergots to sunlight, and found that it became red and then black.

to New Zealand). Stäger [1922], however, found that the sclerotia from wild grasses are often disseminated by natural agencies. Thus the sclerotia on *Brachypodium sylvaticum* remain firmly attached to the flowers of the host; the lower palea of these is supplied with a long hooked awn, which attaches itself to the coat of animals. Sclerotia on *Agropyrum*, *Lolium*, *Alopecurus myosuroides* and *Arrhenaterum elatius* are also transported by animals. The light seeds and ergots of *Calamagrostis epigeios* are carried by the wind, since they adhere to the paleæ, which have a parachute of hairs. Stäger further considers that sclerotia on *Glyceria fluitans*, *Phragmites communis*, *Phalaris arundinacea*, *Molinia cærulea* are specially light, owing to air contained in them, so that they float for a long time on water, and are thus disseminated. Their high content of oil does not sufficiently explain why they float, since sclerotia formed on land plants generally sink.

Ergot in Relation to Agriculture.

Conditions favouring the growth of ergot.—A heavy infection of rye, such as caused epidemics in the past, is rare, and only arises through a coincidence of several circumstances. It has long been known that the chief factor is a wet season, at least on the Continent of Europe (in Ireland the growth of ergot is said to be favoured by a dry summer). There must be enough moisture in the spring for the *germination* of the sclerotia and the development of ascospores, but the *dissemination* of the latter is favoured by dry and windy weather. The atmospheric conditions during the flowering period of the rye are doubtless of the greatest importance; normally this period lasts only for a week, but it may be much prolonged by cold and rain. When infection has once taken place, the growth of the sclerotium is favoured by heat, which probably also increases its alkaloidal content and toxicity. All these factors contributed in exceptional years to make the rye crop particularly dangerous. Rojdestvensky [1927] considers that a rainy spring, a dry sunny interval just before and at the beginning of the flowering period of the rye, and rainy weather during the rest of this period are the conditions most favourable to a luxuriant development of ergot. He states that of recent years the prevalence of ergot in various provinces of Russia has been correlated with their

rainfall, relative humidity and number of overcast days in June and July.

Apart from the weather, local factors may have considerable effect, particularly in hilly country. Often a particular valley or even a single low-lying field was much more heavily ergotised than its neighbours, and led to sporadic outbreaks of ergotism.

The great susceptibility of rye, as compared with other cereals, is based on the fact that rye, unlike wheat or barley, depends largely on cross-fertilisation, and opens its glumes in order to receive pollen from other plants; after fertilisation the glumes are again closed, but when, owing to adverse weather or other circumstances, pollination does not occur, the glumes remain open much longer, and the risk of infection by ergot conidia is thereby increased (Wilson, Hecke). Ergot is generally more abundant on the edge of a field than in the middle, probably because the plants on the periphery are not so readily pollinated, or are more frequently visited by insects.

Measures for the control of ergot.—These depend in general on improved methods of agriculture (the yield of rye in Russia is about 10½ bushels per acre, in Germany, Belgium and Holland, about 24 bushels). Sowing clean seed is of course, important; the ergot can be partly eliminated from the latter by sieving, but better by flotation in a saturated salt solution; a saturated solution of potassium chloride (32 per cent.) is preferred by Nobbe to sodium chloride; it does not damage the seed, and can ultimately be used as a fertiliser (*cf.* also Friblin). This flotation[1] has of late years been used in North Dakota [Weniger 1924], and in Russia [Rojdestvensky 1928]; in the latter country cattle were poisoned by the skimmings. Clean seed does not, however, obviate the infection of the soil by sclerotia which fall off before or during the harvest. Recent attempts to induce Russian peasants to pick the ergot before the harvest failed, even when a good price was offered for it. Deep ploughing is effective, for sclerotia which are buried 25 cm. below the surface do not germinate. Rotation of crops is also very effective, for as a rule sclerotia do not germinate after one year and only cereal crops are attacked. It is further desirable to cut down wild grasses near the rye fields, for these may flower early and become a source of infection before the

[1] The washing of grain before milling, was already suggested by Hellwig [1699]: "thus the black grains would float uppermost."

rye flowers. A homogeneous crop, in which all plants flower at the same time, is desirable, and is favoured by pedigree seed, uniform manuring and sowing, etc. Late flowering varieties should not be grown near early ones and early sowing is recommended.

The relative resistance to ergot of various varieties of barley and of rye has been studied by Henning and by Tschermak, and correlated with the extent to which these varieties open their glumes in flowering. Sterile plants, which keep their glumes open, are a source of infection. Biffen observed that the hybrid of Rivet wheat (*Triticum turgidum*) with *T. vulgare* was attacked by ergot, whereas the parents were not. He concluded that Rivet wheat contains one of the factors necessary to produce susceptibility, but according to Vavilov the explanation is not to be sought on Mendelian lines, but merely in the sterility of some of the hybrid plants, in accordance with the work of Tschermak. Tulasne already observed that *Arundo Phragmites* was usually sterile in the neighbourhood of Paris, and was there particularly liable to be ergotised; so is the sterile perennial hybrid of *Secale cereale* with the wild *S. montanum*. The search for varieties resistant to *Claviceps* should aim at the production of plants which do not open their glumes.

Cultivation of ergot in the field. — Improvements of agriculture in Spain and political conditions in Russia have made ergot scarce, so that its artificial production has been investigated. Attempts by Bonns and by McCrae to do this entirely on a saprophytic medium have been mentioned above. More promising results have been obtained by Hecke, with the artificial infection of rye (*cf.* also Tschermak [1921, 1922], Falck [1922] and Fron [1926]). By simply sowing ergot with rye, less may be harvested than sown, and the yield is at most 1 per cent. of the rye (Hecke). It is necessary to infect the flowering rye artificially by spraying with a suspension of conidia. Although for this purpose 10 drops of honey-dew can be diluted with one litre of water, it is of course better to grow the *Sphacelia* stage. Hecke started with ascospores ejected by germinated sclerotia on to a cover-slip, and grew these spores in 6 to 12 per cent. glucose, 1 to 2 per cent. asparagine and the mineral salts recommended by Naegeli. They grow equally well in malt extract diluted with water (1 : 5; optimum temperature at least 25°). Since the *Sphacelia*

grows only on the surface, large conical flasks were employed, with the medium no deeper than 1 cm.

As regards the rye, the optimum conditions are of course the reverse of those indicated above for the control of ergot. The rye was sown in rows 20 cm. apart, with individual plants also 20 cm. apart, and very early, towards the end of August, at least a fortnight before the ordinary time (Hecke's experiments were made near Vienna). This sparse sowing causes each plant to send up several shoots, which flower at different times, and the flowering period is still further extended (from June to September) by sowing summer rye in the following spring on the same field. The wild *Secale montanum* which depends on cross-pollination even more than the cultivated varieties, is particularly suitable; hybrids between it and the cultivated varieties might be best of all, since they are apt to be perennial and sterile.

Hecke made use of Tschermak's discovery that rye flowers which would normally open after one or two days, can be made to do so almost at once by shaking them or by pulling the ears between the fingers. This manipulation was repeated daily for six days, until no more glumes opened, and each day the newly opened flowers were sprayed with a dilute suspension of conidia, through an atomizer. In this way 100 square metres could be treated by one labourer and produced 2·84 kilos of ergot (260 lbs. per acre). In the following year [1922] Hecke simplified the conditions by having the individual plants of each row only 1 to 2 cm. apart (so that they could be sown with a drill), and induced flowering by merely bending down the ears with a stick. All flowers, whether open or closed, were then sprayed. Since after stimulation they close again within ten minutes, no time must be lost. The full utilisation of the brief flowering period is most important, and Hecke's yield on winter rye was spoiled by the intervention of two public holidays! On summer rye he obtained 527 kilos of ergot per hectare (490 lbs. per acre). The great drawback of the above methods is the large amount of more or less trained labour required during one particular week of the year. Perhaps more is to be hoped from Hecke's experiments with hybrids of *S. cereale* and *S. montanum*. In these opening of the glumes cannot be induced artificially, so this manipulation was left out; he also left out spraying, and yet obtained a yield of 370 kilos

per hectare (340 lbs. per acre). The proximity of the artificially infected summer rye may have had something to do with this. An objection to the use of the hybrids on the large scale is that although they are perennial, they are sterile. Since with suitable laboratory accommodation the spraying fluid can be made available in large quantities, it would perhaps be best to grow ordinary rye by agricultural methods, and to rely on intensive spraying with suitable machinery, and to give up the artificial induction of flowering. McCrea recently carried out some field experiments on a small scale in southern Michigan, and concludes that there labour costs are too high to make the method desirable. Whilst the cultivation of ergot may not be commercially practical at present, it may become so in the future; improvements in agriculture make the drug more and more scarce so that, like other drugs, it may ultimately have to be cultivated, perhaps where labour is cheap, in a relatively warm climate.

Damage to agriculture.—The yield of rye grains is diminished, not only by their conversion into ergot, but also owing to the fact that flowers remain sterile, although they do not bear sclerotia (Seymour and McFarland; Kossobutzky). The elimination of the ergot from the harvested grain causes additional trouble, but may yield a valuable product; before the War the price of ergot was roughly twenty times that of rye.

The harmful effects on human beings are discussed in a separate chapter on ergotism, and are now avoided in nearly all countries. Here the damage to animals may, however, be mentioned, arising from the infection of fodder grasses. Ergotised rye grass (*Lolium perenne*) seems to be a particular source of danger. Tanner [1858] reported that a single breeder in Shropshire lost £1200 in three years from this cause. Cockayne [1912] examined New Zealand rye-grass seed containing up to 30 per cent. of ergot, and ergotism in cattle has been reported from that country by Charlton. Bessey described ergotism in cattle in Iowa and mentioned that an outbreak in Kansas in the winter of 1883-84 was so severe as to have been at first mistaken for foot-and-mouth disease. It was due to ergot on *Elymus canadensis*, cut as wild hay on the prairies, and bearing sclerotia nearly as large as those on rye. Ergotism of cattle in Iowa was again referred to by Stalker [1892] and in south Dakota by Williams [1893]; McNeil and

Pammel [1908] figure gangrenous hoofs resulting from ergotised hay. A Swiss outbreak in 1911 is mentioned by Vatter. More recently ergot on *Paspalum*, a fodder grass from the Argentine, has been a source of trouble. Its poisonous properties were investigated by Brown and Ranck [1915] in Mississippi, and Mitchell [1920] reported poisoning of cattle by the same ergot in Natal. In both cases the symptoms were chiefly nervous, in contradistinction to the gangrene of hoofs reported in other cases. The effects varied from a slight incöordination of movement to complete paralysis (see further under *C. paspali*, p. 108).

The symptoms of gangrenous ergotism in cattle are described and figured in the United States Department of Agriculture (*q.v.*) *Special Report on Diseases of Cattle*. The disease shows itself by lameness in one or more limbs, swelling about the ankle and a small slough or the loss of a toe. An indented ring may develop at any point below the knee or hock, when the distal portion is ultimately shed without loss of blood. Ergot may also cause serious irritation of the digestive tract, lethargy and paralysis. Tannin (to precipitate alkaloid) and castor-oil are given internally. Ergotism is distinguished from foot-and-mouth disease, and from mycotic stomatitis by the lack of lesions in the mouth, and by the presence of lesions at the tips of the ears, tail and lower part of limbs (see Fig. 31).

Forecasting of "ergot" years.—This is a Russian speciality, arising out of recent epidemics. Bakhtin [1925] and Kossobutzky [1929] aim at foretelling in June or July the prospective percentage by weight of ergot in the threshed grain, so that if the contamination threatens to exceed 0·15 per cent. (the maximum officially tolerated by the U.S.S.R.) precautionary measures can be taken. The best indication is afforded by the percentage of ergotised plants in a field, which is on the average forty-three times as great as the percentage of ergot by weight in the unharvested grain (Bakhtin). Kossobutzky considers that half the ergot is eliminated in harvesting and threshing, so that the factor becomes about 86. Bondartzeff [1929] has confirmed this, by finding in an experimental field 0·52 to 0·92 per cent. of ergot in the unharvested and 0·30 to 0·42 per cent. in the threshed grain. The application of the method may be illustrated by the epidemic of ergotism of 1926, when 75 per cent. of the rye plants were said to be infected; this would give

FIG. 31.—Ergotism in Cattle (after Marx).
(Reproduced by permission from U.S. Department of Agriculture *Special Report on Diseases of Cattle.*)

an amount of ergot in threshed grain of $\frac{75}{86}$ or 0·9 per cent.; the amount actually observed in trade samples was usually 0·44 to 1·12 per cent. The percentage of infected ears, and the average number of infected spikelets per ear furnish less reliable indications.

Species of *Claviceps*.

In all some twenty species have been named, eight of which are indigenous to Europe and twelve to America. From Asia and Africa there are only indications of one or two unnamed indigenous species, whilst all the ergots recorded from Australasia appear to have been introduced. Among the characters used in classification, the shape and size of the sclerotium are of minor importance, since they vary a good deal with the host, at least in *C. purpurea*, which occurs on many grasses; the colour of the sclerotium is rather more significant. It is only when the latter germinates that the chief specific characters can be observed, such as shape, size and colour of the stromata; the stipe may be short and stout, or it may be filiform; it may or may not be covered by loose hyphæ; the capitula vary in size, and although usually globular, they are sometimes elongated or even club-shaped. The number and shape of the perithecia, and the extent to which they are distributed over the surface of the capitulum, are also specific characters, as is the extent to which the perithecia are embedded; occasionally they protrude so much beyond the surface of the capitulum that they are almost free. Paraphyses are present in some species, absent in others. The dimensions of the perithecia, asci, ascospores and conidia are also employed in classification; the length of the ascospores, for instance, may be no more than 50 μ, or as much as 300 μ. The ascospores are, however, always very thin (0·5 μ to 1 μ); on germination they may be divided into segments by three (or many?) transverse septa. A list of works containing illustrations of *Claviceps* species, particularly of *C. purpurea*, will be found in Saccardo: *Sylloge Fungorum*, 1910, vol. xix. (*Index Iconum Fungorum*), pp. 331-334. The microscopical features of ergot of rye are well illustrated by Sorauer [1928] and by Gilg, Brandt and Schürhoff [1927].

A. **European species.** — Tulasne in 1853 already gave accurate descriptions of three species.

C. PURPUREA (Fr.), Tul.; Saccardo, *Sylloge Fungorum*, ii. 564.

C. MICROCEPHALA (Wallr.), Tul.; *Sacc. Syll.*, ii. 565.

This species, like the previous one, had already been described as *Kentrosporium*, *Sphæria* and *Cordyceps* by several previous authors. The small sclerotia, mostly 4 mm., sometimes 7 to 9 mm. long, produce filiform stipes, 1 to 2 cm. in length, bearing small capitula hardly 0·7 mm. in diameter (hence the name). It is most abundant on the Common Reed, *Phragmites communis*, Trin.; Rostrup [1897] counted 912 sclerotia on a single stem top. It certainly occurs also on *Aira cæspitosa*, L., *Molinia cærulea*, Moench., *Nardus stricta*, L., and *Poa annua*, L. It has been recorded on a number of other grasses, but seems to have been wrongly identified in some of these cases.

C. NIGRICANS, Tul.; *Sacc. Syll.*, ii. 565.

The sclerotia and stromata are blackish purple, but resemble those of *C. purpurea* in most other respects. This is the only well-defined species not parasitic on Grasses; it occurs on a few of the Cyperaceæ (Sedge family); *Scirpus* (= *Heleocharis*) *multicaulis*, Sm., *S. palustris*, L., *S. uniglumis*, Lk., *S. lacustris*, L.

C. PUSILLA, Ces.; *Sacc. Syll.*, ii. 565.

First mentioned by de Cesati in 1848 as growing on the seeds of *Andropogon Ischæmum*, near Brescia in Lombardy, it was described by him in 1861, but does not seem to have been met with by others. It differs from *C. microcephala* by the straw-coloured stipe and somewhat darker capitulum; the latter is surrounded at its base by a collar-like appendage.

C. SETULOSA (Quel.), Sacc.; *Sac. Syll.*, ii. 566.

Found by Quélet on fodder grasses in mountain pastures in the Jura, it was described by him as a *Cordyceps* in 1876. Stipe flexuose, slender 1 cm. long, straw-coloured, covered at its base with white silken hairs; capitulum globose, 1 mm. in diameter, chamois coloured, covered with fine brown papillæ.

C. WILSONI, Cooke, *Sacc. Syll.*, ix. 998.

This is a very distinct, indeed an aberrant species, originally described and figured as *Barya aurantiaca* by Plowright and Wilson, who found it on *Glyceria fluitans*, Br., near Aberdeen. They regarded it as parasitic on the sclerotium of *C. purpurea*,

because with its spores they could not infect some other grasses which are habitually ergotised by the latter fungus. According to Cooke this is a misconception (similar to that of Tulasne's predecessors about the fructifications of *C. purpurea*). *C. Wilsoni* has been repeatedly met with, in Britain and in Switzerland, and successful inoculation of *Glyceria fluitans* has been recorded. The sclerotium is yellowish-white in colour; the stipe may be much thicker at its base than at its apex; the capitulum is club-shaped, many times as long as broad, and bears perithecia only on its distal half; the latter are very prominent, almost free, giving a very rough appearance to the capitulum. The spores are much longer than in the other European species (140 μ).

C. SESLERIÆ, Stäger; *Sacc. Syll.*, xxii. 509.

Found by Stäger [1907] on *Sesleria cærulea*, Ard., and *S. argentea* in Switzerland. *Melica* spp. could be infected artificially, but the infection did not proceed beyond the *Sphacelia* stage. The ergot of *Sesleria* had previously been identified as *C. purpurea*, but Stäger failed to infect with it typical hosts of the latter fungus. There are also some morphological differences: large conidia (10·5 to 14 μ by 3·5 to 7 μ); a cross-section of the sclerotium shows a dark stellate mass at the centre. This mass is also present in *C. purpurea* (see Micrography, p. 87), but is not so well marked.

C. JUNCI, Adams; *Sacc. Syll.*, xxii. 509.

Adams [1907] found only the *Sphacelia* stage, filling the ovary of *Juncus glaucus*, Ehrh., with an immense number of conidia (7·0 to 10·3 μ × 2·8 to 3·5 μ) (September, Co. Dublin). This is the only record of an infection resembling *Claviceps* in the *Juncaceæ* (Rush family) but in the absence of a germinating sclerotium it is impossible to say to what species of *Claviceps*, if any, the infecting fungus belonged.

***B.* American species.**—By far the most important and best known is that on *Paspalum* spp., particularly on *P. dilatatum* Poir., a valuable fodder grass of the S. American Pampas, which during the first decade of the present century attained considerable prominence in the southern United States and was also introduced as a fodder grass into Natal and other sub-tropical countries, together with its ergot, which is particularly poisonous and seriously diminishes the usefulness of *Paspalum*.

Sclerotia on *Paspalum* were described as long ago as 1822 by Schweinitz as *Sclerotium paspali*, and later by Fries; they were noticed in 1902 in Maryland by Norton. Stevens and Hall [1910] found them in N. Carolina on *P. dilatatum* and *P. laeve* in such quantity that over large areas every plant may bear spikes showing one or more sclerotia. On germination these authors distinguished two species.

C. PASPALI, Stev. et Hall; *Sacc. Syll.*, xxii. 508.

Sclerotia yellow to grey, globose, 3 (2 to 4) mm. in diameter, roughened when mature, usually 2 to 3 stromata; stipe filiform, short to medium, usually not more than 1 cm. long (0·3 to 1·5 cm.); capitulum dull yellow; perithecia all over the capitulum, oval, 340 × 119 μ; asci 174 μ long; spores 101 × 0·5 to 1 μ; conidia 5 × 15 μ.

C. ROLFSII, Stev. et Hall; *Sacc. Syll.*, xxii. 508.

Stipe filiform, but thicker than in *C. paspali*, 1 to 1·5 cm. long; perithecia few, mostly on distal portion of capitulum, cylindrical ovate, 816 × 225 μ; asci 375 × 3 μ; spores 260 to 275 × 0·5 to 1 μ. *C. paspali* was also described and figured by H. B. Brown [1916], who found grass lands in Mississippi heavily infected (often 90 per cent. of the old flowering heads). The sclerotia fall to the ground with the spikelets and germinate in May after a few days of rainy weather, just after the host begins to flower. The honey-dew appeared after artificial infection in seven days, but in the field not until early June, three to four weeks after the germinating sclerotia were found. In favourable weather the sclerotia are 1 to 2 mm. in diameter within one week after the *Sphacelia* stage has been at its height. Sclerotia are largest and most plentiful in September and October; they may themselves, while still on their host, be attacked by moulds (*Fusarium* spp.).

Brown and Ranck [1916] cultivated the fungus artificially and also reported on the poisonous properties of the sclerotia; 1 grm. of the extract kills guinea-pigs within a few hours; cattle perish under the influence of the poison by falling down out of reach of water and feed, or are drowned in shallow water during a nervous paroxysm. The sclerotia and the extract from them did not lose the toxicity in ten months. The *Sphacelia* stage is non-toxic. Similar observations were made a few years later by Mitchell in Natal; the effects are

described as varying from muscular tremors and lack of co-ordination of movements to complete paralysis. Infection occurs through beetles (*Carabidæ*) collecting spores from the sclerotia on the ground and then climbing up the *Paspalum* shoots in order to start a flight. Rosen found ergot on *Paspalum floridanum* in Florida and Shepherd observed a *Sphacelia* stage on *P. dilatatum* and on *Panicum maximum* in Mauritius. A fungus has also been reported on *P. dilatatum* in its original home by Hauman, who called it *Claviceps deliquescens* and states that the "honey grass" is called "Pasto miel" in the Argentine. Soriano believes this fungus to be identical with *C. paspali*, which seems likely (a quite different species *C. lutea* (see below), also occurs on *Paspalum*, however).

The other American species have only been recorded once.

C. PHILIPPII, Rehm; *Sacc. Syll.*, ix. 998.

From Mergui, Chile. Sclerotia large (2 to 2·5 cm.) and quite black in colour. The host is not recorded by Rehm.

C. BALANSIOIDES, A. Möller; *Sacc. Syll.*, xvi. 609.

On *Echinochloa* near Blumenau, S. Brazil. The stipes may reach a length of 8 cm. and the capitula are up to 5 mm. in diameter. According to Möller this species is intermediate between *Balansia* and *Claviceps*.

C. LUTEA, A. Möller; *Sacc. Syll.*, xvi. 609.

On *Paspalum* sp. in Brazil; the pale yellow sclerotia have stipes up to 4 cm. in length.

C. RANUNCULOIDES, A. Möller; *Sacc. Syll.*, xvi. 609.

On *Setaria* spp. near Blumenau, S. Brazil. The perithecia are almost free, so that the capitulum recalls the syncarp of *Ranunculus*.

C. ULEANA, P. Hennings; *Sacc. Syll.*, xvi. 610.

On *Panicum* in Para province, N. Brazil.

C. PATOUILLARDIANA, P. Hennings; *Sacc. Syll.*, xvi. 610.

On grass seeds in Guadeloupe; described by Patouillard as *C. pallida*, but since this name was already in use, Hennings applied a new one. It does not grow from a sclerotium, but from the seeds themselves.

C. PALLIDA (Wint.), P. Hennings; *Sacc. Syll.*, xvi. 610.

Winter first described it as *Balansia pallida*, growing on

Luziola, a grass of N. Brazil. Hennings [1899] ranged it under *Claviceps* and [1900] described a var. *Orthocladae* growing on *Orthoclada* sp.

C. CINEREA, D. Griffiths; *Sacc. Syll.*, xvii. 820.

On *Hilaria mutica* and *H. cenchroides* in southern Arizona; Griffiths [1901]. This is a relatively large ergot from a very dry and hot desert region; the sclerotia are 1·5 to 3 cm. in length and 1·75 to 2·5 mm. in diameter, dark grey at their base (which is permanently invested by the flowering glumes of the host), light grey towards their apex. The short, stout, white stipe bears capitula, 1·75 to 2·75 mm. in diameter; ascospores 100 to 120 × 1 to 1·5 μ. The sclerotia germinate with exceptional rapidity, forming ripe perithecia in twenty days.

C. TRIPSACI, Stevens et Hall; *Sacc. Syll.*, xxii. 509.

On *Tripsacum dactyloides* in N. Carolina. Sclerotia smooth, white to dark brown or black, nearly conical, 4 to 5 mm. in diameter at base; the stipes are apt to fork and are 1 to 1·5 cm. long; the conidia are peculiar, fusoid or lunulate in shape (resembling *Fusarium* spores) and are exceptionally large 17·4 to 37·7 μ × 2·9 to 8·7 μ.

CLAVICEPS? CARICINA, D. Griffiths; *Sacc. Syll.*, xvii. 820.

On *Carex Nebraskensis* Dewey, in Oregon. The germination of the sclerotia was not observed so that it is as the author [1902] says "a wild guess" whether this fungus is a *Claviceps* at all; according to Groh [1911] it is not, but yet this author refers an ungerminated sclerotium on another species of *Carex* in Quebec to *Claviceps* without, however, giving a specific name.

This exhausts the named species of *Claviceps*. An ergot on wild rice, *Zizania aquatica*, L., used as a cereal by the North American Indians, and on *Z. palustris*, L., has been studied by Fyles; the sclerotia germinate very rapidly, sometimes within a few weeks of sowing, and produce numerous stromata (smallest number observed, 11, largest 48). Even broken pieces of ergots produce 3 to 7 stromata, and sclerotia may germinate when merely floating on water. The stipes are lavender in colour and may reach a length of 5 cm.; the capitula are 2·5 mm. in diameter, the spores are 150 to 180 μ long. These and other characters distinguish this ergot from *C. purpurea* with which it has formerly been identified. Its spores, moreover, do not

infect the common hosts of the latter species, but wild rice was even infected with conidia nine months old.

The introduction of *C. paspali* into South Africa has been mentioned above; *C. purpurea* has been found on *Pennisetum* in Cape Colony by H. and P. Sydow.

In tropical **Africa** and in **India** certain cultivated millets are attacked by a "sugary disease" which is almost certainly the *Sphacelia* stage of yet another species of *Claviceps*, although its life history has not been worked out. The fungus seems to have been first recorded from German East Africa by Zimmermann [1904] who had no doubt as to the genus, although he did not obtain the ascogenous stage; he found it on *Pennisetum spicatum*, "Negerhirse" (negro millet). I have seen no further reference until 1926, since when this or a similar fungus has been mentioned in the literature at least half a dozen times. Bunting [1926, 1928] reported from the Gold Coast a "sugary disease" on *Pennisetum typhoideum*, Rich., the bulrush millet; he also found it on a wild *Andropogon*. Ritchie [1926] reported serious damage by a *Sphacelia* to *P. typhoideum* in the Tanganyika Territory, and in Kenya Colony. *Andropogon Sorghum*, Brot. = *Sorghum vulgare*, Pers. (Indian millet or Jowar) was also attacked. In the same year there was yet a third publication, by Ajrekar, describing a disease of Jowar (*Sorghum vulgare*) which disease occurs in the Deccan and Karnatic and is known in Marathi as *Sakharya* (= sugary). The sugary secretion contains numerous conidia ($15\,\mu \times 7{\cdot}5\,\mu$) which germinate in water like those of *Claviceps*. A sclerotium is formed, of which according to Ajrekar the upper portion is overgrown with greyish-white hyphæ and yeasts, while the base is attacked by an entirely different fungus *Cerebella*. Presumably for this reason the attempts to germinate the sclerotium failed. A specimen of *Sorghum* in the herbarium of the Imperial Bureau of Mycology shows, however, numerous slightly curved sclerotia, 10 to 12 mm. × 2 mm. which, but for their pale grey colour and the absence of alkaloid, resemble those of ergot of rye (Fig. 40, p. 208). Ajrekar observed the infection also on *Andropogon caricosus*, and on *Ischæmum pilosum*; true ergot bodies, uninfected by *Cerebella*, were seen only on *Pennisetum Alopecurus*.

The economic importance of the disease is stated not to be great in India. Some varieties of Jowar, particularly those flowering in November and December, are more liable to attack

than others, and the disease is most prevalent in a cold and wet season. Robertson [1928], however, reported that "sugary disease" was very prevalent and severe on fodder *Sorghum* in Mandalay; long hard horn-like sclerotia are produced, and Rhind [1928] also mentions *Sphacelia* in Burma on *Sorghum* and on *Panicum prostratum*.

Ergots on *Calamagrostis javanica* and *Festuca nubigena* from Java are mentioned by Stäger [1910].

No ergots indigenous to Australia or New Zealand seem to have been reported. Wilson [1875] states that the Canterbury Agricultural Association offered a prize for an essay on the recent appearance of ergot in rye and other grasses, and on the best mode of preventing the disease; there are several references to the spread of ergot in **New Zealand** (Cockayne, Kirk) and to ergotism in cattle (Charlton). Cockayne [1912] reported that rye-grass seed (*Lolium perenne*) harvested in the Manawatu district contained 2 to 30 per cent. of ergot. The ergot of New Zealand tall Fescue (*Festuca arundinacea* = *F. elatior*) is referred to on p. 136.

Ergot on wheat seems to have been first noted in Australia by McAlpine [1892]; he believed it to have been transmitted from another imported grass, *Lolium*.

Hosts of *Claviceps* and Biological Races.

A systematic list of European hosts is given by Oudemans, but it is far from complete. Atanasoff mentions 124 species and varieties of grasses, known to be ergotised, with a literature reference to each. The species of *Claviceps* has, however, only been definitely fixed in a limited number of cases, by germination of the sclerotium or by inoculation experiments. Naturally most data refer to *C. purpurea;* after this to *C. microcephala*. In general each species of the fungus is restricted to particular hosts (for instance *C. nigricans* to *Cyperaceæ*); rarely the same host is attacked by more than one species of *Claviceps*. Indeed the specialisation may go further. It has long been known that the parasitic fungi inhabiting a number of host plants may be morphologically indistinguishable, and yet cannot always be transferred from one species of host to another (*cf.*, *e.g.* Reed and Vavilov). This has led to the division of the morphological species of the fungus into various "physiological" or "biological" races, of which the spores can only infect

hosts proper to that race. This phenomenon also applies to at least two species of *Claviceps*. The distribution of the races can only be studied by infection experiments, of which many have been made by Stäger, but so far hardly by other investigators. An idea of the vast scope for experimentation will be gained by considering that, since at least 100 grasses can be infected by *Claviceps purpurea*, 9900 infection experiments can be made with these grasses alone ($n(n-1)$; A to B and B to A). There are even finer gradations of infectivity; conidia and ascospores may not always produce the same result; moreover, on some hosts the infection does not as a rule proceed beyond the *Sphacelia* stage, so that sclerotia are rarely formed in these cases. Stäger mostly infected grasses with diluted honey-dew, either in a greenhouse, or in the open, when the ears have to be protected by gauze. They were sprayed with an atomizer, or the flowers were dipped into the suspension of conidia. As an example we may first mention the biological recognition of a species. Using both conidia and ascospores of the *Claviceps* on *Glyceria fluitans*, Stäger [1903] inoculated this grass and 17 species from other genera. Whilst the *Glyceria* specimens became heavily ergotised, all the other grasses were immune. Indeed this *Claviceps* had already been recognised as a separate species *C. Wilsoni*, on morphological grounds, and has so far only been found on *Glyceria fluitans*. With the biological races inside the limits of the same species of *Claviceps* the results are almost as definite, although doubts may occasionally arise.

Races of *C. purpurea*.—Ergot of rye was transferred by Stäger to some sixteen grasses and according to him constitutes a biological race *secalina* of *C. purpurea* which for the sake of brevity we will here denote by p_1. It infects barley and wheat [Stäger 1903, 1922]. It also infects *Festuca pratensis* (=*elatior*) which is remarkable, since the ergot of the latter grass, according to Smith and Timmis, differs from ergot of rye in yielding the alkaloid ergotamine. The race p_1 infects *Bromus sterilis*, but not *B. erectus*; it infects *Poa cæsia*, *P. hybrida*, *P. pratensis* and *P. sudetica*, but not *P. annua*, nor *P. fertilis*. *P. alpina* and *P. concinna* show an intermediate behaviour, suffering only a slight transitory infection which does not produce sclerotia. Hence within the limits of a single genus of grasses various degrees of susceptibility are encountered. The *secalina* race

produces the *Sphacelia* stage on *Anthoxanthum odoratum*, but no sclerotia, or only rudimentary ones. Yet *Anthoxanthum* is parasitised naturally by an ergot, which, when transferred artificially, still produces abundant sclerotia on it and on some other grasses, including rye and a few other hosts of p_1. Possibly *Anthoxanthum* ergot belongs to a race separate from that typical of rye, but having a number of hosts in common with it (e.g. *Anthoxanthum*, *Arrhenaterum elatius*, *Poa pratensis*, Rye).

The results are more definite with another race p_2, which has as only real host *Brachypodium sylvaticum* [Stäger 1905]. Ascospores from sclerotia formed on this grass also infect *Milium effusum*, and indeed induce on it an abundant secretion of honey-dew, but no formation of sclerotia. The same ascospores further infect *Poa pratensis* and *P. trivialis* but only to a very slight extent; they produce no infection at all on rye, *Anthoxanthum* or other typical hosts of p_1.

The honey-dew from *Milium* infects *Brachypodium* only, but has no effect on any other grass, not even on *Poa pratensis* and *P. trivialis*, which are slightly susceptible to ascospores from *Brachypodium sylvaticum*. Indeed, the conidia from *Milium* do not even infect other species of *Brachypodium*, such as *B. pinnatum*. (A similar difference within the genera *Bromus* and *Poa* was mentioned above in relation to p_1.) According to Stäger there is an interesting relationship between *Brachypodium sylvaticum* and *Milium effusum*; the latter grass flowers in May and becomes infected by ascospores from the sclerotia of the first named, which flowers much later, when ascospores are no longer available. The *Brachypodium* is therefore normally infected by conidia from *Milium*, so that two hosts are required as a rule. (There is a close analogy to this in *Sclerotinia ledi*; a more remote analogy is the well-known case of the Rusts, to which two hosts are essential, *e.g.* the Barberry and a Grass, for the formation of two morphologically distinct generations.)

It appears from Stäger's experiments [1903] that there is yet another race p_3 of *C. purpurea*, on *Lolium perenne* (rye-grass). It infects other species of *Lolium* and also *Bromus erectus*, which are all immune to p_1 and p_2. The *Lolium* race cannot be transferred to the hosts of these other races, in particular not to rye, which is contrary to the common statement that rye

fields may become infected from wild rye-grass growing in their vicinity. It is noteworthy that rye-grass flowers much later than rye (see Fig. 18, p. 86).

Races of *C. microcephala*.—The most abundant host of this *Claviceps* is the common reed, *Phragmites communis*, on which it produces numerous sclerotia, but little honey-dew. It also infects *Aira cæspitosa*, *Molinia cærulea* (on which honey-dew is abundant) and *Nardus stricta*. Stäger was able to start the infection with conidia from *Aira* and from *Molinia;* these four grasses are hosts of a race m_1. Another ergot appears to be limited to *Poa annua*, and could not be transferred to any other grass. Stäger at first considered it to be *C. purpurea*, but after morphological study of the germinated sclerotium he later [1908] concluded that it is a special race (m_2) of *C. microcephala;* his identification of the species is in accordance with that of other authors, *e.g.* Blas and Bondartzeff [1903].

***Claviceps sesleriæ*.**—This ergot was found by Stäger on *Sesleria cærulea* and after inoculation induced a *Sphacelia* stage on *Melica uniflora* and *M. nutans*, which does not, however, occur naturally on the latter grasses, nor does it ever produce sclerotia on them. Some sixteen other species were entirely immune. Because of some morphological differences (taken in conjunction with its biological behaviour) Stäger has described the ergot of *Sesleria* as a separate species of *Claviceps*. *Sesleria* is immune to various forms of *C. purpurea*. On the other hand, *Melica nutans* can be infected by *C. purpurea* [p_1 from *Festuca arundinacea*, Stäger 1908], as well as by *C. sesleriæ*, so that we have here an example of a grass which can serve as host to two species of *Claviceps;* in neither case, however, does the infection proceed beyond the *Sphacelia* stage. There may be some other cases of two ergots on the same grass, but it is evident from Stäger's work that they are rare, much rarer than would appear from the literature. Thus in the *Enumeratio* of Oudemans [1924] some fifty-eight hosts of *Claviceps* are recorded, of which nine are stated to be parasitised by two species. Evidently errors have arisen by mistaking the identity of the parasite; both *C. purpurea* and *C. Wilsoni* are recorded for *Glyceria fluitans*, but Stäger failed to infect this grass with the former fungus. Similarly the mention by Oudemans of *C. microcephala* (in addition to that of *C. purpurea*) on *Anthoxanthum odoratum* and on *Arrhenaterum elatius* is contrary to Stäger's

results. The same applies to the supposed occurrence of *C. purpurea* on *Molinia* and on *Nardus;* these grasses appear to be attacked by *C. microcephala* only.

Few inoculation experiments have been made by botanists other than Stäger. Fyles found nine common grasses immune to the ergot of *Zizania aquatica*, which fungus she therefore considers to be a separate species. McFarland added *Bromus inermis* and *Agropyron repens* to those grasses whose ergot infects rye (*i.e.* to hosts of p_1).

In his paper on wheat ergot Stäger [1922] calls attention to the difficulties of infecting wheat, the glumes of which open daily for a quarter of an hour only, or not at all in cold weather; he is further inclined to question his negative results of 1903 with *Lolium*, which also keeps its glumes closed. Perhaps he went too far; perhaps he distinguished too many biological races; yet his pioneering work in this field deserves special attention. His results have been embodied in the list of ergot hosts given below.

This list is based on that by Rojdestvensky, who in turn utilised that of Atanasoff, together with two Russian herbaria (this accounts for the inclusion of some Eastern, European and Asiatic grasses, not previously recorded as ergotised). I have myself incorporated recent records, chiefly American and tropical, together with hosts of less known species of *Claviceps*. In this way the list has grown to close on 200 species and varieties, or more than three times the number given in the *Enumeratio* of Oudemans. In order to avoid duplication, such as occurs in Atanasoff's list, and results from the use of various synonyms for the same host plant, a uniform system of nomenclature is required; I have adopted that of the *Index Kewensis* and included those other synonyms by which hosts have been recorded in the literature, where, unfortunately, the authority is not always appended to the specific name. One or two references have been added in most cases where the original could be consulted; these references are of unequal value, ranging from the mere statement that the host is infected by a *Sphacelia*, due to some kind of *Claviceps*, to the record of numerous inoculation experiments. Where the species of *Claviceps* has been established by such experiments, or by morphological study, it is indicated (p = *purpurea*, m = *microcephala*, s = *sesleriæ*, w = *wilsoni*, z = the ergot on *Zizania*).

Where the species of *Claviceps* is not indicated it may in general be presumed to be *C. purpurea*. Inoculation experiments are recorded by prefixing the signs + and − ; ± means that the inoculation resulted in a *Sphacelia* stage but not in sclerotia ; ∓ means that infection resulted from ascospores, but not from conidia. With the exception of the experiments + z, and − z, due to Fyles, and two results of McFarland, all the inoculation experiments are due to Stäger. Hence, for example, the letters after *Agropyron repens* mean that an ergot on this grass was identified by Tulasne (on morphological grounds) as *C. purpurea*, and that McFarland succeeded in infecting the *Agropyron* with the race *secalina* of this fungus. Similarly the letters after *Poa prateusis* indicate, that Stäger could infect it with the *secalina* race, and with ascospores, but not with conidia of *Brachypodium* ergot ; further, that he failed to infect it with the *Lolium* race of *C. purpurea*, also with *C. Sesleriæ* and *C. Wilsoni*, and that Fyles could not infect *Poa prateusis* with the ergot of wild rice (*Zizania*).

LIST OF ERGOT HOSTS.

GRAMINEÆ.

AGROPYRON . .	acutum *Roem. et Schult.*	Rostrup [1902].
	barbulatum *Schur.*	
	caninum *Beauv.*	Lind ; Williams.
	cristatum *J. Gaertn.*	Mains.
	divergens *Nees.*	Anderson.
	glaucum *Roem. et Schult.*	Williams.
	inerme *Rydberg.*	Mains.
	junceum *Beauv.*	Jaap.
	junceum *Beauv.* × Elymus arenarius *L.*	Jaap.
	maritimum *Beauv.*	
	occidentale *Scribn.*	
	occidentale *Scribn.* × A. repens *Beauv.*	
	repens *Beauv.*	p Tulasne ; $+p_1$ McFarland.
	rigidum *Beauv.*	
	Smithii *Rydberg.*	Mains.
	spicatum *Scribn. et J. G. Sm.*	
	strigosum *Boiss.*	
	tenerum *Vasey.*	p − z.
	violaceum *Vasey.*	Anderson.
AGROSTIS . . .	alba *L.*	Rostrup [1902] ; Weniger.
	hiemalis *B. S. et P.* = scabra *Willd.*	
	scabra *Willd.*	Weniger.
	Spica-venti *L.* = Apera Spica-venti *Beauv.*	
	stolonifera *L.*	Galama.

AGROSTIS . . .	sylvatica *Huds.* = alba *L.*	
	vulgaris *With.*	Kühn ; Frank.
AIRA	cæspitosa *L.* = Deschampsia cæspitosa *Beauv.*	
	cristata *L.* = Kœleria cristata *Pers.*	
	flexuosa *L.* = Deschampsia flexuosa *Trin.*	
ALOPECURUS . .	agrestis *L.*	p (Tulasne) ; Lind.
	alpestris *Wahl.* = pratensis *L.*	
	alpinus *Sm.*	
	arundinaceus *Poir.*	
	fulvus *Sm.* = geniculatus *L.*	
	geniculatus *L.*	Galama ; m Blas.
	myosuroides *Huds.* = agrestis *L.*	
	pratensis *L.*	(Frank) p_1? $-p_3 - m_1 - z$.
	ruthenicus *Weinm.* = arundinaceus *Poir.*	
	ventricosus *Pers.* = arundinaceus *Poir.*	
AMMOPHILA . .	arenaria *Link.* = arundinacea *Host.*	
	arundinacea *Host.*	p (Tulasne, Lutz) $-$ w.
	arundinacea *Host.* × Calamagrostis epigeios *Roth.*	
	baltica *Link.*	Rostrup (1902).
AMPELODESMA .	tenax *Link.*	Ducellier.
ANDROPOGON .	caricosus *L.*	Sphacelia (Ajrekar).
	Gayanus *Kunth.* var. bisquamulatus Sphac. (Bunting).	
	Ischæmum *L.*	C. pusilla (de Cesati).
	Sorghum *Brot.* = Sorghum vulgare *Pers.*	
ANTHOXANTHUM	odoratum *L.* (p and m Blas) $\pm p_1 - p_2 - p_3 - m_1 - s - w$.	
APERA	Spica-venti *Beauv.*	Galama.
ARRHENATERUM	avenaceum *Beauv.* $+p_1 - p_2 - p_3 - m_1 - m_2 - s - w - z$.	
	elatius *Beauv.* = avenaceum *Beauv.*	
	erianthum *B. et R.*	m Blas.
ARUNDO . . .	arenaria *L.* = Ammophila arundinacea *Host.*	
	calamagrostis *L.* = Calamagrostis lanceolata *Roth.*	
	cinnoides *Muhl.* = Deyeuxia Nuttalliana *Vasey.*	
	Pliniana *Turra.*	
	phragmites *L.* = Phragmites communis *Trin.*	
ASPERELLA . .	Hystrix Humb.	Mains.
ATAXIA	Horsfieldii *Kunth.* = Hierochloë Horsfieldii *Maxim.*	
AVENA	barbata *Brot.*	
	elatior *L.* = Arrhenatherum elatius *Beauv.*	
	fatua *L.*	Ducellier.
	flavescens *L.* = Trisetum pratense *Beauv.*	
	pratensis *L.*	Dietrich.
	pubescens *Huds.*	
	sativa *L.*	(p Tulasne ; Ducellier) ; $-$ z.
BECKMANNIA . .	erucæformis *Host.*	
BRACHYPODIUM .	distachyum *Beauv.*	Mains.
	pinnatum *Beauv.*	(Frank) $-p_2$.
	sylvaticum *Beauv.*	p (Tulasne) $+p_2 - p_3$ – w.
BRIZA	media *L.*	$+p_1$ (also Bondartzeff).
	minor *L.*	

BROMUS	albidus *Bieb.*	
	asper *Murr.*	Rostrup [1902].
	erectus *Huds.*	$+p_3$ $-p_1$ $-p_2$ $-m_2$ $-s$ $-w$.
	inermis *Leyss.*	Mains ; $+p_1$ McFarland.
	marginatus *Steud.* = Brachypodium distachyum *Beauv.*	
	mollis *L.*	Kühn ; Frank.
	pratensis *Lam.* = erectus *Huds.*	
	ramosus *Huds.* = asper *Murr.*	
	rubens *L.*	
	secalinus *L.*	Frank ; Mains.
	sterilis *L.*	$+p_1$.
	vestitus *Schrad.*	Rostrup [1902].
CALAMAGROSTIS .	arundinacea *Roth.* = Deyeuxia sylvatica *Kunth.*	
	canadensis *Beauv.* = Deyeuxia canadensis *Munro.*	
	chalybæa *Fries.*	
	confinis *Nutt.*	Williams.
	epigeios *Roth.*	Bondartzeff [1903].
	hyperborea *Lange*	Weniger.
	javana *Steud.*	Stäger [1910].
	lanceolata *Roth.*	m. Tulasne.
	Langsdorffii *Trin.* = Deyeuxia Langsdorffii *Kunth.*	
	neglecta *Gaertn.* = Deyeuxia neglecta *Kunth.*	
	sylvatica *Bess.*	
	varia (*Schrad.*) *Host.* = Deyeuxia Halleriana *Vasey.*	
CATABROSA . .	aquatica *Beauv.*	Dietrich.
CYNOSURUS . .	cristatus *L.*	m (Blas) — w.
DACTYLIS . . .	glomerata *L.*	(p. Tulasne) ; $+p_1$ $-s$ $-w$ $-z$.
DANTHONIA . .	Parryi *Scribn.*	
DESCHAMPSIA. .	cæspitosa *Beauv.*	$+m_1$ $-m_2$ $-p_2$ $-w$.
	flexuosa *Trin.*	[Wilson ; Rostrup 1902] $-w$.
DEYEUXIA . . .	canadensis *Munro*	Williams.
	Halleriana *Vasey*	
	Langsdorffii *Kunth.*	
	Nuttaliana *Vasey*	Galama.
	neglecta *Kunth.*	Bucholtz.
	sylvatica *Kunth.*	$+p_1$ $-m_1$ $-w$.
ECHINOCHLOA .	*Beauv.* = Panicum *L.*	C. balansiodes.
ELYMUS	akmolinensis *Drobov.*	
	arenarius *L.*	Galama ; p Jaap.
	arenarius *L.* × Agropyron junceum *Beauv.*	
	canadensis *L.*	Bessey.
	condensatus *Presl.*	Buffum, Mains.
	europæus *L.*	Galama ; Rostrup [1902].
	giganteus *Vahl.*	W. G. Smith.
	Macounii *Vasey*	Weniger.
	mollis *Trin.*	
	robustus *Scribn.*	
	sabulosus *Bieb.*	
	striatus *Willd.*	Weniger.

ELYMUS . . .	virginicus *L.*	Weniger.
FESTUCA . . .	algeriensis *Trab.*	(=Avena algeriensis *Trab.* of Ducellier, p).
	arundinacea *Schreb.* = eliator *L.*	Bondartzeff.
	duriuscula *L.* = ovina *L.*	Galama.
	elator *L.*	(Wilson); $+p_1$ $-p_2$ $-w$.
	gigantea *Vill.*	Kühn; Rostrup [1902].
	glomerata *All.*	Galama.
	nubigena *Jungh.*	Stäger [1910].
	ovina *L.*	Bucholtz.
	pratensis *Verz.* = elatior *L.*	
	spadicea.	U.S. Dept. Agric. Plant Disease Reporter, 1930, **14**, 247.
	rubra *L.*	Bucholtz; Rostrup [1902].
	rubra *L.* var. lanuginosa.	Bucholtz.
	sylvatica *Vill.*	
GLYCERIA . . .	aquatica *Wahlenb.*	(p Tulasne).
	distans *Wahlenb.*	[Rostrup 1902] $-p_1$.
	fluitans *R. Br.*	(p Tulasne) $+w$ $-p_1$ $-p_2$.
	nervata *Trin.*	McNeil and Pammel.
	plicata *Fries* = fluitans *R. Br.*	
	spectabilis *Mert. et Kich.* = aquatica *Wahl.*	
HIEROCHLOË . .	borealis *Roem. et Schult.*	$+p_1$ (also Dietrich).
	Horsfieldii *Maxim.*	Stäger [1910].
	odorata *Wahl.* = borealis *Roem. et Schult.*	Weniger.
HILARIA . . .	cenchroides *H. B. et K.*	C. cinerea.
	mutica *Benth.*	C. cinerea.
HOLCUS . . .	lanatus *L.*	(Wilson) $-s$.
	mollis *L.*	(Wilson, m Blas) $+p_1$ $-p_2$ $-s$ $-w$.
HORDEUM . . .	arenarium *Aschers.* = Elymus arenarius *L.*	
	bulbosum *L.*	$-s$.
	distichon *L.*	Wilson.
	europæum *All.* = Elymus europæus *L.*	
	jubatum *L.*	Weniger.
	murinum *L.*	$+p_1$ $-m_1$.
	nudum *Arduini.*	Rostrup [1902].
	vulgare *L.*	$+p_1$ $-m_2$ $-z$.
	vulgare *L.* var. tetrastichum.	
ISCHÆMUM . .	pilosum *Trimen.*	Sphac. (Ajrekar).
KŒLERIA . . .	cristata *Pers.*	Galama; Anderson.
	glauca *D. C.*	Bucholtz.
LOLIUM	italicum *A. Br.* = multiflorum *Lam.*	
	lanceolatum *A. Br.*	
	multiflorum *Lam.*	(p. Tulasne) $+p_3$ $-p_1$ $-p_2$ $-m_2$.
	perenne *L.*	(p Tulasne) $+p_3$ $-p_1$ $-m_1$ $-m_2$. $-s$ $-w$.
	remotum *Schrank.* = perenne *L.*	
	rigidum *Gaud.*	$-m_2$.
	strictum *Presl.* = perenne *L.*	

LOLIUM	temulentum *L.*	(p. Tulasne) $+p_3 - p_1$.
LUZIOLA . . .	sp.	C. pallida.
MELICA	altissima *L.*	Rostrup [1902].
	ciliata *L.*	[Stäger, 1910] ; $-s$.
	nutans *L.*	$\pm p_1 \pm s$.
	uniflora *Retz.*	$\pm s$.
MILIUM	effusum *L.*	$\pm p_2$.
	multiflorum *Cav.*	
MOLINIA . . .	aquatica *Wibel.* = Catabrosa aquatica *Beauv.*	
	cærulea *Mœnch.*	(m Tulasne) $+m_1 - p_1 - p_2$.
NARDUS . . .	stricta *L.*	$+m_1 - p_1 - w$.
ORTHOCLADA .	sp.	C. pallida var Orthocladæ.
ORYZA	sativa *L.*	Frank.
PANICUM . . .	sp.	C. uleana.
	maximum *Nees.*	Sphac. (Shepherd); $-m_2$.
	miliaceum *L.*	(Galama ; Frank) $-m_2$.
	prostratum *Lam.*	Sphac. (Rhind).
PASPALUM . . .	dilatatum *Poir.*	C. paspali and C. Rolfsii.
	floridanum *Michx.*	C. paspali (Rosen).
	laeve *Michx.*	C. paspali.
	setaceum *Michx.*	Galama.
PENNISETUM . .	Alopecuros *Steud.*	sclerotium (Ajrekar).
	spicatum *Rœhm. et Schult.*	Sphac. (Zimmermann).
	typhoideum *Rich.*	Sphac. (Bunting, Ritchie)
PHALARIS . . .	aquatica *Delile* = canariensis *L.*	
	arundinacea *L.*	$+p_1$
	canariensis *L.*	Galama ; Frank.
	cœrulescens *Desf.*	
PHLEUM . . .	Boehmeri *Wibel.*	
	pratense *L.*	Kühn ; Frank.
PHRAGMITES . .	communis *Trin.*	m (Tulasne) ; m_1.
POA	spp.	C. setulosa (Quélet).
	alpina *L.*	$\pm p_1$? or $-p_1 - p_2 - m_2 - s$.
	annua *L.*	$+m_2 \quad -p_1 - w$.
	aquatica *L.* = Glyceria aquatica *Wahl.*	
	cæsia *Sm.*	$+p_1 \quad -m_2$.
	cenisia *All.*	$-m_2$.
	compressa *L.*	$+p_1$.
	concinna *Gaud.*	$\pm p_1$?
	fertilis *Reichb.* = serotina *Ehrh.*	
	hybrida *Gaud.*	$+p_1 \quad -m_1$.
	nemoralis *L.*	$-p_2 - m_1$.
	palustris *H. Mart.* = serotina *Ehrh.*	
	pratensis *L.*	$+p_1 \mp p_2 - p_3 - s - w - z$.
	serotina *Ehrh.*	[Rostrup, 1902] $-p_1$.
	sudetica *Schleich.* = pratensis *L.*	
	sudetica *Haenke* (?)	$+p_1 \quad -m_1 - w$.
	trivialis *L.*	$\mp p_2 \quad -m_1$.

PSAMMA . . .	arenaria *Beauv.* = Ammophila arenaria *Link.*	
	baltica *R. et S.* = Ammophila baltica *Link.*	
SCHENODORUS .	Benekeni.	Rostrup [1902].
	inermis = Bromus inermis *Leyss.*	
	serotinus *Beneken* = Bromus asper *Murr.*	
SECALE	cereale *L.*	$+p_1 -p_2 -p_3 -m_1 -s -w -z$
	cereale *L.* × Triticum Spelta *L.*	Blaringhem.
	montanum *Guss.* = cereale *L.* (*cf.* Hecke);	Bucholtz.
SESLERIA . . .	argentea *Savi.*	s(?) Stäger [1910].
	cœrulea (*L.*) *Scop.*	$+s -p_1 -p_2 -m_1$.
SETARIA . . .	sp.	C. ranunculoides.
SORGHUM . . .	vulgare *Pers.*	Sphac. (Rhind, Ritchie, Robertson) Scler. (Ajrekar).
SPARTINA . . .	stricta *Roth.*	Stäger [1910].
STIPA	capillata *L.*	
	comata *Trin et Rupr.*	Weniger.
	spartea *Trin.*	Weniger.
	viridula *Trin.*	Weniger.
TRIPSACUM . .	dactyloides *L.*	C. Tripsaci.
TRISETUM . . .	pratense *Beauv.*	Rostrup [1902].
TRITICUM . . .	caninum *Ledeb.* = Agropyron strigosum *Boiss.*	
	caninum *L.* = Agropyron caninum *Beauv.*	
	dicoccum *Schrank.*	
	durum *Desf.* = vulgare *Vill.*	
	intermedium *Bess.*	
	junceum *L.* = Agropyron junceum *Beauv.*	
	monococcum *L.*	Lind.
	repens *L.* = Agropyron repens *Beauv.*	
	Rodeti *Trab.*	
	Spelta *L.*	Galama ; p Blas.
	tenax *A. et G.*	
	turgidum *L.* = vulgare *Vill.*	
	vulgare *Vill.*	(p Tulasne) ; $+p_1$.
WEINGÆRTNIA .	canescens *Bernh.* = Corynephorus canescens *Beauv.*	
ZIZANIA	aquatica *L.*	+z.
	palustris *L.* = aquatica *L.*	+z.

CYPERACEÆ.

CAREX	stellulata *Good.* var angustata (?) = echinata *Murr.*	
CYPERUS . . .	sp. (? ; only reported by Kühn).	
ELEOCHARIS . .	palustris *R. Br.*	n Tulasne; Bucholtz; Williams.
SCIRPUS. . . .	lacustris *L.*	n.
	multicaulis *L.* = Eleocharis palustris *R. Br.*	n Lind.
	palustris *L.* = Eleocharis palustris *R. Br.*	
	rufus *Schrad.*	n.
	uniglumis *Link.* = Eleocharis palustris *R. Br.*	n Lind.

JUNCACEÆ.

JUNCUS . . .	glaucus *Sibth.*	(?) *Sphacelia* stage only.

CHAPTER IV

CHEMICAL

THE earliest chemical investigations of ergot, in the eighteenth century, are naturally of little interest to-day. They were undertaken in the hope of ascertaining whether the material was a fungus, and what was the cause of its toxicity. Of such a kind was also an investigation by Vauquelin [1816]. After ergot had been introduced into medicine, the search for its active principles was renewed, and the cock's-comb was soon used as a test object. Wiggers [1831] carried out what was for his time a fairly complete analysis, and traced the activity to a resin; he examined the oil and discovered "cholesterene" and a sugar. Ludwig [1869] already distinguished two sterols, one of which was ergosterol.

Alkaloids were shown to be present by Wenzell [1864], and further investigated by Manassewitz, Ludwig, Blumberg and Ganser, but none was obtained in a state of purity until Tanret [1875] crystallised ergotinine. (The simpler name ergotine was already in use for crude pharmaceutical extracts, such as that of Bonjean.) Tanret not unnaturally thought that he had isolated an important active principle; he indeed obtained such a principle from the mother-liquors of the crystalline alkaloid, but failed to recognise that it was a separate substance, and regarded it merely as amorphous ergotinine. The crystalline alkaloid was later encountered by Dragendorff and Podwyssotzki and by Jacobj, who respectively named it picrosclerotine and secaline; they and other pharmacologists found it to be inert, but for the recognition of the physiologically active alkaloid their chemical methods were inadequate. The high molecular weight of this alkaloid, its amphoteric properties, and the fact that its salts are precipitated by electrolytes, caused it to remain adsorbed on acidic substances, which Kobert and Jacobj described as active principles (sphacelinic acid, chrysotoxin). Kobert indeed distinguished

a second active principle, the amorphous alkaloid cornutine, for which he claimed remarkable pharmacological activity of a different kind.

These preparations, which could not lay claim to chemical purity, owed their activity to a single alkaloid, a hydrate of ergotinine, which was first isolated in the form of crystalline salts by Barger and Carr in 1906, and named ergotoxine. Simultaneously Kraft recognised this second alkaloid and showed that it could be formed from ergotinine and could be reconverted into the latter; he attributed its formation to hydration and called it hydro-ergotinine. Barger and Carr showed by analysis that the two alkaloids do indeed differ by a molecule of water, which had escaped the attention of Tanret.

Much interest was aroused when Stoll [1918] discovered a third ergot alkaloid, ergotamine, which crystallises readily and has a physiological activity indistinguishable from that of ergotoxine. It can be converted into an inactive isomeride ergotaminine. Stoll's new pair of alkaloids are evidently very closely related to the older pair. They occur only in certain specimens of ergot, and it has been questioned whether these are of the official variety. Smith and Timmis [1930] described the crystallisation of ergotoxine, so that now four distinct crystalline alkaloids have been obtained from ergot.

As a drug of great pharmacological interest, ergot has been much more closely investigated than any other fungus, and has thus been found to contain a number of substances of general biochemical interest, which have not been observed in green plants. Ergot contains a number of simple amines, usually found only as the result of bacterial action. It was through the investigation of ergot extracts that the remarkable and unsuspected pharmacological properties of histamine were discovered [Barger and Dale; Kutscher 1910], which have since given rise to a voluminous literature. Ergosterol, first accurately studied as a .constituent of ergot by Tanret [1889 and 1908] has been found widely diffused in nature and has acquired great biological importance as the parent substance of vitamin-D. Ergothioneine, a base discovered in ergot by Tanret [1909], was later encountered in mammalian blood, and may ultimately lead to the recognition of a new unit of protein. Thus the chemistry of ergot has a general interest, exceeding that of any other drug.

In the following account the substances peculiar to ergot are first dealt with in some detail; its non-specific constituents are then disposed of in summary fashion.

A.—Substances peculiar to Ergot.

Ergotinine and Ergotoxine (Hydro-ergotinine).

Ergotinine, the first pure alkaloid to be obtained from ergot, was discovered by Tanret [1875] and so named to avoid confusion with the amorphous ergotin. He extracted with 96 per cent. alcohol, distilled off the alcohol after adding enough sodium hydroxide to make the solution slightly alkaline, and extracted the residue with ether. This results in the formation of soapy emulsions, which make the separation of the ethereal layer very tedious. The latter is shaken with strong citric acid solution, which is washed with ether, made alkaline with ammonia and again extracted with ether. On greatly concentrating, part of the alkaloid crystallises; the rest is obtained as an amorphous precipitate on adding light petroleum; it contains a good deal of ergotoxine. In order to avoid formation of emulsions, Keller first extracted the fat with light petroleum and then the alkaloid with ether, Jacobj and Kraft extracted at once with ether, and after distilling off the solvent, diluted the residual oil with two to three volumes of light petroleum which precipitates a "defatted ether extract" consisting chiefly of the alkaloids, yellow colouring matters and ergosterol; this complex mixture was first properly separated by Kraft, who extracted the crude alkaloids from it by shaking its ethereal solution with tartaric acid.

On a large scale the mixed alkaloids may be precipitated as hydrobromides (Barger and Carr). The residue left on evaporation of the alcoholic tincture is extracted with light petroleum to remove fat and oily matter; it is then dissolved in ethyl acetate and shaken with citric acid solution. Sodium bromide is added and the precipitated hydrobromides are collected. A rough separation of ergotinine from ergotoxine can be effected by repeated shaking of the solution of the mixed hydrobromides in dilute caustic soda with ether; in this way the ergotinine is removed first. Finally, the ergotinine is crystallised from alcohol, leaving ergotoxine and impurities in the mother-liquor; the ergotoxine is crystallised as phosphate.

Smith and Timmis extract the ergotoxine from the mixture of alkaloids by means of methyl alcohol, which leaves most of the ergotinine behind. Ergotoxine is then separated from little admixed ergotinine through the sulphates (Kraft) or phosphates.

Ergotoxine was first obtained by Barger and Carr [1906], from the caustic liquor from which the ergotinine had been extracted. It was neutralised, again made alkaline with sodium carbonate, and extracted with ether. The residue left after evaporation of the ether, together with that from the ergotinine mother-liquors, was dissolved in 80 per cent. alcohol and a slight excess of phosphoric acid in alcohol was added. After standing for some days the ergotoxine phosphate crystallised out and could be recrystallised from alcohol.

The same alkaloid was described a month later by Kraft; he recognised that the amorphous substance left after crystallising out the ergotinine from the mixture of alkaloids was not identical with the crystalline, as Tanret and Keller had imagined, but was a second alkaloid, differing from ergotinine in being much more soluble in alcohol and in having certain salts much less soluble in water. He precipitated the amorphous sulphate by adding sodium sulphate to the solution of the second alkaloid in dilute acetic acid. Without crystallising this alkaloid or any of its derivatives he showed the interconversion of it and ergotinine, and considering the amorphous alkaloid to be a hydrate of the crystalline, he called the former hydro-ergotinine. Barger and Carr established this relationship by analysis of crystalline ergotoxine salts, and ultimately Kraft crystallised his hydro-ergotinine sulphate and found it identical with that of ergotoxine.

The conversion of the amorphous into the crystalline alkaloid may be effected according to Kraft, by short boiling of a concentrated solution in methyl alcohol, or according to Barger and Carr, by boiling with acetic anhydride for a few seconds. In neither case is the yield good; even the boiling with methyl alcohol must not be prolonged, as this decomposes ergotoxine in other ways. The conversion of ergotinine into the amorphous alkaloid appears to proceed quantitatively in the course of several weeks, if solutions in 3 per cent. acetic acid are kept at room temperature. It can be brought about more rapidly by heating on the water-bath ergotinine with one-third of the amount of ethyl alcohol necessary for complete solution, and

containing $1\frac{1}{4}$ molecular proportions of phosphoric acid. In fifteen minutes the ergotinine dissolves, and on cooling ergotoxine phosphate crystallises.

As the result of a large number of concordant analyses of ergotinine and of several crystalline ergotoxine salts Barger and Carr [1907] put forward the formulæ $C_{35}H_{39}O_5N_5$ and $C_{35}H_{41}O_6N_5$ for the two alkaloids, and they have been generally adopted. Tanret's formula of 1879 $C_{35}H_{40}O_6N_4$ for ergotinine was in 1906 modified by him to $C_{35}H_{40}O_5N_5$, but in order to

FIG. 32.—Ergotinine.

make the total number of valencies even, there must be 39 or 41 hydrogen atoms. Tanret's analysis of ergotinine itself, of its hydrochloride, hydrobromide and chloroplatinate, all agree closely with the formula $C_{35}H_{39}O_5N_5$. Kraft's analysis of crystalline hydro-ergotinine sulphate agrees with the formula $C_{35}H_{41}O_6N_5$, and this moreover contains the extra molecule of water required on chemical grounds. It would seem therefore that there is an unusually large amount of support for these formulæ. Nevertheless after the lapse of twenty years I am prepared to admit that a revision is desirable, particularly after Stoll has put forward the similar formula $C_{33}H_{35}O_5N_5$ for two

other ergot alkaloids. There seems to me no doubt whatever that ergotinine contains 5 oxygen and 5 nitrogen atoms; the equivalent is fixed within narrow limits. To fix the exact number of carbon and hydrogen atoms is, however, a difficult matter in so large a molecule which, moreover, contains two methyl groups attached to the same carbon atom; as has been found in such cases, this grouping is apt to escape complete combustion by giving off methane, which results in a low carbon and high nitrogen value. Analyses of all four ergot alkaloids in the same laboratory seem very desirable, particularly since the analytical figures for ergotamine and ergotaminine have not been published.[1]

Ergotinine forms long needles (Fig. 32), the sides of which are not quite parallel; the ends are symmetrically replaced by a pair of faces and the extinction is straight; m.p. usually 219° to 220° (uncorr.), depends on the rate of heating. Smith and Timmis put it as high as 239° (corr.). At 15° it dissolves in about 400 parts by weight of ethyl alcohol, 1000 parts of dry ether, 90 parts of ethyl acetate, 25 parts of acetone; further in 77 parts of boiling benzene, 52 parts of boiling ethyl and 56 parts of boiling methyl alcohol. It is extremely soluble in cold chloroform, moderately so in amyl alcohol, insoluble in light petroleum. $[\alpha]_D^{20^\circ} = +338^\circ$ in saturated solution in ethyl alcohol, after five minutes boiling $+327^\circ$, after three hours $+242^\circ$. The

[1] Since the above sentence was written, Prof. Stoll has communicated to me some micro-analyses of ergotinine and ergotaminine, obtained in his laboratory. At first the carbon content was found too low, but when this difficulty had been overcome, a remarkable agreement was obtained with the formulæ given above for these alkaloids. In the following series of five successive micro-analyses, the first, third and fifth refer to ergotaminine, the second to a specimen of ergotinine prepared in the Sandoz works, the fourth to a specimen of the same alkaloid prepared by Dr G. Tanret.

	Ergotaminine		Ergotinine	
	68·24	6·05		
			68·79	6·38
	67·90	5·98		
			68·80	6·39
	67·88	5·92		
Average .	68·01	5·98	68·80	6·38
Calculated .	68·12	6·17	68·93	6·45
for . .	$C_{33}H_{35}O_5N_5$		$C_{35}H_{39}O_5N_5$	

fall of rotatory power is accompanied by a disappearance of crystallisable alkaloid. $[\alpha]_{578}^{20^\circ} + 363^\circ$; $[\alpha]_{546}^{20^\circ} + 414^\circ$ (Frèrejacque and Hamet). The rotation is higher in non-hydroxylated solvents like acetone, chloroform and ethyl acetate.

$[\alpha]_D + 363^\circ$ to $+396^\circ$ (Barger and Carr); $[\alpha]_{5461}^{19^\circ} = +513^\circ$,

$[\alpha]_{5790}^{19^\circ} = +435^\circ$ for C = 1 in chloroform (Smith and Timmis).

The addition of acid to the alcoholic solution lowers the rotation a little in the cold, more rapidly on boiling (owing to conversion into ergotoxine?). A solution of ergotinine in methyl iodide gradually sets to a thick gel of the methiodide.

Ergotoxine yields a number of salts; the alkaloid has so far been referred to as "the amorphous," but it also has lately been crystallised (Br. Patent 286400 of the Wellcome Foundation and G. M. Timmis; Smith and Timmis). The use of strong alkalies in liberating ergotoxine from its crystalline salts leads to contamination with ergotinine and other impurities which prevent crystallisation, but when the base is liberated by sodium bicarbonate or borax it can be readily crystallised from benzene. It forms six-sided prisms, several millimetres in length, which after drying in air contain 21 per cent. of benzene (approximately $C_{35}H_{41}O_6N_5 . 2C_6H_6$). The benzene is only given off at 90° in a vacuum after very long drying (Fig. 33). In 1 per cent. solution in chloroform :

$[\alpha]_{5461}^{19^\circ} = -179^\circ$ and for the solvent-free base -226°;

$[\alpha]_{5790}^{19^\circ} = -156^\circ$, and for the solvent-free base -197°.

Ergotoxine is therefore strongly lævorotatory, and ergotinine has an even larger dextrorotation. The amorphous ergotoxine of Barger and Carr, liberated by sodium carbonate, ammonia or sodium hydroxide from crystalline salts had $[\alpha]_D$ ranging from $+0{\cdot}6^\circ$ to $+45{\cdot}3^\circ$ and may have been racemised and contaminated with a little ergotinine (?). Tanret's "amorphous ergotinine" gave a much larger dextrorotation and must have contained a considerable proportion of the crystallisable alkaloid.

Ergotoxine is sparingly soluble in carbon bisulphide and separates in stout prisms on spontaneous evaporation of the solvent. It is insoluble in light petroleum, sparingly soluble

in ether, very soluble in methyl and ethyl alcohol, chloroform, acetone and ethyl acetate, but does not crystallise from these solvents. When an acetone solution is diluted with water, the base separates in an amorphous condition; ergotamine readily crystallises under these conditions. The amorphous base is hygroscopic; it softens at 180° (corr.) and melts very indefinitely between 190° and 200°.

Ergotoxine phosphate, $C_{35}H_{41}O_6N_5 . H_3PO_4 . H_2O$, crystallises from 50 parts of boiling 90 per cent. alcohol in clusters of radiating needles or in isolated acicular crystals showing straight

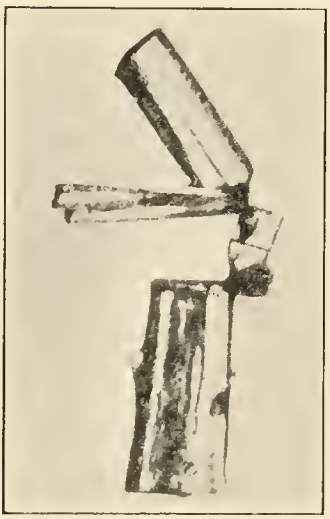


FIG. 33.—Ergotoxine.

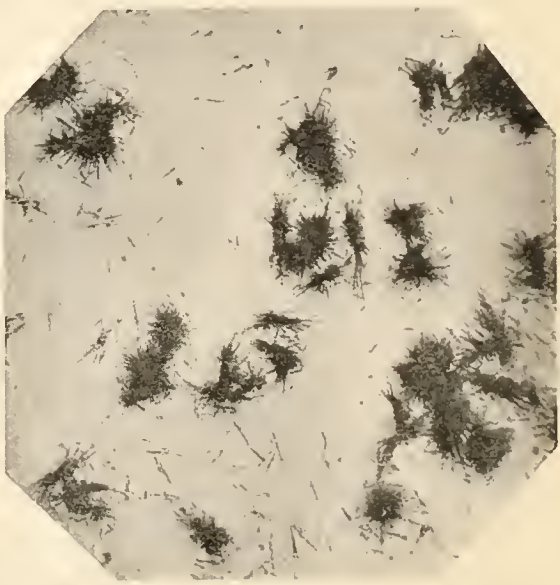


FIG. 34.—Ergotoxine phosphate.

extinction and melting at 186° to 187°. This characteristic salt was first obtained by Barger and Carr and again for instance by Forst. It dissolves in 313 parts of cold water and in 14 parts of boiling 90 per cent. alcohol (Fig. 34).

The *hydrochloride*, B . HCl, forms minute diamond-shaped plates m.p. 205°. It is crystallised by dissolving in 15 parts of warm 90 per cent. alcohol and slowly adding ether. Crystallises less well and is less stable than the phosphate (Barger and Carr).

The *hydrobromide*, B . HBr, forms acicular prisms, m.p. 208° (Barger and Ewins, 1910).

The *normal sulphate*, $B_2 . H_2SO_4$, was obtained by Kraft [1907] and forms minute crystals.

The *acid sulphate*, $B.H_2SO_4$, forms prisms, m.p. 197°, the *nitrate*, $B.HNO_3$, short broad prisms, m.p. 197°, the *picrate*, $B.C_6H_3O_7N_3$, pale yellow needles, m.p. 214° to 215° (Barger and Ewins).

The *normal oxalate*, $B_2.H_2C_2O_4$, from oxalic acid and excess of the base in ethereal solution; m.p. 179°; soluble in 5 parts of boiling absolute alcohol and in 12 parts at 25° (Barger and Carr). The *acid oxalate*, $B.H_2C_2O_4$, is formed by shaking a solution of ergotoxine in xylene with excess of 1 per cent. oxalic acid. Minute prisms m.p. 179° from alcohol + acetone. Does not crystallise so well in the normal oxalate.

The *methane* and *ethane sulphonates* are the subject of Br. Pat. 286582 (Wellcome Foundation and G. M. Timmis). The base and acid are dissolved together in alcohol and the salts are precipitated by cooling or by adding ether. They readily crystallise from alcohol in clusters of needles of the composition $B.CH_3SO_3H.2C_2H_5OH$ and $B.C_2H_5SO_3H.2C_2H_5OH$, m.p. 214° (corr.) and 209° (corr.) respectively. These salts are more soluble in water than any of those previously mentioned, and more stable.

The high molecular weight of ergotoxine (627) makes it and its salts semi-colloids and their crystallisation difficult. This is the reason why the salts are precipitated from aqueous solution by electrolytes. Ergotoxine phosphate for instance, when shaken with water, forms a 1 per cent. colloidal solution, which froths and is opalescent. Addition of any salt or strong acid converts the hydrosol into a gel; the same applies to the (amorphous) salts of ergotinine. Neither alkaloid can therefore readily be extracted by excess of aqueous strong acids, and weak electrolytes such as acetic, tartaric or citric acid should be used. Even then any neutralisation of excess acid produces an electrolyte and precipitates the alkaloids. This is why Kobert and Meulenhoff for instance, did not succeed in removing ergotoxine from the resinous "sphacelinic acid," when this supposed active principle was precipitated from alkaline solution by hydrochloric acid; ergotoxine hydrochloride was precipitated along with the resin.

Ergotinine and ergotoxine are precipitated by general alkaloidal reagents at the same great dilution, except in some cases where ergotoxine is the more sensitive. A faint opalescence is still produced with potassium mercuric

iodide in ergotinine and ergotoxine solutions respectively at 1 : 1,000,000 and 1 : 2,000,000, with potassium tri-iodide at 1 : 200,000 and 1 : 1,000,000, with tannic acid at 1 : 8000 and 1 : 20,000 respectively. Whilst the limits for a number of electrolytes are the same, potassium bromide has 1 : 6000 and 1 : 15,000 and sodium sulphate 1 : 500 and 1 : 7000 for ergotinine and ergotoxine respectively. The small solubility of ergotoxine sulphate, as compared with that of ergotinine, enabled Kraft to separate the two alkaloids.

Colour reactions of the ergot alkaloids.—Tanret, in his first publication [1875] already described colour changes when concentrated sulphuric acid is poured on ergotinine; the yellow colour which first appears gives way after a few hours to a fairly persistent pink. By adding a few drops of alcohol, ethyl acetate or ether the reaction is made much more characteristic and sensitive; after a series of colour changes, the solution becomes blue. The French Codex directs that the alkaloid suspended in a few drops of ether should be added to cold sulphuric acid containing a small proportion of oxides of nitrogen and diluted with one-fifth of its volume of water. The successive colours are: yellow, red, violet, blue. Keller [1897] improved the reaction still further by dissolving the alkaloid in 2 or 3 c.c. of glacial acetic acid, adding a trace of ferric chloride and then pouring concentrated sulphuric acid underneath, without mixing. At the junction of the two layers an intense cornflower blue appears at once; after a time the glacial acetic acid becomes violet, the upper layers of the sulphuric acid green.

Keller's reaction has been included in many pharmacopœias as a test for the alkaloids or for ergot. It is given very distinctly when the acetic acid contains 0·1 mgm. of ergotinine per c.c.; with 0·02 mgm. the colour is just detectable against a white background. This reaction is given also by ergotoxine, ergotamine and ergotaminine, probably with the same intensity, and by extracting the alkaloid from it, 1 grm. of ergot powder is readily recognised.

A modification of the foregoing, or indeed a new reaction, very much more delicate, has been recently described by van Urk; 1 c.c. of a 1 per cent. alcoholic solution of *p*-dimethylamino benzaldehyde is mixed with an equal volume of an alcoholic solution of the ergot alkaloid, and concentrated

sulphuric acid is poured down the side of the test-tube, so as to form a separate lower layer. A blue colour develops at the interface, even when no more than 0·001 mgm. of alkaloid is present. This is a modification of a general reaction for indole derivatives, such as tryptophane, for which Boyd has shown that the development of the blue colour depends on light. M. I. Smith cautiously mixes 2 c.c. of a solution of the alkaloids in aqueous tartaric acid with 1 c.c. of M/60 dimethylamino benzaldehyde in concentrated sulphuric acid, so as to form a homogeneous solution, and exposes this to light. In direct sunlight the maximum blue colour is developed after ten to fifteen minutes, in diffuse daylight after a half to two hours. In this way Smith estimated various preparations of ergot alkaloids colorimetrically and found that the amount of alkaloid (*i.e.*, the depth of colour) was proportional to the physiological activity. Reducing and oxidising agents (H_2O_2, $FeCl_3$, etc.) interfere, as does the yellow colouring matter of ergot, when present in aqueous solution in the colloidal state.

Constitution of ergotinine and ergotoxine.—The price of these alkaloids and their high molecular weight make the investigation of their constitution very difficult. Barger and Ewins [1910] obtained from both, on heating above their melting-points, about 4 per cent. of a crystalline sublimate, *isobutyryl formamide* $(CH_3)_2\,CH\,.\,CO\,.\,CO\,.\,NH_2$. This is only about one-fifth of the theoretical amount; none is formed from ergotoxine phosphate. The formation of this substance, containing a *gem*-dimethyl group, explains the difficulty of analysing these alkaloids, for this group is apt to escape as methane [Haas 1906]. The isobutyryl formamide doubtless contains the same nitrogen atom which is rapidly given off as *ammonia* on boiling the alkaloids with alcoholic sodium hydroxide. This remarkable observation was recently made in my laboratory by Dr A. Soltys, and is without analogy among complex vegetable alkaloids. He further finds that on warming *both* alkaloids react with four equivalents of methyl magnesium iodide, and hence contain four replaceable hydrogen atoms; perhaps two of these are present in an amino group, and a third in an imino group. The molecule contains one methyl group attached to nitrogen, and probably also one attached to oxygen. There are probably several nitrogens in (condensed?) indole nuclei. Free hydroxyl groups appear to be absent.

Destructive distillation in a high vacuum yields a *base* b.p. 88° to 89° having the odour of pyrrolidine. Oxidation with permanganate furnishes *benzoic acid*, and with nitric acid *p-nitrobenzoic acid* is obtained; hence there is no benzoyl, but probably a benzyl group. In what the difference in constitution between ergotinine and ergotoxine consists, remains a mystery, for instance whether these bases are respectively a lactone and the corresponding hydroxy acid. Similarly the nature of the phosphate obtained by heating ergotinine with phosphoric acid in alcoholic solution [Barger and Ewins 1910, 1918] remains in doubt.

Ergotamine and Ergotaminine.

A new physiologically active ergot alkaloid was first mentioned in the Swiss Patents No. 79879 of 1918 and No. 86321 of 1919. In preliminary communications Stoll [1920] and Spiro and Stoll [1921] described two isomeric alkaloids, ergotamine and ergotaminine, $C_{33}H_{35}O_5N_5$, and a fuller description of these was later given by Stoll [1922]. The method of extraction of ergotamine is a novel one (D.R.P. 257272) introduced by Stoll. By addition of a weakly acidic substance, for instance aluminium sulphate, to the powdered ergot, the oil and other substances can be completely extracted from the ergot, while the alkaloids are left behind. After making alkaline, for instance by the passing in of ammonia gas, the alkaloids are then removed in a relatively pure state. Ergotamine crystallises from aqueous acetone; on keeping it in alcoholic solution, more rapidly on boiling its solution in methyl alcohol, it is transformed to a much less soluble and less basic isomeride, ergotaminine, which has hardly any physiological action.

This new pair of ergot alkaloids is evidently closely related to ergotinine and ergotoxine. All four give the same absorption spectrum (Harmsma). All four give Keller's and van Urk's reactions; all four on heating give a sublimate of isobutyryl formamide. (As regards ergotamine and ergotaminine, I have satisfied myself that this is so with specimens kindly sent me by Professor A. Stoll.) The two less soluble alkaloids, ergotinine and ergotaminine, both have a very slight physiological activity, and both have a very high dextrorotation, with $[\alpha]_D$ about + 380° in chloroform. The conversion into the two physio-

logically active alkaloids, ergotoxine and ergotamine, is accompanied in either case by an enormous change of rotation $[\alpha]_D$ becoming respectively $-155°$ and $-156°$. Further, it has been established by Dale and Spiro, by Rothlin and by others (see p. 156) that the various pharmacological effects are given by ergotoxine and ergotamine with equal intensity, within the limits of experimental error. Since, moreover, no empirical formula of an ergot alkaloid can be considered to be established with absolute certainty, it was at first considered possible by some investigators that ergotoxine and ergotamine might be identical. Such a possibility must, however, be dismissed. There was always the fact that the corresponding slightly active alkaloids, ergotinine and ergotaminine (into which the two active ones can be converted) are very different, ergotamine being much less soluble than ergotinine. Stoll [1928] failed to crystallise ergotoxine prepared from the crystalline ethane sulphonate under conditions in which ergotamine readily crystallises, and inoculation with the latter base likewise failed to induce crystallisation. Smith and Timmis [1930] crystallised ergotoxine from benzene, but were then unable to crystallise it from aqueous acetone, which is easy in the case of ergotamine. "The evidence . . . shows quite clearly that the four alkaloids are definite and distinct substances" (Smith and Timmis).

The question next arises, why ergotamine and ergotaminine were overlooked by previous observers. Stoll [1921] suggests that this may have been due to the use of ergots which either never contained ergotamine, or in which the ergotamine had been destroyed; Stoll, however, considers the principal cause of the failure to isolate ergotamine to have been the use of unsuitable methods of extraction. Nevertheless, the failure by others to isolate ergotamine continued even when they used the method of Stoll. Forst, who used a different method, is the only other author who has indicated the presence of ergotoxine and ergotamine in the same ergot. The former was readily isolated as the crystalline phosphate, but the identification of the latter alkaloid, crystallising from ether and melting at 180° to 185°, is far from certain.

Smith and Timmis examined a large number of commercial specimens of ergot of rye from many countries, and always isolated ergotinine and ergotoxine, and these only. When

they, however, examined the ergot of *Festuca elatior*, from New Zealand, they obtained instead ergotamine and ergotaminine, and that by the same method as was employed by Kraft for isolating ergotinine and its hydrate. Smith and Timmis accordingly consider that the isolation of ergotamine and ergotaminine does not depend on the special method of extraction, insisted on by Stoll, but on the nature of the ergot. To this Stoll [1930] has replied that he always used official ergot of rye. Smith and Timmis have suggested that although the host was rye, the parasite may have been a different species of *Claviceps*. As is pointed out in Chapter III., the ergot of *Festuca elatior* seems, however, to be *C. purpurea*, and even of the same biological race as that of rye. An examination of the alkaloids of other species and races of *Claviceps* is desirable, but the alkaloidal content is apparently influenced by other factors. Stoll [1921] has stated that specimens of ergot not infrequently contain no demonstrable amounts of ergotamine.

Stoll is of the opinion that ergotaminine does not occur as such in ergot, and is a secondary product formed from its isomeride by alcohol and acids. Smith and Timmis, using the method of Kraft, obtained a mixture of the two bases from *Festuca* ergot, and dissolved out the ergotamine by treatment with three parts of methyl alcohol; the alcoholic solution was diluted with ether and then extracted with citric acid; on rendering alkaline with sodium carbonate ergotamine was precipitated.

Ergotamine crystallises from aqueous acetone in rectangular plates (Fig. 35) having according to Stoll the composition $C_{33}H_{35}O_5N_5 . 2H_2O . 2C_3H_6O$ and decomposing at 180°; $[\alpha]_D = -155°$ (0·6 per cent. in chloroform) $[\alpha]_D = +40°$ in ethyl alcohol. According to Frèrejacque and Hamet ergotamine shows mutarotation in alcohol; in one experiment the angle observed rose from +0·63° to +1·02° in one hundred hours; (conversion into ergotaminine?). Smith and Timmis found that the dry alkaloid, placed in a bath at 205° and slowly heated, decomposes fairly sharply at 213° to 214° (corr.); they give $[\alpha]^{20°}_{5790} = -159°$ and $[\alpha]^{20°}_{5461} = -181°$ (1 per cent. in chloroform). Ergotamine crystallises with various solvents of crystallisation; from methyl alcohol in pyramids, from ethyl alcohol in felted needles, from benzene in long, thin prisms (Stoll). The solvent,

as in the case of ergotoxine, is retained very tenaciously even when the crystals are heated for a long time in a high vacuum. According to Smith and Timmis ergotamine is insoluble in light petroleum, less soluble than ergotoxine in benzene, in chloroform and in ether; it is readily soluble in nitrobenzene and in pyridine. It is soluble in dilute sodium hydroxide, but not in sodium carbonate solution.

Like ergotoxine, ergotamine is a weak monacid base; its salts are generally rather more soluble in water than those of ergotoxine, although for instance the sulphates of both bases have

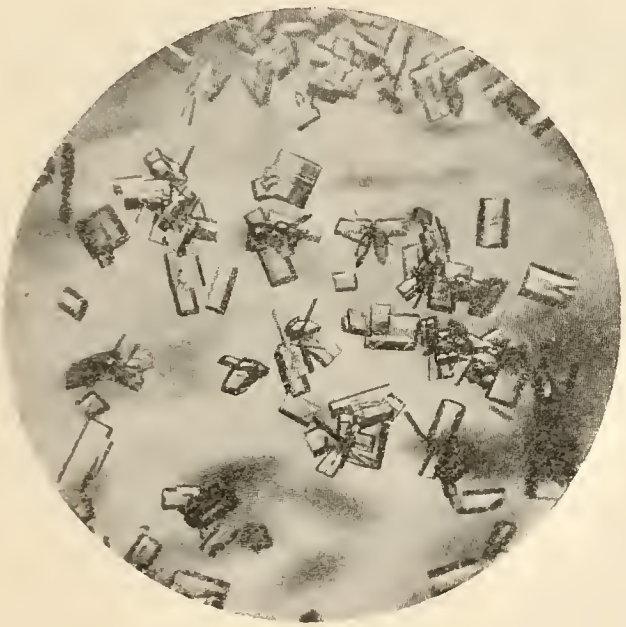


FIG. 35.—Ergotamine.

a very slight solubility. Ergotamine tartrate is known commercially as gynergen and femergin. Ergotamine phosphate forms rectangular plates from alcohol (Fig. 36) (the characteristic ergotoxine phosphate crystallises in needles). With excess of oxalic acid a normal oxalate is formed; ergotoxine yields an acid oxalate.

Ergotaminine is according to Stoll isomeric with ergotamine. It separates from alcohol in characteristic plates, in the form of an isosceles triangle, of which the basal corners may be truncated (Fig. 37); m.p. 252° (corr.) when placed in a bath at 240° and slowly heated (Smith and Timmis). $[\alpha]_D^{20^\circ} = +381^\circ$ in

0·6 per cent. solution in chloroform (Stoll); $[\alpha]_{5790}^{18^\circ} = +385^\circ$ and $[\alpha]_{5461}^{18^\circ} = +450^\circ$ in 0·5 per cent. solution in chloroform (Smith and Timmis; $[\alpha]_{D}^{21^\circ} = +366^\circ$, $[\alpha]_{578}^{21^\circ} = +389^\circ$, $[\alpha]_{546}^{21^\circ} = +465^\circ$ in 0·45 per cent. in chloroform (Frèrejacque and Hamet).

Ergotaminine is characterised by its very slight solubility in most organic solvents, which is much less than that of

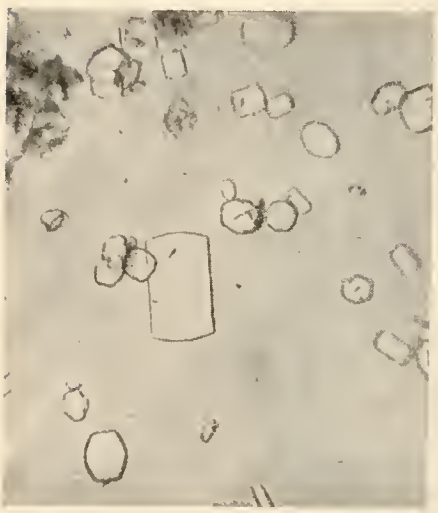


FIG. 36.—Ergotamine phosphate.

FIG. 37.—Ergotaminine.

ergotinine (and very much less than that of ergotamine and ergotoxine). Thus the solubility of ergotinine in alcohol at room temperature is 1 : 400, of ergotaminine 1 : 6400, by weight (Frèrejacque and Hamet). The latter base is somewhat more soluble in chloroform and nitrobenzene, readily in pyridine and glacial acetic acid. Like ergotinine it does not form any crystalline salts. The transformation of ergotamine to ergotaminine is reversible, as in the case of the other pair of ergot alkaloids.

Secale Amino-sulphonic Acid.

In his work on ergot, Kraft exhausted the drug with chloroform and then extracted it with acidulated water. After adding an excess of basic lead acetate, the filtrate was freed from

excess of lead, concentrated, and precipitated with potassium bismuth iodide. A crystalline red precipitate produced by the latter reagent was decomposed with silver carbonate, and the filtrate was acidulated with hydrochloric acid and evaporated over sulphuric acid. Betaine chloride crystallised; the mother-liquor from this was evaporated to dryness and extracted with absolute alcohol, which left a little betaine chloride behind. On prolonged keeping the alcoholic solution deposited colourless crystals, which, once formed, were found to be insoluble in absolute alcohol, but could be recrystallised from dilute alcohol or a little water. They deliquesced in air. This substance was strongly acidic; Kraft regarded it as a constituent of Kobert's ergotic acid, a mixture which contains in addition mannitol and a complex carbohydrate (mannan? *q.v.*). Secale amino-sulphonic acid, so obtained, forms colourless prisms, melting at 200°. Kraft assigned to it the formula $C_{15}H_{30}O_{18}NS$, but the number of hydrogen atoms must be odd and $C_{15}H_{29}O_{18}NS$ fits his analyses closely. The nitrogen is present in a primary amino group; on potash fusion sulphate and sulphite are formed, whence Kraft concluded that a sulphonic acid group is present. Hence the formula $C_{15}H_{26}O_{15}(NH_2)(SO_3H)$ and the name. This interesting substance deserves further investigation; conceivably it is related to the sugars.

Colouring Matters.

There seem to be three well-defined colouring matters in ergot.

I. **Sclererythrin**, a crimson or violet substance, limited to the walls of the cortical hyphæ, in which it is deposited as a salt, probably of calcium. It was named and investigated by Dragendorff and Podwyssotski [1877]. The substance is dissolved out by alcohol, by alkalies, and by ether containing sulphuric acid. Its characteristic absorption spectrum has been repeatedly used for the detection of ergot (see p. 225). According to Tschirch [1922, 1923] a dilute solution in ammonia shows three bands at 550 to 575, 515 to 530 and 485 to 495 $\mu\mu$. In acid solution there are two, at 527 to 543 and 485 to 503 $\mu\mu$; of these two the former is the darker and narrower. Tichomirow [1885] already showed that the bands are shifted towards the red when the acid solution is made alkaline.

Sclerojodin of Dragendorff and Podwyssotski is, according to Tschirch, impure sclererythrin.

II. **Ergochrysin**, $C_{21}H_{22}O_9$ [Jacobj 1897], is doubtless identical with *sclerocrystallin*, $C_{10}H_{10}O_4$, of Dragendorff and Podwyssotski [1877] and with *secalonic acid*, $C_{14}H_{14}O_6$, of Kraft [1906]. Perhaps the second, and oldest, name should be applied to the substance, but the description of Dragendorff and Podwyssotski is meagre and their analysis is inaccurate. At the present day Jacobj's name has some advantages for indexing. He not only analysed the substance more or less correctly, but also determined its molecular weight. There is no doubt that secalonic acid is identical with ergochrysin, for I have found the molecular weight of a specimen sent me by the late Dr Kraft to be in accordance with Jacobj's formula (see Freeborn). The analyses of both authors seem to me to fit the formula $C_{21}H_{20}O_9$ slightly better than $C_{21}H_{22}O_9$. (A formula with 28 carbon atoms is not wholly excluded).

When an ethereal extract of ergot is mixed with light petroleum, the oil remains in solution and a yellow precipitate is formed, from which the alkaloids may be extracted by redissolving the precipitate in ether and shaking with an organic acid. The mixture of colouring matters in the ether yields ergochrysin and also a much more soluble, amorphous hydrate of this substance ($C_{21}H_{24}O_{10}$ or $C_{21}H_{22}O_{10}$ = scleroxanthin of Dragendorff and Podwyssotski who gave the formula $C_{10}H_{10}O_4 + H_2O$). Ergochrysin (= secalonic acid) is indeed so little soluble in ether, that Kraft obtained it by extracting ergot, already exhausted with ether, by chloroform. The yield was 0·2 per cent. of the ergot employed. The substance forms lemon yellow needles, m.p. 244°. It is insoluble in water or petrol, scarcely soluble in carbon bisulphide or carbon tetrachloride, very little in methyl alcohol or ether, moderately in ethyl acetate. It dissolves in 160 parts of boiling and in 200 parts of cold ethyl alcohol, in 100 parts of boiling benzene and in 50 parts of boiling glacial acetic acid. It is best recrystallised from chloroform or acetone, requiring about 50 parts of either solvent. The alcoholic solution is slightly acid to litmus and gives a reddish brown coloration with ferric chloride. It is a phenolic acid, dissolving in sodium carbonate with the evolution of carbon dioxide. From such a solution the crystalline substance can at first be precipitated, although in diminished

yield, but on standing it is entirely converted to the amorphous hydrate; this change occurs rapidly in sodium hydroxide solution. According to Kraft secalonic acid is a lactone acid and the hydrate a dicarboxylic acid. On heating to 255 to 260° water and carbon dioxide are given off. Ergoxanthein of Wenzell [1910] is an amorphous yellow pigment, not characterised at all (= scleroxanthin?).

III. **Ergoflavin** is the name now suggested for a hitherto unnamed yellow pigment $C_{15}H_{14}O_7 . H_2O$, examined in my laboratory by Freeborn [1912]. It had been extracted by sodium carbonate from crude ergot alkaloids (obtained by percolation with ether). Forst [1926] obtained it from an aqueous acetone extract of ergot; recently I have found it to the extent of a few per cent. in a mixture consisting mainly of a very soluble colouring matter (scleroxanthin) obtained in the commercial production of the alkaloids. This substance resembles ergochrysin in its sparing solubility in organic solvents (1 : 100 in cold alcohol) and in its solubility in alkalies. It gives in alcoholic solution a brownish green coloration with ferric chloride. It is sharply distinguished from ergochrysin by a much higher melting-point, 338° (350° after regeneration from its acetyl derivative), by its different behaviour to alkalies, and by its composition and molecular weight, $C_{15}H_{14}O_7 . H_2O$. The molecule of water is given off *in vacuo* over sulphuric acid. Dilute sodium hydroxide converts the yellow substance into a colourless crystalline hydrate, $C_{15}H_{16}O_8$, from which the anhydride is readily regenerated, and boiling 50 per cent. sodium hydroxide produces no further change. On potash fusion at 320° a volatile fatty acid is formed (isovaleric?). Although it is only present in small quantity, the stability of this colouring matter facilitates its separation from ergochrysin; the two are entirely distinct.

B.—Substances not peculiar to Ergot.

Inorganic Constituents.

Fresh ergot contains 4·4 to 4·8 per cent. of water; on keeping it may rise to 10 per cent. (Dieterich). The ash content is stated to range from 2·2 to 7 per cent.; 4 per cent. seems to be an average figure (rye grains contain only 1·8 to 2·3 per cent. of ash). A complete analysis of an **ash** was given by Herrmann [1869] as follows: NaCl 1·50, K_2O 30·06,

Na_2O 0·65, CaO 1·38, MgO 4·88, Al_2O_3 0·59, Fe_2O_3 0·86, MnO 0·26, P_2O_5 45·12, SiO_2 14·67, total 99·97. (The composition of the ash of rye grains is similar except that they contain more MgO and much less SiO_2). Several pharmacopœias prescribe a maximal ash content of 5 per cent. for ergot of rye, the Dutch pharmacopœia one of 4 per cent. The chief constituent of the ash is potassium phosphate, present in the ergot as KH_2PO_4, which contributes to the acid reaction of aqueous extracts. This salt was present to the extent of 40 per cent. in a commercial specimen of the "active principle" clavin [Barger and Dale, 1907].

Carbohydrates.

The characteristic sugar of ergot and other fungi is **trehalose**, $C_{12}H_{22}O_{11}$, present in variable amounts (of the order of 0·1 per cent.). It was already discovered by Wiggers [1831]. He gave a quarter of a gram of crystals to Liebig, who with Pelouze, analysed them during a visit of the latter to Giessen. As the crystals were not quite pure, Pelouze and Liebig [1836] considered them to be mannitol, but Mitscherlich [1858], who also received some, found them different from mannitol and therefore prepared more; in one case he obtained 2 grms. from 2 kilos of ergot, but some samples of ergot gave no sugar; he published crystallographic details and called the new sugar mycose [1858]. Later it was identified with trehalose from Trehalla manna. It may be isolated from an aqueous extract, by precipitating with basic lead acetate, removing the excess of lead from the filtrate and concentrating. It does not readily crystallise out, not even from a hot 50 per cent. solution in water, so that inoculation is desirable. It requires more than 100 parts of boiling alcohol for solution. It does not reduce, forms no osazone and is hydrolysed to two molecules of glucose. According to Buchheim [1875], the sugar of ergot may undergo transformation to lactic acid, which would account for the acid reaction and small sugar content of some ergots. This alleged transformation requires further study.

Mannitol, $C_6H_{14}O_6$, m.p. 166°, does actually occur in ergot in spite of the erroneous observation of Pelouze and Liebig. It was found by Ludwig and by later investigators, such as Kraft. Indeed, it is a common constituent of the higher fungi,

where mannitol and trehalose seem to replace each other mutually to some extent.

Clavicepsin, $C_{18}H_{34}O_{16}.2H_2O$, was extracted from ergot by Marino-Zuco and Pasquero [1912], by means of 95 per cent. alcohol in a yield of 1·5 to 2 per cent. The hydrated substance melts at 91°, the anhydrous at 198°; $[\alpha]_D^{20^\circ} = +142{\cdot}27^\circ$. It is extremely soluble in water, but very slightly in alcohol, and is easily hydrolysed into two molecules of glucose and one of mannitol.

$$C_{18}H_{34}O_{16} + 2H_2O = 2C_6H_{12}O_6 + C_6H_{14}O_6$$

Clavicepsin deserves further investigation, particularly in relation to trehalose.

Mannan is an obscure polysaccharide, obtained from ergot by Voswinkel [1891]. It is regarded as a hemicellulose and furnishes mannose on hydrolysis.

Glycerides and Sterols.

The presence of a large quantity of fatty oil in ergot was known to some of the earliest investigators. It was examined to some extent by Herrmann [1869], Ludwig [1869], and Ganser [1870] and more recently by Mjöen [1896], Rathje [1908], Zellner [1920], Dieterle, Diester and Thimann [1927], Matthes and Schütz [1927] and by Baughman and Jamieson [1928]. Ether usually extracts about one-third of the weight of the ergot, but even prolonged extraction with light petroleum leaves some behind. For complete exhaustion the ergot must be repeatedly powdered and extracted again. Kraft [1906] found it necessary to shake the finely powdered ergot ten times with ether, and thus extracted some two-fifths of its weight. In addition to fats, there are also extracted by ether ergosterol, alkaloids and yellow colouring matters, which can partly be precipitated by distilling off the ether and adding petrol. Accordingly the composition, as well as the yield, varies according as the oil is obtained with petrol (Mjöen; Zellner, 21 per cent.), with ether (Rathje) or merely expressed (Dieterle and co-workers). The density at 20° (or room temperature) is 0·925 (0·9170 to 0·9259); the refractive index at 20° 1·471 (1·4685 to 1·4739). Matthes and Schütz found the oil to be markedly dextrorotatory (10·5° to 10·7° in a d.m. tube) and this they attribute to the hydroxy oleic acid isolated by them.

The amount of non-saponifiable matter is given variously as from 0·35 to 1·037 per cent.; about 1 per cent. seems nearest the mark. Of this at most one-third is ergosterol (Dieterle). The oil obtained by extraction with ether contains all or nearly all the alkaloid present in the ergot. Rathje found 0·6 per cent. of the oil to be alkaloid, Kraft 0·5 per cent.

Freshly powdered ergot gives up no alkaloid to petrol, but when it has become rancid, some alkaloid can be extracted by petrol. The following data were obtained:—

Number.	Baughman and Jamieson.	Matthes and Schütz.	Dieterle, Diester and Thimann.	Rathje.	Mjöen.
Saponification .	196·9	195·4	193	179·3	178·4
Iodine (of oil) .	73·8	66·6-70·1	69·55	74·0	71·08
Iodine (of acids).	101·2	...	...	...	75·09
Reichert-Meissl .	0·3	...	0·47	0·63	0·20
Hehner . .	...	96	96·1	96·25	96·3
Acid . . .	...	...	13·19	11·38	4·95
Acetyl (of oil) .	7·3	...	60·4	29·12	62·9
Acetyl (of acids).	...	73	...	77	75·1

The Reichert-Meissl number indicates an amount of volatile fatty acid of about 1 per cent. The higher acid numbers given above correspond to about 6 per cent. of free fatty acid, but fresh ergot oil may have one-sixth of this amount. In accordance with the iodine number, the oil is a non-drying one. The high acetyl number already made Mjöen attempt the isolation of a hydroxy acid, but none was isolated until Matthes and Schütz obtained a large quantity of a hydroxy oleic acid, which is a characteristic constituent of the oil. Apart from the acetyl number, its presence is indicated by the high density and refractive index and by the optical activity of the oil. According to Matthes and Schütz the fatty acids are distributed as follows: 28 per cent. solid, mostly palmitic, with some higher ones; 36 per cent. hydroxy oleic; 32·4 per cent. oleic; 3·6 per cent. linoleic. Baughman and Jamieson found 62·5 per cent. oleic, 8·77 per cent. linoleic, 0·3 per cent. myristic, 21·5 per cent. palmitic, 5·3 per cent. stearic and 0·7 per cent. arachic acid, but no hydroxy acid. The latter was further examined by Matthes and Kürschner [1931]. It is octadecene-9-ol-12-acid-1, an oily liquid; $[\alpha]_D^{15^\circ} + 6{\cdot}59^\circ$, $n_D^{20^\circ}$ 1·4720.

The non-saponifiable part of the oil contains characteristic sterols — Wiggers [1832] already found "cholesterene" and Ludwig [1869] found two varieties melting at 141° and 160° respectively. These were studied later by Tanret [1885, i.; 1890; and particularly 1908]. The higher melting sterol, present in much the larger amount, was called **ergosterol** by Tanret, $C_{27}H_{41}OH \cdot H_2O$. Dehydrated at 105° it quickly absorbs moisture from the air. It crystallises from alcohol in wide, monoclinic lamellæ, and from ether in monoclinic needles, m.p. 162°; $[\alpha]^{19°}_{5461} = -127°$, in chloroform [Rosenheim and Webster 1927]. It is purified through the acetyl derivative, m.p. 180° to 181°. Tanret named the lower melting compound of Ludwig **fungisterol**, $C_{25}H_{39}OH \cdot H_2O$, m.p. 144°; $[\alpha]_D$ −22·4° in chloroform. The acetyl derivative melts at 158·5°. Fungisterol gives a ruby-red colour with 90 per cent. sulphuric acid in a few seconds; with ergosterol a dirty red colour only appears at the end of one minute.

Both ergosterol and fungisterol are widely distributed among fungi and traces of the former accompany the cholesterol of the higher animals.

The fact that ergosterol on irradiation yields vitamin-D has of late brought it into great prominence and led to the investigation of its adsorption spectrum, constitution, and derivatives. It is an alcohol with three double bonds, which can be reduced to a hydrocarbon differing from cholestane and related substances. The amount of ergosterol in ergot is about 0·1 per cent. [Kraft 1906; Dieterle, Diester and Thimann 1927].

It is a curious fact that ergot contains a considerable quantity of **vitamin-D** (about one-eighth to one-quarter of that in cod-liver oil), whereas the rye germ contains hardly any [E. Mellanby, Surie and Harrison 1929]. Both the rye germ and fungi generally contain ergosterol, but the ergosterol in whole ergot is not converted into vitamin-D by strong sunlight, probably owing to the opaque exterior. How the vitamin-D originates in ergot is a mystery. All samples, whether Spanish or Russian, were found to be definitely antirachitic.

Acids.

The *lactic acid* of ergot is, according to Buchheim, derived from trehalose by fermentation.

Succinic acid was found by Engeland and Kutscher and is probably derived from aspartic acid.

Amino Acids.

Buchheim [1875] discovered leucine in ergot. Much later Vahlen [1906] described an "active principle" clavin having the composition $C_{11}H_{22}O_4N_2$; the molecular weight in water was, however, only half that demanded by this formula, suggesting that Vahlen was dealing with a mixture of leucine and valine. Barger and Dale [1907] obtained from ergot a mixture of amino acids corresponding to clavin, in a yield of 0·07 per cent. It consisted largely of leucine, and probably also contained aspartic acid. Van Slyke [1909] separated clavin into 39 per cent. leucine, 22 per cent. isoleucine and 37 per cent. valine. Fränkel and Rainer [1916] obtained from ergot a minute quantity of tyrosine and histidine in crystals, and in one case reactions for tryptophane. That amino acids occur in ergot could to some extent be inferred from the presence of various amines, their decarboxylation products. Rye grains contain neither amino acids nor amines [Holtz and Müller 1925]. The fungus must therefore have formed them from the rye protein.

Amines.

Trimethylamine ["Propylamine" of Walz 1852] was shown by Brieger [1887] to be derived from the choline.

Putrescine and *cadaverine* were the two first putrefactive amines found in ergot, by Rieländer [1908].

Isoamylamine contributes slightly to the pressor effect of ergot extracts and is present in traces [Barger and Dale, 1909, ii.]; 20 to 30 mgm. of the crystalline oxalate was isolated from 3 kilos of ergot, or about 0·0005 per cent. of isoamylamine itself.

p-Hydroxyphenylethylamine (*tyramine*) was isolated in minute quantity from ergot by Barger [1909] and identified as the dibenzoyl derivative. The losses in the complicated process of extraction are great; on physiological grounds the amount present would appear to be of the order of 0·01 to 0·1 per cent. Tyramine was also obtained from ergot by Burmann [1912].

β-Iminazolyl-ethylamine (*histamine*) is by far the most potent of the amines of ergot. It was isolated from *ergotinum dialysatum* of Wernich by Barger and Dale [1910, ii.]. It is present in perfectly fresh ergot, an extract of which was found

to cause contraction of the isolated uterus within half an hour of the removal of the ergot from the rye. During the process of dialysis the amount, however, increased, by enzymic or by bacterial action. Enough of the dipicrate was obtained for analysis.

δ-Guanidylbutylamine (*agmatine*) was obtained from ergot by Engeland and Kutscher [1910, i. ii.].

It will be seen that from ergot some six amines have been obtained, which are formed from the amino acids leucine, tyrosine, histidine, lysine, arginine (and ornithine) by decarboxylation. Normally this decarboxylation is the result of bacterial action and bacteria may well be responsible for production of most of the amines in ergot extracts. It seems certain, however, that histamine at least occurs as such also in fresh ergot. Nor is this very surprising since fungi are more closely related to bacteria than to the higher plants.

Other Simple Bases.

Choline occurs of course in ergot, as a decomposition product of lecithin; it has been isolated from it by Brieger [1886], by Kraft, by Rieländer and by Tanret [1914].

More interesting is the occurrence of the very potent *acetyl choline*, responsible for a muscarine-like effect shown by some samples of ergot with marked intensity. Ewins [1914] isolated 0·2 grams of acetylcholine chloroplatinate from 1600 c.c. of a liquid extract of ergot, prepared according to the British Pharmacopœia. The separation from choline, present in much larger amount, is difficult, particularly on account of the extraordinary rapidity with which acetylcholine is hydrolysed by alkali.

Dudley [1929] isolated acetylcholine from horse's spleen and finds that Ewins' chloroplatinate was actually choline-acetylcholine dichloroplatinate which is less soluble than the acetylcholine salt, and much less soluble than the choline salt. Ewins' yield has therefore to be halved. The chloro aurates of choline and acetylcholine do not form a co-ordination compound, like that of the chloroplatinates.

Betaine was isolated from ergot by Kraft [1906] using potassium bismuth iodide, and later by Rieländer [1908].

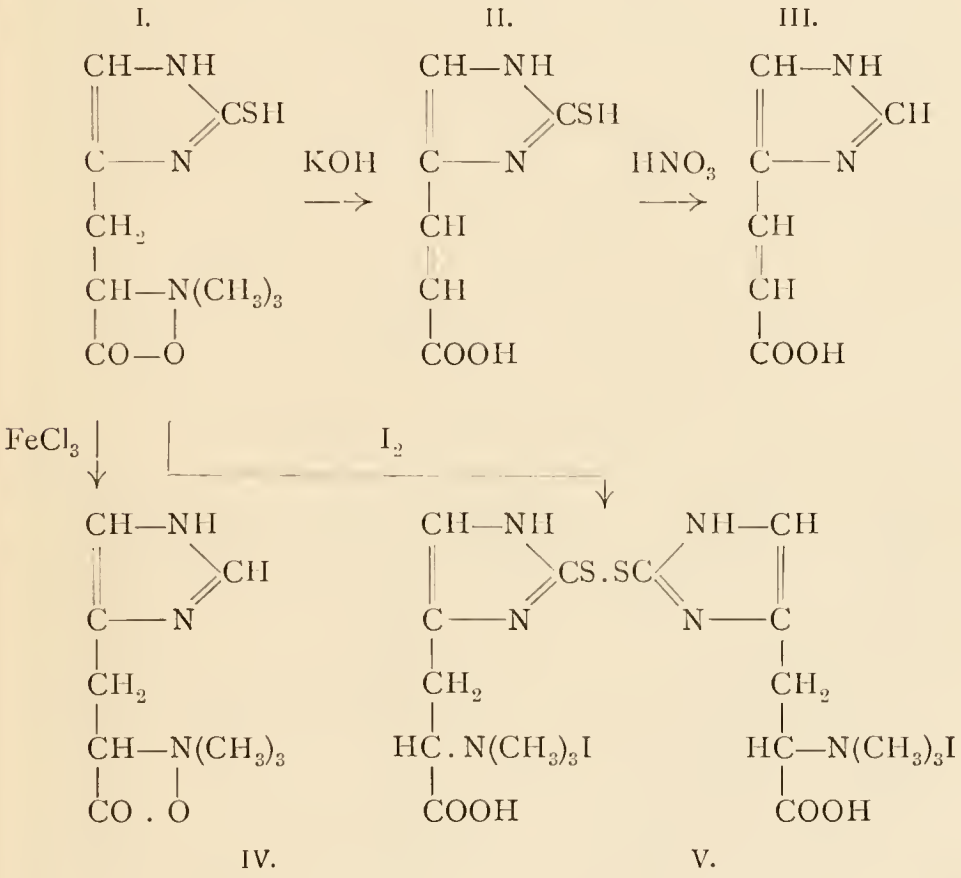
Ergothioneine was discovered in ergot by Tanret [1909]. For its preparation the ergot is extracted with 90 per cent.

alcohol; after evaporation of the latter, the aqueous residue is freed from fat and resin by filtration; 20 per cent. sulphuric acid is then added to precipitate colouring matters, and after removal of the acid with baryta, the filtrate is precipitated with basic lead acetate. After filtering again, the excess of lead is removed with sulphuric acid and the solution is made alkaline and extracted with chloroform to remove the complex ergot alkaloids. It is then acidified with acetic acid and precipitated completely with a warm 8 per cent. solution of mercuric chloride. The mercury precipitate is filtered off, washed, suspended in a large bulk of water and decomposed by hydrogen sulphide. After removal of the mercuric sulphide, the filtrate is evaporated under reduced pressure to a syrup from which ergothioneine chloride soon crystallises. The yield is 0·1 per cent. of the ergot employed. From the chloride the base can be obtained in various ways, for instance by boiling with excess of calcium carbonate, filtering, concentrating and adding alcohol. The free base is recrystallised from boiling 60 per cent. alcohol.

Ergothioneine crystallises in leaflets and needles of the composition $C_9H_{15}O_2N_3S$, $2H_2O$. It dissolves in 8·6 parts of water at 20°, but requires more than a thousand parts of boiling 95 per cent. alcohol; it is insoluble in ether, chloroform or benzene. $[\alpha]_D = +110°$; m.p. 290° on the Maquenne block. The isolation from ergot (yield 0·065 per cent.) has lately also been described by Eagles [1928]. Ergothioneine does not act on litmus; the salts are precipitated even in dilute solution by potassium tri-iodide and by mercuric chloride. With sodium *p*-diazobenzenesulphonate a cherry-red colour is produced. This reaction, together with the composition and other properties led Barger and Ewins [1911] to the constitutional formula I, according to which ergothioneine is the betaine of 2-thiol histidine. Boiling with concentrated potassium hydroxide removes trimethylamine, leaving an unsaturated acid (II), which on boiling with nitric acid loses its sulphur atom, changing to urocanic acid (III). On heating with ferric chloride the sulphur only is eliminated, and histidine betaine (IV) results. The latter substance occurs in other fungi. Finally on adding iodine in alcoholic solution two molecules combine to form a quaternary iodide (V) much less soluble than the salts of ergothioneine. The crystals of the dimeric iodide have the remarkable property of taking up excess of iodine from an aqueous solution and

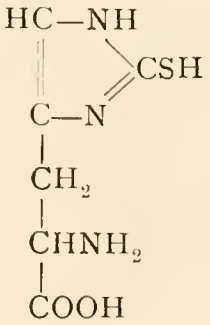
becoming steel grey or blue. The blue crystals are obtained directly by evaporating ergothioneine with excess of an alcoholic iodine solution; this constitutes a most characteristic reaction for the substance.

For a number of years ergothioneine remained a curiosity, peculiar to ergot, but like other constituents of the drug (histamine, ergosterol) it ultimately acquired considerable



biochemical importance. A slight discrepancy in two methods of estimating blood sugar led Benedict to the recognition of a reducing substance in the blood, which Newton, Benedict and Dakin [1927] and Eagles and Johnson [1927] simultaneously identified as ergothioneine. This substance reduces Folin's special phosphotungstic acid reagent used for the estimation of uric acid. It occurs in mammalian blood corpuscles, particularly of the pig, in very varying small amounts (at most 0·05 per cent. in the pig, in man on the average 0·005 per cent.). Hunter [1928] describes an intense purple-red colour with sodium

p-diazobenzene sulphonate and 10*N* sodium hydroxide, which he used to estimate the substance. Among many samples of pig's blood Eagles and Vars [1928] found one to contain no ergothioneine. This came from pigs fed on garbage. Transference of these animals to a diet rich in maize led to the appearance of ergothioneine in their blood. This led to the recognition of the thiolglyoxaline ring in zein, and also in other cereal proteins and egg albumin, but not in caseinogen or gelatin. It seems therefore that ergothioneine arises out of a precursor in rye protein, perhaps a new amino acid, thiolhistidine.



The isolation of this substance from zein has so far been unsuccessful, but as a preliminary it has been synthesised by Ashley and Harington. Its methylation, both in ergot and in the pig, would be a matter of some interest, particularly since methylation in animals is rare.

Uracil, $C_4H_4O_2N_2$, a dioxypyrimidine, was isolated from ergot by Ricländer [1908]. It was previously only known to occur as a constituent of nucleic acid, but like the amino acids, it seems to be present in ergot in the free state.

Guanosine, Vernine, $C_{10}H_{13}O_5N_5$, is a somewhat larger fragment of nucleic acid. Vernin was isolated from ergot by Schulze and Bosshard [1887] after they had discovered it in various leguminous seedlings. Schulze [1910] found it to be identical with guanosine, a guanine pentoside, which is formed by the splitting-off of phosphoric acid from guanylic acid, a mononucleotide of the pancreas. Guanosine (or vernine) is hydrolysed to guanine and *d*-ribose, according to the equation :

$$C_{10}H_{13}O_5N_5 + H_2O = C_5H_5ON_5 + C_5H_{10}O_5.$$

CHAPTER V

PHARMACOLOGICAL AND CLINICAL

THE first animal experiments with ergot seem to have been those on poultry by Tuillier, in 1630, and published by Dodart [1676] (Chap. I.), who wrote: "M. Tuillier . . . ayant appris . . . que le seigle cornu était la cause des gangrènes, qui étaient alors très-fréquentes, voulant connaitre si ce grain en était véritablement la cause, il en fit donner à plusieurs animaux de sa basse-cour, qui en moururent."

Salerne [1755] reported some experiments made by him in 1748, including one on a pig which died without developing gangrene, but Read [1774] induced gangrene in the ear of a pig after seventeen days' feeding with ergot; next day the ear was cast off and a day later the animal died.

In the heated German controversy on the cause of ergotism, mentioned in Chapter I., animal experiments were quoted by Schleger [1770] in support of his view that ergot is innocuous. In these and other experiments the dose was too small, as was pointed out by Tessier [1778] in the first detailed investigation of the effects of ergot. He observed gangrene of the beak in ducks, and of the feet, ears and tail in pigs. The ultimate recognition of the poisonous character of ergot was, however, the result of human suffering rather than of animal experiments. The chemical investigation of ergot in the nineteenth century led to more extensive use of animals which were generally poisoned in the intact state. Kobert and his pupils made much use of the cock's-comb test, and carried out toxicological experiments on other animals, but were not very successful with the detailed physiological analysis of the action of ergot, nor did Jacobj [1897] go much further in this direction. His pupil Jolly [1905] dealt with the effects of ergot on the circulation; this prize dissertation is, however, chiefly valuable for its bibliography of 496 references, mainly pharmacological. The real pharmacology of ergot starts with the fundamental work of

Dale [1906] on chrysotoxin and later [Barger and Dale 1907] on pure ergotoxine. Using mostly cats with the brain destroyed, and artificial respiration, he showed that ergotoxine causes a primary stimulation of plain muscular tissues, especially the arteries, the uterus and the sphincter of the pupil, followed by a secondary selective paralysis of the motor elements of the so-called "myoneural junctions" associated with innervation by the true sympathetic system and stimulated by adrenaline, the autonomic nerves of cranial and sacral root origin retaining their normal function.[1]

Dale's work made it clear that ergot, and the various impure active preparations which had been made from it (chrysotoxin, sphacelinic acid, etc.), contained a principle producing a characteristic and easily recognisable physiological effect, and this was found to be the alkaloid ergotoxine (= hydroergotinine, see Chapter IV., p. 126).

Such minor activity as ergotinine may possess is of the same kind, and the alkaloid ergotamine, subsequently discovered by Stoll, has an action which for practical purposes, is indistinguishable from that of ergotoxine. Hence the important active principles preformed in ergot and peculiar to it are alkaloidal. In addition, however, certain liquid extracts of ergot showed experimentally effects on the blood-pressure, and on the isolated uterus, which are due to non-specific amines which Barger and Dale subsequently identified. The therapeutic use, in place of ergot, of these amines, which are much more readily synthesised than extracted from ergot, has been advocated, particularly in Germany; but of recent years, largely owing to the exact clinical investigation of ergotamine, opinion has swung back to the view that the therapeutically valuable constituents of ergot are the alkaloids, and accordingly much attention has been paid to their biological assay; recent revisions of national

[1] A paralysis of the sympathetic was indeed mentioned much earlier by G. B. Brunner [1860] who wrote: "Eine Lähmung des Sympathicus aber haben wir experimentell nachgewiesen." At this time, however, very little was known about the sympathetic, and nothing about the active principles of ergot or adrenaline. Most of the liquid extracts contained very little alkaloid and owed their activity, as we now know, to simpler amines. Nevertheless, Sollman and Brown [1905] observed that such extracts obliterated the stimulant effect of adrenaline and dilated the spleen, but, unlike Dale, they had no potent alkaloidal preparation at their disposal.

pharmacopœias have also aimed at securing a definite amount of active alkaloid in the liquid extracts.

Pharmacological Properties of Ergotoxine (= Hydro-ergotinine) and of Ergotamine.

The primary stimulation of plain muscle and subsequent specific paralysis of the true sympathetic system was first observed by Dale by means of the blood-pressure and is illustrated in Fig. 38.

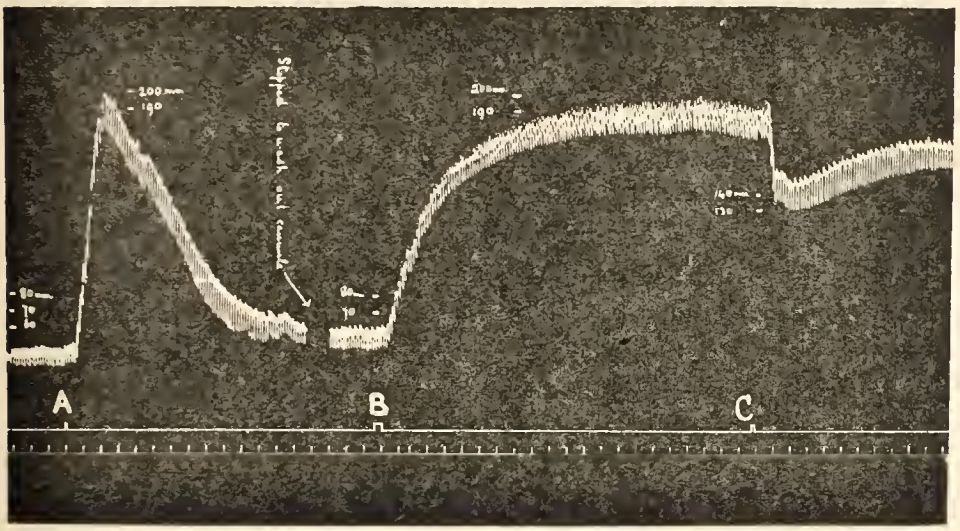


FIG. 38.—Vasomotor reversal. Pithed cat, 2 kilos. Artificial respiration. Carotid blood-pressure. The time marker shows ten-second intervals. (Reproduced from *Biochemical Journal*, 1907, 2, 248.) For explanation, see text.

At A, 0·5 mgm. adrenaline produces the usual transitory effect. At B, 1 mgm. of ergotoxine phosphate causes a slower and much more prolonged rise to about the same level. At C, 0·05 mgm. of adrenaline now causes a fall of blood-pressure. This vasomotor reversal may also be shown by stimulating the splanchnic nerves, or by injecting nicotine. Both these procedures lead to accelerated output of adrenaline from the suprarenal gland, and it has even been suggested that the action of ergotoxine is to reverse the vasoconstrictor effect of adrenaline and not that produced directly by sympathetic impulses. There can be no doubt, however, that many direct motor effects of sympathetic nerves are replaced by inhibition

after ergotoxine, including that on the small blood-vessels, though the depressor effect of splanchnic stimulation after ergotoxine is largely due to output of adrenaline.

In the case of some organs the motor sympathetic effect may be abolished, without being replaced by an inhibitor effect; in that case sympathetic stimulation has no result. Finally, there are muscles normally inhibited by sympathetic stimulation or adrenaline (*e.g.* small intestine of the cat, dog, monkey) which according to Dale are still so inhibited after ergotoxine. He wrote: "The only explanation which fits all the facts is that the paralysis, already shown to be confined to the myoneural junctions of the true sympathetic, is further limited to those of motor function, leaving those concerned with inhibition relatively or absolutely unaffected." More recently, however, abolition of inhibition by adrenaline has been demonstrated in certain cases, so that the reversals obtained by Dale were probably due to a relative rather than an absolute immunity of the inhibitory components. Thus Rothlin [1929] found that the inhibition by adrenaline of the dog's gut *in situ* may be completely abolished by doses of ergotamine, insufficient to annul the pressor action of adrenaline (see his Figs. 8*a*, 8*b* and 9). In the isolated small and large intestines of the guinea-pig and rabbit *in vitro*, the inhibitory action of adrenaline is abolished by a dose of ergotamine twice as large; for the isolated virgin uterus of the cat from 10 to 40 times as much ergotamine as adrenaline is required; with the isolated uterus of the guinea-pig, and particularly of the rat, no abolition of adrenaline action could be obtained.

The state of affairs is therefore rather complicated, and varies with the animal, the organ, and even with the condition of the latter (pregnant or non-pregnant uterus), as shown in the table (p. 155) given by Dale [1906 and 1907; the cases marked with an asterisk are from his second paper; it should, however, be noted that as detailed above, Rothlin could abolish the inhibitory action of adrenaline, by means of ergotamine, in the small and large intestines of the dog, the rabbit and the guinea-pig, *in vitro* and *in vivo*].

As regards the ease of abolition of the vasomotor effect of adrenaline, the order is: cat, pig, dog and ferret, rabbit, cock. The abolition in the last case was never complete with the largest doses of ergotoxine employed.

All these effects were observed by Dale more than twenty years ago, using either ergotoxine or Jacobj's chrysotoxine (which contained about 2 per cent. of ergotoxine). Since then other examples of the antagonism to adrenaline have been observed, some with ergotoxine, others with the more recently discovered ergotamine. It may be as well to show first that

Organ.	Effects of stimulating Sympathetic Nerve Supply or injecting Adrenaline Intravenously.	
	Before Ergot.	After Ergot.
Arteries (cat, dog, ferret)	M	I
„ (rabbit)	M	Nil or weak M
„ (pig,* goat*)	M	Nil
„ (cock*)	M	Very resistant to paralysis
Cardiac muscle	M	Nil or weak M
Spleen (cat)	M	I
Stomach (cat)	I	I
Small intestine, (cat, dog, monkey)	I	I (but see Rothlin)
Large intestine (cat)	I	I (but see Rothlin)
Ileo-colic sphincter (cat)	M	Nil
Internal anal sphincter (cat)	M	I
Gall-bladder	I	I
Fundus of urinary bladder (cat)	I	I
„ „ „ (ferret)	M	I
Base of bladder and urethra (cat)	M	Nil
Bladder (pig*)	I	Nil
„ (goat*)	M	I
Pilo-motor muscles	M	Nil
Dilatator iridis	M	Nil with adrenaline weak M with cervical sympathetic
Uterus (cat, non-pregnant)	I or M and I	I
„ (cat, pregnant)	M	I
„ (rabbit)	M	I (slight)
„ (monkey)	M	I
Retractor penis (dog)	M	Nil

M = motor effect; *i.e.*, increase of tone; augmentation or acceleration of rhythm.
I = inhibition; *i.e.*, relaxation of tone; cessation, weakening or slowing of rhythm.

for practical purposes the pharmacological actions of these two alkaloids are identical [Dale and Spiro 1922]. Since these authors had first separately studied ergotoxine and ergotamine respectively, they arranged to co-operate in an investigation of both, and published jointly the results of a comparison between the two alkaloids, in order to avoid confusion. Spiro [1921; Spiro and Stoll 1921] had found ergotamine extremely active on the isolated uterus, and since ergotoxine

had not been closely studied in this respect, there was at first an impression that it was less active. However, the actions of the two alkaloids, in a dilution of $1{\cdot}25 \times 10^{8}$ on the separated horns of the same virgin guinea-pig's uterus in Ringer's solution, were found by Dale and Spiro to be indistinguishable.

The same was found at a dilution of $2{\cdot}5 \times 10^{6}$ with the virgin cat's uterus, and at a dilution of $1{\cdot}25 \times 10^{7}$ with that of the rat. Ergotamine further showed the same action on the blood-pressure of the decerebrate cat, as had been previously reported by Dale for ergotoxine. In either case the vasomotor reversal is brought about by doses of 0·5 to 1·0 mgm. per kilo. Ergotamine causes blueing and gangrene of the cock's-comb in much the same way as ergotoxine; somewhat larger doses of the former alkaloid were required, but many more experiments would be needed to establish even a quantitative difference. As detailed in the section on biological assay, Pattee and Nelson [1929] have also recorded a small quantitative difference in this action of the ergot alkaloids; they consider 1 c.c. of a standard U.S. Patent extract to be equivalent in its action on the cock's-comb to 0·45 mgm. ergotamine and to 0·40 mgm. ergotoxine.[1] The general toxic effects of ergotamine and ergotoxine, tested successively on the same cat, were also found by Dale to be extremely similar.

After the publication of this paper by Dale and Spiro, Broom and Clark [1923] described their assay method on the rabbit's uterus and considered ergotoxine to have half the activity of ergotamine; but a further examination of the relationship between these alkaloids, by Burn and Ellis [1927], who used Broom and Clark's method, led to the result that, after allowance has been made for the different proportion of base in ergotamine tartrate and ergotoxine phosphate, the two alkaloids have the same activity, within the limits of accuracy of the method. If there is a quantitative difference, it is less than 10 per cent. Rothlin [1923] found the greatest similarity between his own extensive experiments with ergotamine and those of Dale with ergotoxine. He considered the chief difference to be that the former does not paralyse the respiratory centre to the same extent as the latter. Since he himself did not experiment

[1] According to Dr Rothlin (private communication) there is an arithmetical error and the ergotoxine was not quite pure.

with ergotoxine, the difference may be more apparent than real.[1]

We may now well consider the further observations on ergotoxine and ergotamine together. Where an action is attributed to either, it may be presumed that the statement applies to an equal quantity of the other, unless the contrary is indicated. Dale's original vasomotor reversal may be shown in other ways. Thus ergotamine abolishes the constriction of isolated rings of the mesenteric artery of the ox, caused by adrenaline, and a similar effect is obtained on perfusion of the rabbit's ear or the hind limb of a frog [Rothlin 1925]; the last-named preparation has been used for biological assay (*q.v.* p. 196, method 3). The effect of perfusing ergotamine (and ergotoxine) has also been studied by Heymans and Régniers [1927] who, however, attribute to it a vasodilator action only. Hamet [1926] has investigated the paralysis of the renal vasomotors by ergotoxine, ergotamine, ergotinine (and yohimbine).

The primary pressor effect which Dale observed with ergotoxine in the decerebrate cat is not always shown by the rabbit under urethane. Here small doses of ergotamine (0·05 to 0·1 mgm. per kilo) cause a small but prolonged rise of blood-pressure, but larger doses (0·3 to 0·5 mgm. per kilo) are depressant according to Rothlin [1923] who at first did not observe any primary depression in the cat or dog. Salant, Nadler and Brodman [1928] found it occasionally in the cat, but it was always abolished by removal of both adrenal glands. Rothlin has later (private communication) also occasionally observed a lowering of the blood-pressure after the first injection of ergotamine.

The abolition of the motor action of adrenaline on the

[1] Later Rothlin [1928] writes: "Die Auffassung (Clark, Rigler und Silberstern, Hamet usw.), dasz Ergotoxin geringere pharmakologische Wirksamkeit als Ergotamin besitzt, wird durch unsere ausführlichen Nachuntersuchungen an verschiedenen Testobjekten nicht bestätigt. Die Ansicht von Dale und Spiro, welche die pharmakologische Gleichwertigkeit zuerst nachwiesen, ist nach unserer Auffassung richtig. Die schwächere Wirkung von Ergotoxin verschiedener Autoren beruht wahrscheinlich auf der Verwendung von unreiner Substanz und auf den methodischen Schwierigkeiten des quantitativen pharmakologischen Nachweises." Raymond Hamet [1927] in a review of the action of ergot alkaloids, was evidently not aware of the accurate work of Burn and Ellis and persists in the statement that ergotamine is much the most active.

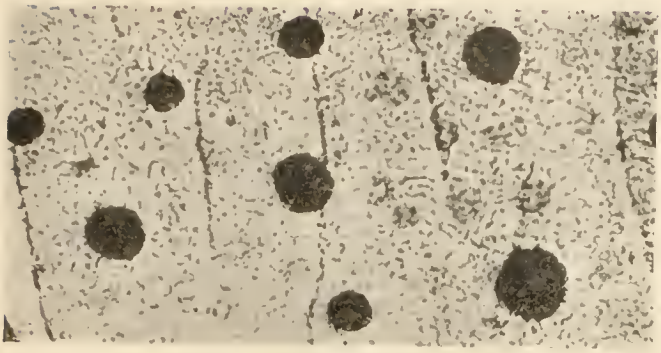
isolated uterus of the rabbit (see Dale's table, above) was utilised quantitatively by Broom and Clark; their method is dealt with below in the section on biological assay. With the same object in view, Stroband [1928] experimented with the uterus of the cow, the hedgehog and the pig, also with the vagina and vas deferens of the pig, but found none of these as good as the rabbit's uterus. Seel [1926] also used the pig's uterus. Knaus [1928] found that ergotamine causes a persistent contraction of the isolated puerperal uterus of the rabbit (forty minutes post-partum). The effect is produced slowly and the drug is not readily washed out, so that it seems therapeutically desirable. Similar conclusions were reached by Schübel and Gehlen [1928] with the cat's uterus *in situ*.

The motor effect of adrenaline, in a dilution of 10^6, on the isolated seminal vesicle of the guinea-pig is abolished by ergotamine at the much higher dilution of 3×10^7, but in various other examples of this antagonism the ergotamine required is 1 to $1\frac{1}{2}$ times that of the adrenaline [Rothlin 1929].

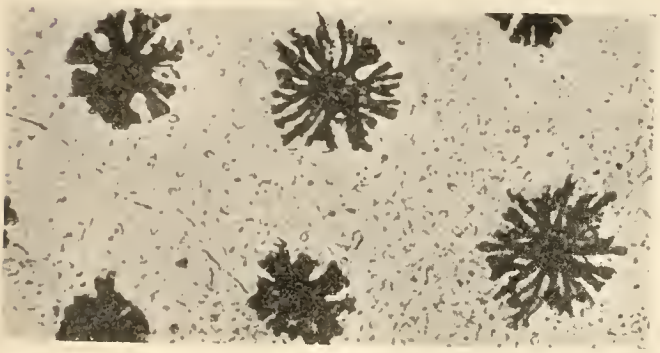
An interesting example of the reversal of the motor effect of adrenaline was discovered by Spaeth and Barbour [1917]. The melanophores (of *Fundulus*), which are considered to be functionally modified smooth muscle cells, contract under the influence of adrenaline; after keeping in an ergotoxine solution they become half-expanded, and adrenaline then expands them fully (Fig. 39).

Ergotamine is stated by Curtis [1928] to reverse not only the pressor effect of adrenaline, but also that of ephedrine, if the two drugs are used in approximately equimolecular proportions. According to Tainter [1929] and Rothlin (private communication), however, ephedrine is in this respect similar to tyramine; its pressor action can at most be abolished, not reversed.

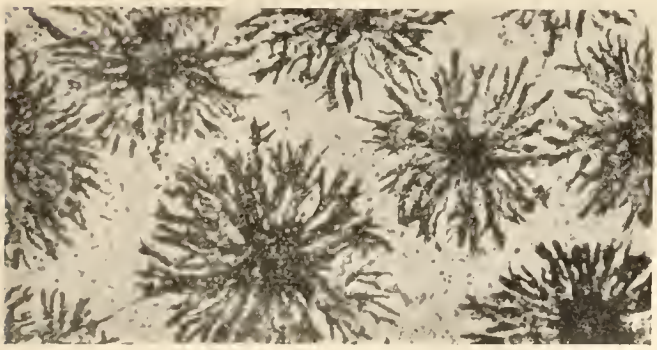
All these effects of ergotoxine and ergotamine relate to the abolition or reversal of an adrenaline *motor* effect. Contrary to Dale's expectation, referred to above, a number of *inhibitor* effects of adrenaline are also abolished by the ergot alkaloids. Planelles [1925] found an example of this kind in the isolated small intestine of the guinea-pig. Rothlin [1925, 1929] observed this effect not only with the small, but also with the large intestine of the guinea-pig, further with the small and large intestine of the rabbit and with the small intestine of the dog and rabbit *in situ*. Tokieda [1927] observed it with the rabbit's



Adrenaline.



Ergotoxine.



Adrenaline, after Ergotoxine.

FIG. 39.—Melanophores of *Fundulus*. (See text.)
(After Spaeth and Barbour.)

gut, as also did Issekutz and Leinzinger [1928]. Thienes [1929] found that the inhibition of the rabbit's duodenum by adrenaline is abolished by ergotamine, but observed no action on the colon of the rabbit, cat and guinea-pig. Planelles and Rothlin recorded peristalsis by Trendelenburg's method, most others by the simpler method of Magnus. The small intestine of the rabbit and guinea-pig has been used quantitatively by Leinzinger and Kelemen (see section on biological assay). Mendez [1928] is not wholly convinced that the ergot alkaloids can in these cases abolish an inhibition due to adrenaline. A further example of the effect is furnished by the coronary arteries [Rothlin 1925]. The arteries of the heart (coronary) and of the lungs are peculiar in not being constricted by adrenaline. Finally Baur [1928] has used the amnion of the fowl and the goose; twisted strips of this delicate membrane in Tyrode solution have their movement inhibited by adrenaline, and the inhibition is abolished by ergotamine. The amnion is stated to be a pure smooth-muscle structure free from nerves.

It has long been known that an injection of adrenaline raises the **blood sugar**; Miculicich [1912] already showed that this hyperglycæmia is abolished by ergotoxine. Fröhlich and Pollak [1914] next found that the mobilisation of sugar by adrenaline in the perfused frog's liver is also stopped by ergotoxine. Using ergotamine, Lesser and Zipf [1923] obtained a similar effect and found, moreover, that 5 to 10 mgm. per kilo lowers the blood sugar of normal rabbits by about 14 per cent. The latter result was confirmed by Seidel [1927] and extended to man, in whom, especially when diabetic, 0·25 to 0·375 mgm. ergotamine lowers the blood sugar. The effect in human diabetes was also studied by Moretti [1927] and by Bouckaert and Schaus [1927]. Both papers suggest that hyperglycæmia of nervous origin may be corrected by ergotamine, and the latter authors give an injection of 0·5 mgm. ergotamine, followed by 50 grm. of glucose by the mouth, in order to test, for instance, whether a glycosuria is due to a cerebral tumour. Under the influence of ergotamine the sharp transitory rise in blood sugar is, in such cases, largely prevented, but it is hardly affected when the diabetes is pancreatic in origin. The hypoglycæmic action of ergotamine is further illustrated by an observation by Burn [1923] that intravenous doses of 5 mgm. of ergotamine tartrate per kilo make rabbits much more susceptible to small

doses of insulin, given two hours later. Similarly Minkowski could with ergotamine sensitise a patient to insulin, who was previously refractory to it. The adverse effect of ergotamine on sugar production extends to alimentary glycosuria [Pollak 1929], to that due to magnesium salts [Lang and Rigo 1929], and to the mobilisation of glycogen in the isolated frog's liver by histamine [Geiger 1929].

Lesser and Zipf, as well as Moretti, attribute the smaller production of sugar under the influence of ergotamine to the existence of a "sugar tonus" due to endocrine glands under the control of the sympathetic, which is paralysed by ergotamine and stimulated by adrenaline. Rothlin [1928] fully confirmed the abolition of adrenaline hyperglycæmia by ergotamine, but could not observe that this alkaloid produced a fall of blood sugar in normal animals; hence he does not agree with Lesser and Zipf in postulating a "sugar tonus." Against the numerous positive observations recorded above, there is only the failure of Farrar and Duff [1928] to check adrenaline hyperglycæmia by ergotamine (these authors found a rise of 0·025 per cent. in the blood sugar).

An even more general effect of ergotamine than that on sugar production is its effect on the **basal metabolism**. This is lowered in hyperthyroidism and exophthalmic goitre (Porges and Adlersberg, Adlersberg and Porges, Merke, Noyons and Bouckaert). In normal rabbits, less so in thyroidectomised ones, Marine, Deutsch and Cipra [1927] found a striking fall in the heat production. They consider that a powerful sympathetic depressant like ergotamine should be tried therapeutically in exophthalmic goitre and quote references to clinical experiments. The diminution of heat production by ergotoxine and ergotamine results in a lowering of the rectal temperature by 2 to 3° C. in normal rats and rabbits, also in animals in which the body temperature has been raised artificially [Rigler and Silberstern 1927]. In accordance with this Abderhalden and Wertheimer [1927] find that 0·25 to 0·5 mgm. ergotamine depresses the basal metabolism in rats and may neutralise the effect of injected thyroxin for days on end. Hence they conclude that thyroxin acts via the sympathetic. [*Cf.* also Epstein, 1929, on thyroxin diuresis.] There is, however, a good deal of contradiction as to the effect of ergotoxine on the body temperature. Dale [Barger

and Dale 1907] noticed a considerable rise, particularly in rabbits. This was also observed by Miculicich [1912] and by Githens [1917]; the latter found a fall of temperature in rats, mice and pigeons. The difference from ergotamine is according to Brink and Rigler [1929] more apparent than real; they attribute the rise to decomposition of ergotoxine on keeping. There is a similar disagreement about the effect of the alkaloids on the rise of body temperature due to β-tetrahydronaphthylamine; according to Cloetta and Waser [1915] ergotoxine increases this effect, according to Skowrónski [1929] ergotamine has no action on it.

Whilst ergotoxine and ergotamine depress the nerve-endings of the true sympathetic in the heart, the effect on the **parasympathetic** appears to be in an opposite direction. Rothlin [1923] observed that the fall of blood-pressure due to stimulation of the central end of the depressor nerve (in the rabbit) or of the vagus (in the cat), can be abolished by ergotamine (in the cat the afferent depressor fibres are bound up with the trunk of the vagus). Heymans and Régniers [1929] confirmed Rothlin's observations and showed that the same is true of the stimulation of the carotis sinus (sinus nerve of Hering). Rothlin further showed that ergotamine increases the susceptibility of the vagus action on the heart to electrical and chemical stimuli (acetyl choline). Loewi and Navratil [1926] found that treatment of the isolated frog's heart with ergotamine and subsequent washing out with Ringer's solution abolishes the power of the heart to destroy the vagus substance or acetyl choline (the two are very probably identical). The sensitisation of the vagus by ergotamine is therefore attributed to the failure of the heart to destroy the vagus substance. [*Cf.* also Amsler, 1920 (ergotoxine); Kolm and Pick (1921, i., ii.); Navratil, 1927; Agnoli, 1927; Otto, 1928.] Hess also showed parasympathetic stimulation by ergotamine in the case of the cat's eye. According to Koppányi [1929] the miosis resulting from intraocular injection of ergotamine tartrate is caused by sympathetic paralysis.

Injection of 0·25 mgm. of ergotamine tartrate lowers the intraocular pressure in glaucoma [Thiel, 1926, i.; Heim, 1927; Michail, Bendescu and Vancea, 1928].

According to Urechia and Popoviciu [1927] ergotamine increases the phosphorus and lowers the calcium in the blood.

Mednikianz [1928] states that the increase in the residual nitrogen, given off by a bull's testis perfused with Ringer-Locke's solution under the influence of adrenaline at 10^{-6} is abolished by ergotamine at 10^{-5}. This would be another example of the adrenaline-ergotamine antagonism, but the figures are not very convincing. Finally two effects on enzyme action *in vitro* may be mentioned. U. von Euler [1929] finds that ergotoxine phosphate and ergotamine tartrate, both in concentrations of about 10^{-12} increase tissue oxidation, as measured by the methylene blue method; both alkaloids abolish the powerful stimulus of adrenaline to oxidation. No inversion is indicated in these experiments. Matthes [1930] finds that relatively high concentrations of ergotoxine and of ergotamine inhibit the destruction of acetyl choline by a blood enzyme (the alkaloid eserine does this in very low concentration).

General Toxic Effects.

According to Dale [Barger and Dale 1907] **frogs** gradually recover from doses of pure ergotoxine up to 5 mgm. and show a fatigue somewhat similar to the veratrine-like effect described by Kobert for cornutine, but the strychnine-like spasms with $\frac{1}{12}$ mgm. described by Kobert as highly characteristic of cornutine were not seen by Meulenhoff, Dale or other observers in frogs. These cornutine convulsions are one of the mysteries of the pharmacology of ergot, and seem likely to remain so. With ergotamine Rothlin [1923] found in frogs similar effects to those described by Dale. He, however, places the lethal dose at 1 mgm. per 30 grm. body weight; death does not intervene until after two to four days.

The white **rat** seems rather resistant to ergotamine. After subcutaneous doses of 25 to 100 mgm. Rothlin observed dyspnœa, and later the animals scratch themselves violently as the result of itching or tingling; large doses cause isolated contractions of the limbs. After eight to ten hours the animals are normal, but five to seven days later the extremity of the tail becomes gangrenous and is shed.

The **guinea-pig** is even more resistant; the intravenous lethal dose of ergotamine is above 36 mgm. per kilo (Rothlin). Dyspnœa, erection of the hair and convulsions were observed; the latter appear at once with large doses, and develop after five

to fifteen minutes with small ones; ten to twelve hours later the animals appeared normal and no late symptoms were observed. Jaquet [Kraft 1906] also obtained convulsions in guinea-pigs (using hydro-ergotinine = ergotoxine). One guinea-pig survived after an injection of 10 mgm. but another was killed by 50 mgm.

The **rabbit** showed considerable individual variations in Dale's experiments with ergotoxine; 5 mgm. per kilo given in a single injection generally proved fatal within two hours, and the rectal temperature rose to 44°. Four mgm. in a rabbit of 1420 grm. on one occasion produced gangrene of both ears after a fortnight, and the shedding, without any bleeding, of the peripheral two-thirds six weeks after the injection.[1] On the other hand, starting with smaller doses, considerable tolerance may be developed; a rabbit received 56·5 mgm. in the course of forty-seven days, including 4, 5, 5·5, 5 and 10 mgm. on successive days without showing any gangrene or other permanent damage within three months. (Gangrene is more readily induced in the rat's tail or cock's comb.)

The protocols of Dale's experiments with rabbits and ergotoxine record "jerky movements," "occasional convulsive movements," "persistent fine tremors and occasional twitching of the limbs." "The animal appears to be hyperexcitable, a slight touch on the back eliciting a sharp contraction of all the muscles of the body," "teeth chatter." Rothlin, working with ergotamine, observed two and a half to three hours after intravenous injection general attacks of clonic and tonic convulsions, during one of which the animal died in a state of rigidity resembling that of strychnine poisoning. In view of the obviously wide variation among rabbits in resistance to these alkaloids, the fact that Rothlin gives 10 mgm. as the intravenous lethal dose of ergotamine, while Dale found that a dose of 5 mgm. of ergotoxine per kilo was fatal to most rabbits, does not suggest any significant difference of general toxicity between the two. The minor qualitative differences between the two observers' accounts of the symptoms are not such as to suggest such wide differences of action as would

[1] Dr Dale informs me that, in view of the fact that this followed the injection of ergotoxine in somewhat strongly alkaline solution into the vein of the ear, he has some doubt as to the true significance of the effect, which was only seen in this one rabbit.

warrant the attribution to one of the gangrenous type and to the other of the convulsant type of ergotism. Both produce gangrene and both, in rapidly fatal doses, cause certain acute nervous symptoms. Neither by itself has been shown to produce chronic effects on the nervous system which, as Mellanby has found, occur when ergot is administered to animals deficient in vitamin-A. (See page 23.)

In the **cat**, after intramuscular injections of ergotoxine, Dale observed vomiting, intense constriction of the pupil, ataxia and muscular weakness, hyperexcitability and profuse salivation. Identical symptoms were noted by Rothlin after 5 to 7 mgm. ergotamine per kilo; he also mentions isolated muscular twitches. A dose of 15 mgm. per kilo left the animal apparently normal after twenty-four hours. On the other hand, Dale states that a dose of 5 mgm. of ergotoxine phosphate may prove fatal. In a large female cat in the last week of pregnancy, 3 mgm. induced the birth of three dead kittens, without serious effect on the mother, but in other cases no abortion was produced. Ergotoxine causes, indeed, a tonic contraction of the uterus, which may lead to asphyxiation and expulsion of the fœtus, but does not necessarily do so. Jacobj mentions a case of abortion in the cat, but Davidson [1882] quotes one and Kobert [1884] four cases of pregnant women who took ergot and died before abortion occurred. A more recent case, ending in identical fashion, was described by Rosenbloom and Schildecker [1914]. There were clonic convulsions; the contraction of the uterus was noted visually; the stools were bloody and contained pieces of the mucous membrane of the intestine. Nine hours before death the temperature rose to 103° F. The history of ergotism epidemics does not permit of an estimate of the lethal dose for man whose susceptibility seems to vary greatly. Twenty-five per cent. (and even more) of ergot in grain has repeatedly been recorded; this would imply a very large daily dose, which often caused death, but by no means always produced abortion (see Chapter II.). In Davidson's case two handfuls of ergot powder proved fatal, but did not terminate the five months' pregnancy.

For older experiments in which attempts were made to produce abortion or to study the effect of ergot on the uterus, the monograph by C. W. Edmunds and Worth Hale [1911] should be consulted. At first [mainly 1876-86] the uterus was

used *in situ;* after 1904 and particularly after 1908 (Kehrer) the isolated uterus in warm oxygenated Ringer's solution was employed which, however, chiefly indicates histamine. The domestic fowl was the first animal to be used for investigating the toxicity of ergot, and Lorinser [1824, chapter i.] paid special attention to the cyanosis of the cock's-comb (at the time when ergot began to be used in official medicine). The **cock** has since been used largely, by Kobert and his pupils, by Jacobj, by Santesson, almost exclusively by Meulenhoff and others. It was not proved that the therapeutic effect of the drug is inseparably connected with the cock's-comb reaction, until Dale found the latter to be due to ergotoxine; the test is now official in the U.S. Pharmacopœia, for standardising the liquid extract.

Dale found the cock more resistant to ergotoxine than mammals of the same weight, and particularly resistant to the vasomotor reversal; this may be connected with the comparative ease with which gangrene can be produced. There is a good deal of individual variation and some evidence for the development of tolerance. Intravenous doses amounting to 9 mgm. in one day, 17 mgm. and also 30 mgm. in the course of two days all proved acutely fatal. Ergotoxine phosphate by the mouth, 80 mgm. in all, had little effect; injection of $7 + 10 + 10 + 10 + 10 + 10 = 57$ mgm., mostly into the breast muscle, caused gangrene, and part of the comb was shed four weeks after the last injection. The rate of absorption is evidently of great influence on the production of gangrene. In order to delay absorption, an alcoholic solution of the free base (ergotoxine) was injected subcutaneously, 10 mgm. on each of three days; the tips of all digitations and the hinder part of the comb (the most sensitive) were shed a fortnight later. Besides the cyanosis the symptoms of acute poisoning in cocks include ataxia, dyspnœa, drowsiness, diuresis, and in fatal cases ulceration of the bowel and a high body temperature. Dale and Spiro [1922] observed identical symptoms in the same cock from injection of 1·6 mgm. of ergotoxine phosphate and of ergotamine tartrate respectively on successive days. In another cock, receiving repeated injections of ergotamine tartrate over a period of ten days, gangrene of the digitations of the comb began after a total of 51 mgm. had been injected, and extended after a further and final dose of 24 mgm. With

2 to 3 mgm. of ergotamine per kilo Rothlin obtained cyanosis (in half to one hour), ataxia, dyspnœa and drowsiness. Gangrene of the comb, part of which was shed after two to three weeks, was also produced in some cases.

The administration of ergot itself by the mouth (best in pills, mixed with flour) favours slow absorption and gangrene. Meulenhoff [1899] found consistently that 16 grm. of ergot was an acutely fatal dose; this can hardly have represented more than 30 to 40 mgm. of ergotoxine, which would indicate a better absorption than in Dale's experiments with pure ergotoxine by the mouth. The above mentioned toxicological experiments should be sharply differentiated from the assay method of the U.S. Pharmacopœia, which utilises merely the coloration of the cock's-comb produced by 0·5 c.c. of a standard fluid extract. According to Pattee and Nelson [1929] this is equivalent to 0·2 mgm. ergotoxine, or only about one-hundredth of the lethal dose (see further in the section on biological assay). The histology of the gangrenous cock's-comb has been investigated by W. Jacobj [1924].

The histological changes in the blood-vessels and other organs have been studied in various animals by Grigorjeff; compare also Grünfeld and Krysinski; for changes in the spinal cord in man see Tuczek and Walker, in the dog, E. Mellanby.

Pharmacological Action of Ergotinine and of Ergotaminine.

There has been much controversy about the activity of ergotinine. Most investigators have considered it slightly active; some found it inactive; others, particularly French observers, have declared it to be the most potent principle of ergot. There was never any dispute about the quality of the action; such activity as ergotinine may possess is entirely of the kind shown by ergotoxine; it is merely a question of quantity. We must, in the first place, eliminate from the discussion all clinical and pharmacological experiments in which an alkaloid was used, which was not wholly crystalline [*e.g.* clinical: Chahbazian, 1884; pharmacological: Wertheimer, 1892; Plumier, 1905]. Kobert [1884] who used a very pure specimen, prepared by Tanret himself, and consisting exclusively of well-formed crystals, declared it to be inactive. Jacobj [1897] made the same statement for his well-crystallised secaline

(=ergotinine). Meulenhoff at first considered ergotinine to be inactive but later [1899, see especially footnote, pp. 115-117] he ascribed to it some activity. A small cock (800 grm.) was given on successive days, 100, 50 and 50 mgm. of the crystalline alkaloid by the mouth, and died on the day following the last dose, having shown the typical symptoms of ergot poisoning. An ergot with 0·11 per cent. alkaloid (determined chemically) had uniformly a lethal dose of 16 grm. per kilo. On the assumption that the ergot contained only ergotoxine or ergotamine, the lethal dose of these would be 18 mgm. per kilo as compared with 250 mgm. per kilo of ergotinine. Hence the last named alkaloid could at most have one-fourteenth of the potency of the former. Meulenhoff's method of administration gets over the difficulties referred to below of dissolving the ergotinine, but a conversion to ergotoxine in the alimentary canal is not excluded; such a conversion in the subcutaneous tissues may, in part, explain the toxic effect of ergotinine on guinea-pigs by hypodermic injection, recorded by Kraft [1896].

The question has been complicated by Tanret's assumption, that his "amorphous ergotinine" was identical with the crystalline; in reality it consisted largely of ergotoxine (or ergotamine?). A further difficulty lies in the fact that crystalline ergotinine is in a form singularly unsuited for injection. If an alcoholic solution is injected, the alkaloid would probably be at once precipitated. Unlike most alkaloids, ergotinine requires for solution a large excess of acid. The French Codex recommends dissolving the finely powdered crystals in lactic, acetic or formic acid containing not more than an equal volume of water, and giving therefore a solution containing 50 per cent. of the acid. Now Kraft showed that in a solution of ergotinine in 3 per cent. aqueous acetic acid, a partial conversion to hydro-ergotinine could be demonstrated chemically already after one day at room temperature. Barger and Dale [1907] found that with 1·2 molecules of phosphoric acid the conversion was complete in boiling alcoholic solution within ten minutes. They could also make ergotinine more active by adding a little sodium hydroxide to the solution in alcohol. Hence they found the potency of ergotinine in producing the vasomotor reversal in the cat to vary within wide limits, from about one-quarter of that of ergotoxine to a very small fraction according to the method used for solution. They therefore

considered that "the activity of ergotinine is negligible in comparison with that of ergotoxine." More recently Tiffeneau [1921] has laid stress on its activity, as have Simonnet and G. Tanret [1926]. The latter authors found that for the action on the isolated guinea-pig's uterus a concentration of 1 in 37500 was required. According to Dale and Spiro [1922], as indicated above, both ergotoxine and ergotamine have a well-marked action on this organ at a dilution of 1 in 125,000,000, so that ergotinine would appear to have less than $\frac{1}{3000}$ of the activity of the other two alkaloids. Raymond Hamet [1926, i.] finds ergotamine to be 300 times more active than ergotinine, by determining the minimal doses of these alkaloids, necessary to abolish the sensitivity of the renal vasomotors to adrenaline [dog's kidney *in situ*; Hamet, 1926, ii.]. Incidentally Raymond Hamet found ergotinine and ergotaminine to be substantially equal in potency.

Similar conclusions were reached by Rothlin [1928]. Taking the mean results from many experiments by several methods (*in vitro*, isolated rabbit's uterus, isolated seminal vesicle of the guinea-pig; *in vivo* abolition of the depressor phenomenon and inhibition of renal vasoconstrictors and of the intestine) he arrived at the following table of relative potency :—

	As Base.	As Tartrate.
Ergotamine	1	1
Ergotaminine	0·1	0·17
Hydro-ergotinine = Ergotoxine . .	1	1
Ergotinine	0·003-0·005	0·01

Rothlin also showed by pharmacological assay, that the transformation of ergotaminine to ergotamine, and of ergotinine to ergotoxine, in the form of tartrates, is complete in either case in about four weeks at room temperature in aqueous solution.

Tyramine, Isoamylamine.

The observation that many aqueous extracts, prepared according to the British Pharmacopœia, raise the blood-pressure much more than can be accounted for by the traces of chloroform soluble alkaloids in them, led Barger and Dale [1907] to

postulate some other pressor principle in these extracts. After it had been found that certain putrefactive amines [Barger and Walpole 1909] possess a pressor action of the same type, Barger and Dale [1909, i., ii.] were able to show that this pressor action of ergot extracts is due to tyramine, and in a small measure also to isoamylamine. Both are sympathomimetic amines [Barger and Dale 1910, i.] and their physiological action has been described in detail by Dale and Dixon [1909]. The pressor effect in the decerebrate cat is similar to that of adrenaline, but not quite so evanescent; adrenaline is something like 1000 times as active as isoamylamine, and something like 100 times as active as tyramine.

Dale found the isolated uterus of the virgin cat inhibited by tyramine, but Tate and Clark [1921] consider the action on the kitten's uterus variable; the human uterus contracts [Lieb 1915; Barbour 1917]. In contradistinction to adrenaline, tyramine causes contraction of the isolated guinea-pig's uterus, even at a dilution of $2{\cdot}5 \times 10^5$ [Guggenheim 1912]. Tainter [1926], who has made a detailed study of the action of tyramine on smooth muscle, concludes that the drug acts for the most part directly on muscle, although there are undoubted examples of its action on the sympathetic. Tyramine is further distinguished from adrenaline in being antagonised by cocaine [Tainter and Chang 1927]. Vanysek [1914] distinguishes tyramine by its action on the isolated intestines of the dog, the rabbit and the cat. The first of these is inhibited, the second is stimulated, the third is initially stimulated, and then inhibited. He considers the third may serve to demonstrate tyramine in an ergot extract.

Clark [1910] made some clinical experiments with tyramine, and found that in healthy subjects 30 to 100 mgm. by the mouth produced a slight rise of blood-pressure and 20 to 50 mgm. injected caused a rapid and well-marked rise. The relative inactivity of oral doses was accounted for by Ewins and Laidlaw [1910]; the amine is converted by the liver into *p*-hydroxyphenyl acetic acid. (For the pharmacological behaviour of tyramine consult also Guggenheim, 1924, pp. 313-316.) The amount of tyramine in liquid extracts of ergot is much too small to be of practical importance.

Histamine (Iminazolylethylamine).

Attention was first directed to the powerful physiological action of this substance when Barger and Dale [1910] isolated it from ergotinum dialysatum of Wernich [1872] in their search for a substance acting on the isolated guinea-pig's uterus. Its physiological effects were studied by Dale and Laidlaw [1910, 1911, 1919], Dale and Richards [1918] and by many others. Simultaneously with Barger and Dale, and independently of them, Kutscher [1910] described a base from ergot having the same action as histamine, but certain supposed differences made Kutscher write: "Die physiologische Wirkung spricht also gegen die Identität von Imidazolyläthylamin und der Sekale base, wenn die Analyse und die Pauly'sche Reaktion es auch wahrscheinlich machen, dasz es sich um nahe verwandte Substanzen handeln muss." This view, maintained in a more detailed paper by Ackermann and Kutscher [1910] was shown to be erroneous by Barger and Dale [1910, iii.].

The voluminous literature on histamine which has appeared during the last two decades is outside the scope of this monograph, and only a few points will be dealt with.

Dale and Laidlaw found that large guinea-pigs (800 to 1000 grm.) were invariably killed by 0·5 mgm. of histamine given intravenously and Leschke [1913] puts the minimal lethal dose for smaller animals at 0·1 mgm. The isolated guinea-pig's uterus contracts in very high dilutions of histamine, and a distinctly perceptible effect is still obtained at $2{\cdot}5 \times 10^8$ (Dale and Laidlaw). This dilution is only slightly greater than the corresponding one for ergotamine and ergotoxine; Rothlin puts it for all three bases at 1 to 2×10^8. There is, however, an important difference, in that the effect of histamine can be readily abolished by washing out, whereas the highly complex alkaloids are firmly adsorbed and cannot be readily removed by washing (*cf.* p. 196). On intravenous injection the blood-pressure of the cat is lowered by dilatation of the capillaries, although the arteries are constricted [Dale and Richards; *cf.* also Quagliariello 1914]. Unlike that of the guinea-pig, the isolated rat's uterus is inhibited [Guggenheim 1914], as is that of the mouse. For a general account of the pharmacological behaviour of histamine consult Guggenheim [1924, pp. 215-222], Hamet [1928] and especially the monograph by Feldberg and Schilf [1930].

It is certain that histamine occurs in aqueous extracts of ergot, but its occurrence in the drug itself has been doubted by some. Barger and Dale [1910, ii.] obtained a contraction of the uterus, similar to that produced by a trace of histamine, with an extract prepared within half an hour of plucking the ergot from the rye; this would seem to exclude bacterial or enzyme action, but the quantity of histamine present was, in any case, very small. Since histidine is known to be decarboxylated by bacteria, and fungi are nearer to bacteria than to the higher plants, there is nothing surprising in its presence in ergot; histamine, moreover, occurs in many tissues of the higher animals [Barger and Dale 1911; Abel and Kubota 1919; Best, Dale, Dudley and Thorpe 1927; Thorpe 1928; Dale and Dudley 1929]. Its occurrence in fresh ergot also follows from the work of Forst [1926] who extracted ergot powder with a mixture of equal volumes of acetone and water and distilled off the acetone. The alkaloids were precipitated and the histamine was estimated in the aqueous filtrate by means of the isolated guinea-pig's small intestine; 0·001 to 0·0026 per cent. of histamine was found in the ergot. It is not even necessary to remove the alkaloids; the alcoholic percolate tested directly, indicated the same amount of histamine. Thompson [1929] found very variable, and on the whole considerably larger amounts of histamine (see the table on p. 201).

Of course when an aqueous ergot extract is kept, further quantities of histidine may be decarboxylated, whether by bacterial or by ferment action; hence the activity of *ergotinum dialysatum*. Bourne and Burn [1927] found 0·01 per cent. of histamine in the *Extractum Ergotæ Liquidum* B.P., Thompson 0·02 to 0·08 per cent.; the latter states that if fermentation is not prevented (by chloroform, dilute alchol or cold) amines are sometimes formed as fast as they are extracted. Wiechowski and Halphen [1923] state that by allowing ergot to ferment in water for three days at 37° its activity (as measured by the isolated guinea-pig's uterus!) increases three to ten times, and that the corresponding activity of the mushroom *Boletus edulis* increases a hundredfold. The German Patents 388875 and 431512 are concerned with this fermentation process, but if histamine is therapeutically desirable it would seem preferable to make it synthetically, or if from histidine, by a more rational bacterial decarboxylation.

The powerful effect of histamine on the guinea-pig's uterus, and its occurrence along with tyramine in ergot, soon led to the use of synthetic products. "Ernutine" of Messrs Burroughs, Wellcome & Co. contains ergotoxine, with synthetic histamine and tyramine; the ergotoxine, at one time omitted, was later restored. Tyramine alone ("Systogen," "Uteramin") was stated to be a complete substitute for ergot in subcutaneous doses of 5 mgm. after delivery [Heimann 1912]. Kehrer [1912] was the first to try histamine, but cyanosis, convulsions and other serious symptoms made him issue a warning against its use. It was next tried by Jaeger [1913, i.]; after delivery he obtained with oral doses of 1·5 mgm. three times daily as good results as with ergot, and better than in the untreated controls. Before delivery Jaeger had to give as much as 8 mgm. subcutaneously, and although powerful uterine contractions were produced within a few minutes and the action of the drug lasted for one to one and a half hours, there were nearly always secondary anaphylactic symptoms, erythema, etc.; the blood-pressure regularly fell 20 to 30 mm. This induced Jaeger [1913, ii.] to try a mixture of tyramine and histamine, which under the name of "tenosin" (*cf.* U.S. Patent 1178730, of 11th April 1916) had some vogue during the War when ergot was scarce. The proportion of tyramine was gradually raised from 1 : 4 to 1 : 50, and ultimately [Jaeger 1920] the dose recommended was 0·125 mgm. histamine plus 6·25 mgm. tyramine in 1 c.c. of water. Jackson and Mills [1919] examined pharmacologically the effect of mixtures of histamine and tyramine, which superficially resembles that of pituitary extract; they consider the use of histamine disadvantageous.

The use of tenosin and the amines has been condemned by Rübsamen [1920, 1921]. He registered the uterine contractions during labour and considers that the amines are too soluble to give a prolonged action. A graphical method was also employed by Bourne and Burn [1927] in a paper dealing mainly with pituitary extract; 10 mgm. tyramine acid phosphate intravenously had hardly any effect; 2 mgm. of histamine hypodermically produced a very vigorous action which disappeared after fifty minutes and the uterus then remained quite inactive for forty-five minutes; 1 mgm. ergotamine tartrate hypodermically gave, after an initial delay of fifteen to twenty minutes a powerful contraction lasting sixteen hours, during

which period delivery took place. Bourne and Burn conclude that since liquid extract of ergot contains very little histamine and tyramine, it is impossible to suppose that these amines are "responsible for the traditional value of ergot." They further consider it clear "that none of the ergot alkaloids have a place in labour proper, before delivery of the child or placenta," but they suggest that a hypodermic injection of 2·0 mgm. histamine and 0·5 to 1·0 mgm. of ergotamine or ergotoxine might be the ideal agent for arresting a post-partum hæmorrhage, since the immediate action of the histamine would be followed by the prolonged action of the alkaloid.

Agmatine was stated by Engeland and Kutscher [1910, i.] to have an action on the uterus similar to that of histamine, but this is due to the fact that they tested it in a concentration 50 to 100 times as great as that of histamine giving a maximal effect. Dale and Laidlaw [1911] pointed this out and themselves obtained no effect at all on the guinea-pig's uterus with 1 in 25,000 agmatine. On the isolated cat's uterus 1 in 50,000 produced much less effect than histamine 1 in 2,500,000.

Acetyl choline.—The powerful effect of this substance in lowering the blood-pressure was recognised by Hunt and de Taveau [1910]. As little as 0·0000000024 mgm. per kilo given intravenously produces a distinct depression in the cat. Larger doses (0·01 to 1 mgm. per kilo) stimulate the parasympathetic system and thus produce an inhibition of the heart, resembling that due to muscarine. This inhibition was observed by Dale [1914] to be given by many ergot extracts, with varying intensity. It was closely parallel to their stimulant action on intestinal muscle, and both effects were abolished by atropine. Hence Dale suspected the presence in these extracts of muscarine, but a search for the latter substance revealed the presence of acetyl choline. Ewins [1914] then isolated a minute quantity of the crystalline platinichloride of acetyl choline from 1600 c.c. of a liquid extract, prepared according to the British Pharmacopœia. In this difficult work the activity of the various fractions was estimated by means of an isolated loop of rabbit's intestine, according to Magnus's method.

According to Reid Hunt [1917] and Dale and Richards [1918] the lowering of the blood-pressure by minute doses of acetyl choline is due to a purely peripheral action on the blood-vessels. The extreme potency of acetyl choline may be illus-

trated by the following figures. The isolated heart of the frog shows inhibition at a dilution of 10^9, and Guggenheim and Löffler [1916] found that an equally low concentration still caused a perceptible contraction of the isolated guinea-pig's intestine. The isolated uterus of the guinea-pig shows contraction at a dilution of 2×10^7 [Fühner 1916]. A quantitative relationship between acetyl choline and the amount of atropine necessary to antagonise it has been worked out by Clark [1926, ii.].

Ewins showed that acetyl choline is present in ergot itself and can be extracted from it by alcohol. It is not the result of ferment action. On the other hand, it is very easily hydrolysed by alkalies.

As a curiosity it may be mentioned that Boruttau and Cappenberg [1921] attribute the therapeutic activity of the "Shepherd's Purse" (*Capsella Bursa Pastoris*), which was used as a substitute for ergot in Germany during the War, to acetyl choline, and claim to have isolated acetyl choline from it by Ewins's method. They even suggest a chemical assay of the drug, assuming quite unjustifiably that the platinichloride of acetyl choline can be quantitatively separated from that of choline by the insolubility of the former in water; *cf.* Dudley [1929] who isolated acetyl choline from horse's spleen. Tyramine is also stated to be present in *Capsella*, and its presence has been attributed to a fungus which commonly attacks the plant. Jaeger [1920] examined four commercial *Capsella* preparations pharmacologically; he concludes that, although they have some action on the uterus, they are much inferior to ergot. Franz [1923] also condemns the use of *Capsella*.

Clinical Applications.

The introduction of ergot into medicine was discussed in Chapter I. At first the drug was used in the form of a powder [*Pulvis ad partum*, Paulizky 1787; *pulvis parturiens*, Stearns 1808; *poudre obstétricale*, Desgranges; *poudre oxytocique*, Bordot] and was only administered before birth, to hasten labour, as is clear from the titles of early publications: "Remedy for quickening childbirth" (Stearns); "la propriété . . . d'accélerer la marche de l'accouchement" (Desgranges); "emploi . . . pour accélerer ou déterminer l'accouchement . . . dans le cas d'inertie

de la matrice" (Villeneuve). Although from the beginning its use was only advised when certain conditions were satisfied (as to conformation of the pelvis, dilatation of the cervix, and presentation of the fœtus), accidents soon supervened [*cf.* p. 18; *pulvis ad mortem* of Hosack, 1822] and now ergot preparations are almost exclusively used *post-partum*. "Fast alle Geburtshelfer verwenden die Sekalepräparate ausschliesslich in der Nachgeburtsperiode, und die meisten auch da erst nach der Geburt der Placenta" [Stoeckel 1925]. "Practically all American authorities deprecate strongly its use during labor, or before delivery of the placenta" [Nelson and Pattee 1928]. "Oggi, maggiormente rafforzato rimane il precetto di riservarne l'uso ad utero completamente vuoto" [Amati 1925].

The clinical application of ergotins (Bonjean, Köhler, Merck, Niebergall, Rippetoe, Yvon) lies outside the scope of this book, which only attempts to give a brief account of the modern clinical application of pure active principles. The use of the non-specific amines (histamine and tyramine) in place of ergot has already been dealt with (p. 173); that of the alkaloids remains to be discussed.

Tanret's **ergotinine** was the subject of some favourable clinical reports, particularly in France (see also Eulenburg); but in discussing the pharmacology of this alkaloid, reasons were given for attributing the effects either to "amorphous ergotinine" (containing ergotoxine) or to hydration of ergotinine to ergotoxine in solution. Under Kobert's influence more or less successful clinical trials were reported with "cornutine" (which as a commercial article seems to have been impure ergotoxine). Thus Krohl [1894] used the involution of the uterus; impure alkaloids were also tried by Graefe, Palm and Thomson.

Singularly few clinical reports have appeared on the use of pure **ergotoxine.** Sharp [1911] found its action, when injected, similar to that of ergot, more prompt, but more evanescent. Kehrer [1911] considered the injection of 1 to 2 mgm. ineffective. The statement in the British Pharmaceutical Codex of 1923 that "ergotoxine . . . is disappointing and gynecologists are now generally agreed that it is not the active constituent of ergot they want," was not written by a clinician, and is hardly supported by published reports—there are practically none. Considering that ergotoxine is pharmaco-

logically indistinguishable from ergotamine, the statement in the Codex is rather surprising; the great disparity in the number of clinical reports on the two alkaloids is due rather to the greater ease with which these reports are obtained by manufacturers on the Continent, as compared with Britain. Compare in this connection a letter by Dale [*Lancet*, 22nd November 1930, ii. 1149] who points out that identity of clinical action can only be proved strictly by clinical trial, but that in this case the pharmacological identity establishes a presumption in favour of clinical similarity. Moreover, Kauffmann and Kalk who studied the effects of intravenous injection of both alkaloids in the human subject found no important difference between them (see below, p. 180); 0·25 mgm. ergotoxine produced, however, more pronounced secondary symptoms than 0·5 mgm. ergotamine.

Since 1921 an extensive literature on the clinical use of **ergotamine** has appeared, particularly by German and Swiss authors. Among the favourable and even enthusiastic reports are some by directors of large clinics. Döderlein declares Gynergen to be the best of the present-day ergot preparations; it is somewhat strange, however, that Stoeckel, in a long paper on *post-partum* hæmorrhage considers secacornin, gynergen and tenosin to be the best; the first of these contains little alkaloid and comparatively much histamine; the second is a preparation of pure alkaloid; the third is a synthetic histamine preparation without any alkaloid at all. Thus a prominent clinician is not so convinced of the essential importance of the alkaloids as are most pharmacologists, although he further gives his impression that the constancy of the action of ergot preparations has of late increased, especially in the case of gynergen. On the other hand, the Council on Pharmacy and Chemistry of the American Medical Association [*J. Amer. Med. Assoc.*, 1929, **92**, 1521] desires the specific constituents of ergot, for it voted to omit secacornin and some German and American preparations, because they do not contain enough alkaloid. Guggisberg, Director of the Berne clinic, states that fresh ergot contains no proteinogenous amines at all, whereas Thompson found in a series of ten ergot samples a percentage of histamine ranging from 0·012 and 0·015 to 0·125 and 0·150 per cent. (see p. 201); the latter samples were (presumably fresh) Spanish ergot, with a high alkaloidal content, yet contained

more histamine than proprietary preparations like ergotitrin, in which the formation of histamine is encouraged; such a preparation has also had clinical advocacy (Finger).

The numerous clinical reports on ergotamine leave no doubt that this alkaloid is effective, and since it is a pure substance, the dosage is certain; but the possibility does not seem wholly excluded that some other constituent of ergot, or of ergot extracts, may be of use, perhaps in combination with the alkaloids.

Apart from the general expressions of opinion already referred to, there are more detailed reports, equally favourable to ergotamine, particularly by von Mikulicz-Radecki and by Uter. Most authors recommend a *post-partum* hypodermic or intramuscular injection of 0·5 to 1 c.c. Gynergen-Sandoz which is a 1 : 2000 solution of ergotamine tartrate, so that the dose is nearly 0·25 to 0·5 mgm. of the alkaloid. In order to obtain a very rapid effect, gynergen has been given intravenously. Wetterwald found that 0·25 c.c. (= 0·125 mgm. ergotamine tartrate) often acted promptly, but on the whole he prefers 0·5 c.c. (as does von Mikulicz-Radecki). With 1 c.c. Wetterwald obtained in 30 per cent. of his cases unpleasant secondary symptoms, such as headache, vomiting, sweating, and in rare cases cyanosis of the lips and limbs. After an intravenous injection of 0·75 c.c. (0·375 mgm. ergotamine tartrate) von Mikulicz-Radecki obtained within two minutes a prolonged maximal contraction of the uterus. In the puerperium and for gynecological out-patients (Pfeilsticker), 2 to 3 tablets of 1 mgm. each are recommended to be given by the mouth. The oral dose is of course much higher than the hypodermic, but it is known from animal experiments that the ergot alkaloids are absorbed from the gut only to a limited extent (see particularly Burn 1929, who estimates that in cats something like 30 per cent. is absorbed). If the oral dose is placed at 2 mgm. of alkaloid, this would correspond, in the case of an ergot with the minimum alkaloidal content of 0·05 per cent. demanded by the German Pharmacopœia, to 4 grm. of the drug; in the case of an exceptionally good ergot, with 0·2 per cent. of alkaloid, it would represent 1 grm. of the drug; 1 to 4 grm. is the usual dose of ergot powder.

A few authors have used ergotamine in order to accelerate birth, but even with the pure alkaloid the range between the

effective and harmful dose is too small. Weinsheimer gave 0·25 to 0·5 c.c. of gynergen in thirty-nine cases, with completely open os uteri and had to use the forceps in two cases to save the child. Amati used it in ten cases before birth (0·5 to 1 c.c. injected, or 25 drops by the mouth). Schnitzer discusses this use of ergotamine by various authors and is opposed to the practice. In several of his own cases the fœtus was asphyxiated, even after doses of only 0·1 to 0·2 c.c. (repeated).

Similarly ergotamine is of little use for the termination of pregnancy at an early stage; this entirely corresponds to the older toxicological experience with the drug itself (see p. 229). Schimmel succeeded with two pregnancies in the third month, with at most three injections of 2 c.c. per day, but failed in the second month in spite of enormous doses (32 c.c. during eight days and 18 c.c. during five days; a total of 25 mgm. of ergotamine tartrate). Schnitzer abandoned the attempt after five injections of 0·2 c.c., and some earlier authors likewise failed. If an abortion has already begun, it can, however, be hastened by small doses, according to Schnitzer.

Since the introduction of ergotamine into obstetrical practice, a number of cases of severe gangrene, sometimes fatal, have been attributed to it by certain authors. Caffier, Ellerbroek, Spiro and Saenger (who collected fourteen alleged cases) have discussed this question critically and come to the conclusion that in nearly all the published cases the gangrene should be attributed to sepsis rather than to ergotamine. In two or three cases altogether excessive doses were given (*e.g.* 117 mgm. in the course of twenty-five days). It is not quite easy to induce gangrene in the cock's-comb, even with very much larger doses than are apt to be administered therapeutically, and the clinical picture of puerperal gangrene does not correspond to that observed in epidemics of ergotism. In this connection a case of attempted suicide may be mentioned (Nielsen) in which the husband of an out-patient swallowed 15 gynergen tablets (= 15 mgm. ergotamine tartrate). He showed a severe vaso-neurosis resembling erythromelalgia, but recovered completely in a few days. Doubtless only a fraction of the 15 mgm. was absorbed from the intestinal canal.

The contractions of the human uterus, during labour under the influence of hypodermic ergotamine, have been recorded graphically in a few cases by Amati and by Bourne and Burn.

The latter found it necessary to give 1 mgm. of ergotamine tartrate to obtain powerful contractions; as stated above, Schimmel gave the same dose (= 2 c.c. of gynergen) in an attempt to terminate pregnancy. Such doses must be regarded as exceptionally high, and most authors have not gone beyond 0·5 mgm. = 1 c.c. (For use of excised human uterus see Flury.)

Apart from its chief application, in obstetrics and gynecology, ergotamine has been used clinically in other diseases in order to paralyse the sympathetic, and these experiments have also supplied a certain amount of information as to dosage and action. They have mostly already been discussed above, in connection with the pharmacology of the ergot alkaloids (Seidel; Moretti; Bouckaert and Schaus; Porges and Adlersberg; Merke; Noyons and Bouckaert; Thiel; Heim; Michail, Bendescu and Vancea). Trautmann and Tzanck have used gynergen as an inhibitor of the sympathetic in certain migraine-like conditions, and Rütz as a preliminary to operations for exophthalmic goitre. Finally, Kauffmann and Kalk made some general observations on the effect of ergotoxine and ergotamine, injected intravenously in doses of 0·25 to 0·5 mgm.; the results were the same with either alkaloid, namely, giddiness, dullness, sensation of pressure in the head, gastric pains, cyanosis, a rise of blood-pressure through 20 to 60 mm., a slowing of the pulse to 50 and below, inhibition of intestinal peristalsis and gastric secretion, diminution of urinary secretion, and urobilinuria for twenty-four hours. Zorn also found a rise of blood-pressure in women after intravenous injection of ergotamine. The clinical application of histamine and tyramine has already been discussed in connection with their pharmacology (p. 173).

CHAPTER VI

PHARMACEUTICAL AND FORENSIC

THE introduction of ergot into official medicine and the pharmacopœias [U.S.P. 1820] was mentioned in Chapter I. At first the drug was given as a powder (*pulvis parturiens*) or as an infusion. Sometimes the grounds were not separated, as in Turkish coffee. Wiggers [1831] showed that the active principle is associated with a resin insoluble in water. Bonjean [1841], however, produced a water-soluble "ergotin," of no great activity, which found its way into the pharmacopœias and is still in almost all of them. Their treatment of ergot illustrates various degrees of pharmaceutical policy, ranging from an extreme conservatism in the British Pharmacopœia to progressive liberalism in that of the United States. There are, however, indications that the new edition of the B.P. now in course of preparation will embody a distinct advance. At present the policy of a pharmacopœia may be judged by its liquid extract; the U.S.P. 6th revision, 1883, adopted 40 per cent. alcohol; in the four subsequent revisions 49 per cent. alcohol was prescribed; in 1890 the German introduced 20 per cent. alcohol, presumably as a compromise between the U.S.P. preparation and Bonjean's ergotin. At the present day the majority of pharmacopœias still use an alcohol of about 20 per cent., although experimental evidence has long been available to show that stronger spirit is required.

Ergot in the Pharmacopœias.

The following have been consulted: Argentine [1928], Austrian [1906], Belgian [1906], British [1914], Danish [1907], Dutch [1926], French [1920], with its supplement [1926], German [1926], Greek [1924], Hungarian [1909], Italian [1929], Japanese [1921], Norwegian [1913], Rumanian [1926], Russian [1929], Spanish [1905], Swedish [1925], Swiss [1907]

and United States [1926]. They will be distinguished by the first letters of the names given above.

All the pharmacopœias define ergot as the sclerotium of *Claviceps purpurea*, and either state explicitly that it is developed on rye (B.P., U.S.P.) or merely imply its origin by such names as *secale cornutum* or *fungus secalis* (Au.). The same species on other hosts would nowhere appear to be admissible, although it might satisfy all the tests which are given. The Norw. P. directs that ergot shall be collected before the rye is fully ripe, the Be. P. that it should be collected from the nearly ripe ear (*cf.* p. 205). Various dimensions are given for the sclerotium; the extreme limits are from 10 to 45 mm. in length (Russ., U.S.); the Swiss P. with a maximum length of 25 mm., attempts to exclude the largest sclerotia, which are apt to contain a smaller proportion of alkaloid [Hartwich 1912]. A few prescribe a maximum ash content (4 per cent. Du.; 5 per cent. Au., Ital., Russ., Swe., Swiss). The drug must be kept dry and entire (over quicklime, *e.g.* Du., Ge., Hung., Swe.; with a little chloroform against insects, F., Russ.). As a result of an international agreement, all except the Russian direct that ergot more than one year old should not be used. This is a wasteful restriction [*cf.* Burn and Ellis 1927; Thompson 1930]. If properly preserved, old samples of a good year may be better than fresh ergot. The Russian P. prescribes an annual biological assay of stored ergot, but by an unsuitable method (see below).

The tests for recognition of the drug are extremely simple in the B.P. which merely mentions its macroscopic appearance, taste and the odour on triturating with sodium hydroxide. This odour (of trimethylamine) is attributed to methylamine by Ar. and F. Microscopic characters figure in a number of pharmacopœias; Ge. states that the cells of the pseudo-parenchyma are 3 to 12 in diameter, the U.S.P. that they are less than 15; oil globules are occasionally mentioned; Russ. uses chloral hydrate to recognise them.

The most frequent chemical test for the drug is the sclererythrin reaction, mentioned in various forms; in the U.S.P. in the approved modification due to Hilger [1885]. Tanret's or Keller's reaction is also commonly employed, in the Russ. P. for the recognition of the powder, in most others as a test for the official extracts (original Tanret reaction for ergotinine

in F., modified Tanret in Du., Keller's in Au., Ge., Gr., Hung., Ital., Jap., Rum., Russ., Swiss). General alkaloidal tests are applied to the extracts with tannin and mercuric chloride (Au., Du., Ge., Ital.) and with potassium mercuric iodide (Ar., Du., Russ., Swiss).

Most pharmacopœias have two preparations, a soft extract purified by alcohol (Bonjean's ergotin) (this is the only one in the Spanish P.), and a fluid extract (the only one in the recent Ge. and U.S.P.). Bonjean's ergotin [1841], much in vogue in the last century, is essentially an aqueous extract, which after concentration is precipitated by adding alcohol to make about 50 or 60 per cent.; the filtrate is evaporated. It should be noted that the alcohol is not used to extract the alkaloids (which were unknown to Bonjean), but as a precipitant of impurities. Preparations of this type contain little alkaloid, perhaps a fifth of that in the ergot [Meulenhoff 1902; Burger recommended high doses]. They may also contain histamine.

Carr and Dale [1913], in reviewing the ergot preparations of the B.P. pointed out that these should be designed to contain all the ergotoxine of the drug. The additional presence of active amines might be beneficial, but the chief object should be to secure the presence of the alkaloids. (Incidentally this shows that others, and not they, brought the amines into vogue). The extraction of the alkaloids is attempted with varying degrees of success in the liquid extracts, in which alcohol and acids are used. The official methods of preparing a liquid extract may be grouped as follows:—

I. Extraction without acid.

A. No acid is used subsequently.

Distilled water			B.P.
18 per cent. alcohol			Japanese
45 „	„		German
45 „	„	+ glycerine (5 per cent. of drug)	Austrian
18 „	„	+ glycerine (5 per cent. of drug)	Hungarian

B. Acid is added after the extraction.

70 per cent. alcohol;		0·16 N hydrochloric	Danish
20 „	„	0·15 N „	Belgian
18 „	„	0·11 N „	Russian
16 „	„	0·16 N acetic	Norwegian

II. Extraction by means of acid.

49 per cent. alcohol		0·17 N hydrochloric	U.S.P.
18 „	„	0·16 N „	Greek
18 „	„	0·45 N acetic	Italian
50 „	„	0·33 N „	Argentine
18 „	„	0·15 N „	Rum., Swed., Swiss.
70 „	„	0·033 N tartaric.	Dutch
Water ; 0·013 N tartaric ; then $CaCO_3$.			French

Au., Be., It. and U.S.P. use drug defatted by petrol. The concentration of the alcohol is expressed by volume (approximately). The amount of acid is expressed as the normality, which it would have if diluted to the final volume of the preparation, but this figure does not represent the degree of acidity actually resulting. The French preparation is treated with excess of chalk and presumably becomes neutral; the second (dilute) percolate of the German is neutralised with sodium carbonate. But apart from this neutralisation of the whole or of part of the extract, the constituents of the drug cause considerable buffering, which was first investigated by Wokes and Elphick [1930]. In the U.S.P. process, hydrochloric acid is only added in the initial maceration, and the percolation is carried out with neutral alcohol; but in a particular example the P_H remained between 4·0 and 5·0 throughout the percolation, although the menstruum used for maceration had a P_H below 1·0. On continued percolation with neutral alcohol the P_H slowly rises and approaches neutrality; on continued percolation with acid alcohol the P_H slowly falls. Both results show that the buffering substance is slowly washed out; it is doubtless acid potassium phosphate, which in decimolar solution has a P_H of 4·0. According to Wokes and Elphick, the P_H of ergot samples may vary from 5·3 to 6·2, that of the U.S.P. extracts made from them ranges from 3·0 to 5·0. The German (D.A.B. VI.) method of extraction with neutral alcohol is only efficient with acid ergots (P_H not greater than 5·5). The final P_H is of importance for the keeping of properties of the extract; according to Swanson it should be below 3. In this respect the U.S.P. and the others using hydrochloric acid are in the more favourable position.

Although the acid influences the P_H at whatever stage it is added, it is evident that when added to the second percolate, before evaporation, but after the extraction is over (group I., B)

it will not assist in removing the alkaloids; this can only be the case in group II. A second, and no doubt the principal factor favouring the extraction of the alkaloids is alcohol of sufficient strength. Meulenhoff [1902] already established by chemical assay, that all the alkaloid is extracted by 70 per cent. alcohol, but not by weak alcohol or water. The new German P. relies on alcohol entirely, and in the Austrian and Danish it is the chief factor; 18 to 20 per cent. alcohol, which most pharmacopœias prescribe, is too weak for the purpose. The B.P. of 1914 is in the unique position of using only water for the extraction (alcohol is added later as preservative). The French extract is made with an excessively dilute aqueous solution of tartaric acid and probably contains little more alkaloid than the British. Linnell and Randle [1927] assayed the extracts, made according to several pharmacopœias, by the method of Broom and Clark, and found only the Dutch and U.S.P. extracts to have an adequate amount of alkaloid; their criticism of the German method has, however, to be modified; Wokes and Elphick [1930] find that this method is but little inferior to that of the U.S.P. when applied to acid ergots (P_H below 5·5). With less acid ergots (P_H above 6·0), the American method may extract twice as much alkaloid as the German. Prybill and Maurer [1928], using Broom and Clark's method, and that of Keller-Fromme, found the U.S.P. method to be the best, the German not quite so good, the Austrian and Swiss to be much inferior. Harmsma compared the Dutch, German and U.S.P. preparations by the Broom and Clark, the Keller-Fromme and a spectrographic method. The following table gives the results of these three investigations:—

	Austrian.	Dutch.	French.	German.	Swedish.	Swiss.	U.S.P.
Harmsma . . .	...	107	...	87	...	...	100
Linnell and Randle .	16	70	16	...	4	...	100
Prybill and Maurer .	25	...	...	92	...	15	100

Since Linnell and Randle unfortunately do not give the alkaloidal content of the ergot employed, all the results have had to be reduced to those with the U.S.P. method. (Using ergots with 0·1 per cent. or less of alkaloid, Harmsma and Prybill and Maurer found that the U.S.P. method extracted 75 to 80

per cent. of the amount available.) In the above table, the averages of Harmsma's results by three methods of assay have been used; her results by the Broom and Clark method would indicate that the U.S.P. extract is quite as good as the Dutch, or even slightly better. Prybill and Maurer's biological assays were too few to be of use, so that only the mean values of the chemical assays have been recorded.

The table clearly shows the superiority of the Dutch, German and U.S.P. extracts; possibly the Danish is equally good. In the preparation of all these much stronger alcohol is used than in that of the others, which contain at most one-fifth of the alkaloid in the drug, about the same fraction which Meulenhoff [1902] found in Bonjean's ergotin. In agreement with Meulenhoff, Linnell and Randle conclude that 50 to 60 per cent. alcohol should be employed; they also consider that the tartaric acid of the Dutch method should be doubled (0·5 per cent. instead of 0·25 per cent.). They, Prybill and Maurer and other authors all advise defatting, which appears to be of some advantage, both in the making of a liquid extract and in the chemical assay of the alkaloids. Cold petroleum ether does not remove more than one-third to one-half of the fat actually present. It can, however, quite well be omitted (Forst, following Meulenhoff) without serious loss of alkaloid.

Wokes and Elphick [1930] state that defatting increases the extraction efficiency of alcohol to an extent which *probably* justifies the expenditure involved.

Among recent pharmacopœial revisions that of the Argentine probably also secures a good extract on account of the strong alcohol used; the Greek is similar to the U.S.P. except that much weaker alcohol is employed.

Most pharmacopœias prescribe that after a reserved percolate has been obtained equal in volume to 85 per cent. of the final extract, the second percolation should be continued to exhaustion. In order to ascertain when this point has been reached, the Dutch P. prescribes a Keller test on 2 c.c. of the percolate (not entirely satisfactory, according to Harmsma). Others *e.g.* the Rumanian, continue the percolation until the Mayer reaction is negative. Most are not so precise; the German states that 4 to 5 parts of the menstruum are necessary (3 parts suffice according to later writers). The extraction proceeds asymptotically (Wokes and Elphick), and it may not be worth

while to continue the second percolation too long, on account of the cost of solvent and labour, and destruction of the small quantity of alkaloid extracted in the last stages. Even when evaporating at 37° under reduced pressure in a nitrogen atmosphere, from 20 to 30 per cent. of the alkaloid in the solution is destroyed, and unless special precautions are taken in the manufacture of soft extracts, intended for subsequent dilution to the official strength, the losses are very considerable. The best that seems possible in the case of these commercial preparations, intended for export, is to attain an alkaloidal content of 0·5 to 1 per cent., with loss of half the activity of the Spanish or Portuguese ergot necessary for this purpose. (Soft extracts made with water contain very little alkaloid.) With a drug, rich in alkaloid, the first percolation could be prolonged considerably in making a U.S.P. extract, which is itself finally standardised, but not a German one, which is intended to contain all the alkaloid of the drug. Such questions, mainly of interest to manufacturers, are discussed by Linnell and Randle and particularly by Wokes and Elphick [1929, 1930].

Several pharmacopœias prescribe a minimum content of solids in the liquid extract (14 per cent. Norw., Swed.; 15 per cent. Be., Du.; 16 per cent. Swiss; 20 per cent. Au.). This is of course no measure of the alkaloidal content, and therefore of little use. Defatting seems to increase the total solids by nearly one-half, to an average of 25 per cent. (hence the high minimum of Au.; it is not clear how the glycerine acts in the latter, and how it is got rid of in estimating total solids).

Special features.—In France, the home of Tanret, crystalline ergotinine is official. Physical constants and Tanret's reaction are given for its recognition, as are directions for dissolving it in concentrated organic acids (which in time effect a partial transformation to ergotoxine). The corrected formula, $C_{35}H_{40}O_5N_5$, of the 1926 supplement obviously still requires a revision of the hydrogen. Ergotinine is also included in the Rumanian and Spanish pharmacopœias. No other constituents are official, but histamine is used for biological assay by the Russian.

The U.S.P., as a pioneer, introduced in its tenth revision [1926] biological standardisation by the cock's-comb test. The selection of a composite extract as standard is open to criticism, not because there is no safety in numbers but because the

extract deteriorates. This point is discussed on p. 212. The Russian pharmacopœia [1929] devotes nine pages and two illustrations to a description of the biological assay of ergot by the isolated uterus of a guinea-pig (weighing 150 to 250 grm.); histamine is the standard. This estimation of a non-specific constituent, instead of the alkaloids, is quite unsatisfactory (see p. 204). A further peculiarity of this pharmacopœia is the mention of antidotes for ergot poisoning (emetics, cardiac stimulants, chloroform and amyl nitrite against convulsions).

The German pharmacopœia [1926] fully acknowledges the importance of the alkaloids by including a method for their chemical assay, and by insisting that they must be contained in the drug to the extent of *at least* 0·05 per cent. This may ensure the activity but not the uniformity of the liquid extract. The preparation of the latter is peculiar in dispensing with acid, and was largely influenced by the work of Forst [1926]; it should not be forgotten, however, that Meulenhoff showed [as long ago as 1902] the utility of strong alcohol. In the concentration of the dilute percolate, the precipitation and neutralisation with sodium carbonate may cause considerable loss of activity, according to Wokes and Elphick [1930]. The assay process is a compromise between Forst's work and that of Keller and Fromme. According to Prybill and Maurer, the new methods were adopted somewhat hurriedly. Nevertheless the new German liquid extract appears to be but little inferior to that of the U.S.P. and is no doubt an improvement on its predecessor (of type I., B, with hydrochloric acid). The alkaloidal assay has received more adverse criticism (see p. 191).

In comparing the German with the U.S.P. it should be noted that the latter requires a much better ergot. After aging for six months, the U.S.P. extract must still equal a standard, corresponding to about 0·05 per cent. ergotoxine or ergotamine. The freshly prepared extract must therefore contain a good deal more alkaloid, the drug itself still more, so that most Russian ergots cannot be used (*cf.* p. 219 for effect on prices). The German pharmacopœia requires only 0·05 per cent. in the drug, and this determined by a chemical method, which includes ergotinine in the result. The B.P. retains some obsolete preparations rarely used, such as the *Infusum Ergotæ*, *Tinctura Ergotæ ammoniata* and *Injectio Ergotæ hypodermica*; the second of these has been discussed by Wokes and Elphick [1930]; the

last named is merely the soft extract dissolved in water with a little phenol added. (For criticism of infusion see Caffier.)

Chemical Assay.

The chemical assay depends on a determination of the total alkaloid and the assumption is usually made that this quantity is a measure of the physiological activity; the validity of this assumption will be discussed below. The determination of the alkaloids is based on their extraction by ether and their removal from ethereal solution by acid, and is only complicated, in comparison with other drugs, by the fact that the ergot alkaloids have an unusually high molecular weight and are only very slightly soluble in excess of mineral acid; the oil present in the drug may further give rise to troublesome emulsions. The more or less pure alkaloids are usually weighed [Keller 1894, 1897; modification by Fromme, see Cæsar and Loretz 1905, 1910], but they may be titrated [German Pharmacopœia 1926], or an alkaloidal extract (which may be less pure) is estimated colorimetrically [Smith and Stohlman 1930], or even spectrophotometrically [Harmsma 1928]. The method of Keller-Fromme is as follows:—

Twenty-five grm. dry ergot powder is defatted with light petroleum (until a drop of the percolate leaves no grease stain on filter paper), and after adherent petrol has been evaporated by gentle warming, the powder is mixed with 125 grm. ether and after some minutes with 1 grm. magnesium oxide and 40 c.c. of water. After shaking for half an hour 3 grm. powdered gum tragacanth are added, in order to make the ergot powder cake together, and after shaking again the ethereal solution is filtered through cotton-wool. 100 grm. or a smaller aliquot portion is shaken successively with 25, 20 and 15 c.c. of 0·25 per cent. hydrochloric acid. (The last extract should show no Mayer reaction; if it does, the ether is shaken a fourth time, with less acid.) The acid solution is shaken with 0·3 grm. infusorial earth and filtered. The filtrate is made alkaline with ammonia and extracted successively with 25, 10 and 10 c.c. of ether. The ethereal extracts are evaporated in a tared flask and dried in a desiccator to constant weight.

In the case of samples rich in alkaloid, the hydrochloric acid extract may show a deposit, which Keller and Fromme filter off, but according to Meulenhoff [1899, p. 133] and Harmsma [1928] this consists of minute acicular crystals of an alkaloidal

hydrochloride, and should be left in suspension before making alkaline. This is in accordance with the very small solubility of ergotoxine hydrochloride in excess of acid [Barger and Carr 1907]. Leinzinger and Kelemen [1928] compared the original Keller-Fromme method with nine modifications, using the same sample of ergot. Such small changes as the substitution of ammonia or sodium carbonate for magnesia in the original extraction lowered the result from 0·185 per cent. to 0·130 per cent. and 0·080 per cent. respectively (perhaps on account of the acidic properties of ergotoxine). The substitution of chloroform for ether lowered the result to 0·120 per cent. Meulenhoff [1902] is also quite definite that magnesium oxide should be used for ergot itself; for liquid extracts he prefers a few drops of ammonia and then proceeds according to Keller; but these extracts, made with alcohol, are not so suitable as the drug itself. Gadamer and Neuhoff [1926] have urged against the Keller-Fromme method that the amines are also extracted and weighed with the alkaloids. This objection is ill-founded and has scarcely even a theoretical basis. The amount of the amines is small, compared with that of the alkaloids, and their partition coefficient between water and ether is wholly in favour of the water. It is impossible to extract histamine from aqueous solution by ether, and many extractions are necessary in order to remove an appreciable quantity of tyramine. Nevertheless the desire to remove the amines has led to the adoption by the German Pharmacopœia of 1926, of a method which involves filtering off precipitated alkaloid and titrating it. In order to have a sufficient quantity, four times as much material is used as in the original method.

100 grm. coarsely powdered ergot (not defatted) is shaken with 4 grm. of magnesium oxide and 1000 c.c. of water. After adding 300 grm. ether the mixture is occasionally shaken during three hours; 100 c.c. more water and 10 grm. of gum tragacanth are added, and after shaking again the ether is filtered through cotton-wool. One grm. talcum powder and 20 c.c. of water are added to the ethereal filtrate, and after vigorous shaking for three minutes the suspension is allowed to settle completely and the clear solution is filtered through a folded filter. 180 grm. of the filtrate (= 60 grm. ergot) are shaken successively with 50 c.c. 0·25 per cent. hydrochloric acid, 10 c.c. of water, and again with 20 c.c. of the acid. These three aqueous extracts are mixed, heated in water of 50° for twenty minutes and

filtered; the filter is washed twice with 5 c.c. of water. The filtrate and washings are made just alkaline to litmus by means of sodium carbonate until no more alkaloid is precipitated. After settling for twelve hours, the precipitate is collected on a hardened filter paper and washed free from chloride. The moist precipitate is then washed into a small flask with 30 c.c. of water; 3 c.c. of decinormal hydrochloric acid and 3 drops of methyl orange solution are added, and the mixture is titrated back with decinormal potassium hydroxide. At most 2·5 c.c. of alkali should be required, so that at least 0·5 c.c. of acid was neutralised by the alkaloids. Assuming an average molecular weight for the latter of 600, 0·5 c.c. decinormal hydrochloric acid = 30 mgm. of alkaloid, or 0·05 per cent. in the 60 grm. of ergot finally involved (0·05 per cent. is the minimum alkaloidal content prescribed).

This complicated method seems to give results agreeing with that of Keller-Fromme, but has met with repeated criticism. Wessel [1928] complains that it gives rise to emulsions, which can be avoided by first defatting the ergot, as prescribed by Keller and Fromme. (Likewise Prybill and Maurer failed to get results until they defatted.) Ammonia should be used instead of sodium carbonate for liberating the alkaloids, and they should be weighed, since such a small titration difference as 0·5 c.c. cannot be accurate. Gatty-Kostyal and Derlatka [1929] also prefer weighing to titration. Defatting with petrol (prescribed by Keller and Fromme, but not by the German Pharmacopœia) does not remove any alkaloid from fresh ergot, but from old ergot alkaloid is lost owing to the presence of free fatty acids [Meulenhoff 1899; *cf.* p. 207]. The German Pharmacopœia of 1926 has been influenced in its preparation of the liquid extract, and to some extent in its analytical method, by Forst's process of extracting the alkaloids with 50 per cent. aqueous alcohol or acetone. This leaves the oil in the ergot and no preliminary defatting is therefore employed. Oettel [1930] has elaborated Forst's process into a method of analysis, which presents several peculiar features.

250 grm. of ergot is percolated with three times the weight of the above mixed solvent, and the alcohol (or acetone) is completely removed at 35 to 40° *in vacuo*. The solution is made just alkaline to litmus with sodium carbonate and the crude alkaloids are filtered off. The filtrate may have to be extracted with ether. The crude alkaloids are dried *in vacuo* and extracted with dry chloroform. Impurities are precipitated by adding two volumes of ether, and the

alkaloids are then extracted by shaking with aqueous saturated sulphanilic acid solution, from which they are again carefully precipitated by sodium carbonate. They are filtered off, dried *in vacuo* and weighed.

The alkaloids, when extracted by ether and acid in some such way as the above, can be estimated colorimetrically in a more or less crude condition by means of the very delicate reaction of van Urk with dimethylamino benzaldehyde, given by all the alkaloids with equal intensity (see p. 132). Smith and Stohlman [1930] have thus assayed ergot preparations, and found that of 38 fluid extracts 26 agreed within 15 per cent. with the method of Broom and Clark (the agreement with the cock's-comb method was much less satisfactory).

The crude extracted alkaloids have also been determined spectrophotometrically, by Harmsma [1928]. Ergotinine, ergotoxine and ergotamine have almost identical ultra-violet absorption spectra. The method agrees pretty closely with that of Keller-Fromme, but is of course too complicated for routine work.

Since all these chemical methods of alkaloidal assay estimate the very slightly active ergotinine along with the real active principles, their validity has been doubted. The further question arises whether the less active alkaloids are really present in ergot as such. As regards ergotaminine Stoll is of the opinion that this alkaloid is only formed artificially by the reagents in some extraction processes. It is more difficult to believe that ergotinine does not exist as such in ergot, but there is nevertheless some indirect evidence against its occurrence, at least in appreciable quantity. Forst [1926] reported that the total alkaloid isolated by him by a special process (*q.v.*, p. 191) was equal in activity to ergotamine, as judged by Masuda's method of biological assay. Leinzinger and Kelemen [1928] found that the more or less crystalline alkaloid weighed in the Keller-Fromme method agreed within 10 per cent. with ergotamine, as judged by the biological assay of Issekutz and Leinzinger. Unfortunately neither biological method employed for control is well established, and where the much more accurate method of Broom and Clark was employed to check the chemical results, the latter were found distinctly too high; Harmsma observed a discrepancy of about 20 per cent., and Prybill and Maurer found a similar difference.

Wokes and Elphick even state that the mixed alkaloids, obtained by Forst's method, were found by Linnell to be only half as active as ergotoxine. Probably Forst's method and that of Keller and Fromme estimate a proportion of ergotinine, which is almost inactive in the pharmacological assay; possibly also decomposition products of the alkaloids, or other impurities. The latter was certainly the case in many of the older assays [*cf.* Meulenhoff 1902]. Thompson [1930] has put forward the view that there is only one alkaloid in ergot, which according to the method of extraction may be isolated as ergotamine, ergotinine or ergotoxine. His evidence is likewise indirect: he obtained in one experiment two-thirds of the activity (as measured according to Broom and Clark) in the form of amorphous ergotoxine, and in another experiment, with the same ergot, he isolated three-quarters of the active material as ergotamine, using Stoll's process of extraction; in a third experiment he obtained ergotinine, when neither the marc, nor the mother-liquor, nor the ergotinine exhibited any appreciable activity. It is further conceivable that, even if ergotinine is present in ergot as such, it is transformed into ergotoxine when given clinically by the mouth; in that case the therapeutic effect would be more nearly represented by the chemical assay than by that of Broom and Clark. In any case, however, the chemical methods of Keller and Fromme and probably also of Smith and Stohlman are convenient in giving at least a rough idea of the value of a particular specimen of ergot. Although these methods may only give the therapeutic value within 25 per cent., or even within 50 per cent., samples of ergot vary by several thousand per cent.

Whilst the methods so far discussed give the total alkaloid with fair accuracy, and doubt only arises in interpreting the results, attempts to estimate the alkaloid by precipitation with silico-tungstic acid [Goris and Liot 1924; Damonte 1927] must be regarded as failures. The precipitate is ashed, and the silica produced is weighed, but since the precipitation in the dilute solutions involved is far from complete, the results are much too low (Leinzinger and Kelemen; Harmsma).

Finally some rough tests may be mentioned which are only semi-quantitative. Tschirch [1926] extracts 1 grm. of ergot with 20 c.c. of ether, 20 c.c. of water and 10 drops of ammonia; after gentle shaking and the lapse of two hours, the ether is

separated and evaporated. The residue is dissolved in glacial acetic acid, and sulphuric acid containing ferric chloride is poured under, without mixing. A blue coloration at the junction of the two layers implies a minimum of 0·02 per cent. alkaloid (0·2 mgm.). The acetic acid shows a green fluorescence due to ergosterol. Harmsma found the test rather more delicate than Tschirch indicated. Thorough shaking, which would seem necessary for complete extraction, leads to very resistant emulsions. Similar rough tests for ergot and its extracts have been described by Arends [1925] and by Hering [1928, 1929]. Evers [1927] measured the intensity of the blue coloration by means of a Lovibond tintometer, after the glacial acetic acid had been *mixed* with 50 per cent. sulphuric acid; on comparison with the biological assay he could only conclude, that in the absence of a blue colour the preparation is inactive. Arends also attempted to use the Mayer reaction as a rough test. A fluid extract mixed with 5 parts of water and 1 part of Mayer's reagent should give at once a turbidity, and on standing a precipitate.

Biological Assay.

In his introduction to *Methods of Biological Assay*, by J. H. Burn [1928], Dale emphasises the general conditions governing this assay. The measurements should be comparative, with reference to an accepted standard, which should be, or should owe its activity to the active principle of therapeutic value. As long as the test measures this principle, the biological reaction employed need have no relation to the therapeutic effect. In order to reduce the effect of individual variations, it is desirable to compare the known and unknown on the same animal or organ, and further to eliminate variations of the living agent with time. This statement may be illustrated by the cock's-comb test of the United States Pharmacopœia. A fluid extract is compared with a standard extract, and the action is due to the therapeutically valuable alkaloids. The biological reaction (cyanosis of the comb) has no relation to the therapeutic effect on the uterus. It is desirable to make the comparison on the same animal, and the variation in its susceptibility between the tests should be known and allowed for.

The first difficulty in the biological assay of ergot preparations is the multiplicity of their active principles. Fortunately the

two therapeutically valuable ones, ergotoxine and ergotamine, are quantitatively identical in their action, at least for all practical purposes; such action as ergotinine may have is probably due to its conversion into ergotoxine, and is in any case of the same kind. The non-specific amines, of which only histamine need be considered, are present in ergot itself in quantities so small that they do not contribute appreciably to the therapeutic effect, but some preparations of ergot may contain enough histamine to interfere with the assay of the alkaloids. It therefore becomes desirable to utilise a specific pharmacological property of the latter. Such a property is the reversal or abolition of the motor and inhibitor effects of adrenaline on a large number of organs (as detailed in Chapter V.), and this at once leads to several methods, which may be judged by Dale's above-mentioned general criteria.

1. **Vasomotor reversal in the pithed cat.**—This is Dale's oldest method; about 0·5 mgm. of ergotoxine per kilo reversed the effect of 0·1 mgm. adrenaline. Since a prepared animal is required for each test, the method is laborious, and since only one test can be made with it, the method is inaccurate, owing to individual variations. These variations have been studied by Burn [1929] in a series of twenty cats; whilst the mean was 0·507 ± 0·06 mgm. per kilo, in close agreement with Dale's figure, the extreme limits were 0·12 and 1·07 mgm. The method has been used qualitatively by Rothlin and Schegg [1925], and also by Schübel and Straub in their recent examination of proprietary ergot preparations. Although this method cannot be compared as to accuracy with that of Broom and Clark, it is quite specific, whilst the latter is not entirely so; according to Rothlin and Schegg both methods should therefore be applied; they found for instance that secalan Golaz was active, when tested by Broom and Clark's method, and yet produced no vasomotor reversal. The reversal of the motor effect of adrenaline on the cat's uterus *in situ* in early pregnancy requires 1 mgm. ergotoxine per kilo, and later still more.

2. **Abolition of the motor action of adrenaline on the isolated uterus of the rabbit** (preferably non-pregnant).—This method worked out by Broom and Clark [1923] has met with general approval and has been recommended by the International Commission on Biological Standards of the League of Nations. A uterus can be divided into several strips with which tests can

be carried out simultaneously and repeated many times. Thus individual variations can be eliminated. Broom and Clark's method has been employed by Rothlin and Schegg, Schegg, Braun [1925], Langecker, Gaddum [1926], Burn and Ellis, Linnell and Randle [1927], Harmsma, Prybill and Maurer [1928], Pattee and Nelson, Wokes, Swanson [1929], Thompson [1929-30], Schübel and Manger, Smith and Stohlman [1930]. For practical details, see Burn [1928]. The discrimination obtained is according to Broom and Clark 30 per cent., but in exceptional cases it may be 10 per cent., according to Burn. Pattee and Nelson, Swanson and Thompson all agree that with practice a 10 per cent. accuracy is obtainable; according to Smith and Stohlman the accuracy is only to 25 per cent., although results often appear to be accurate to 10 per cent. The first-named authors and Swanson advise the use of large rabbits; according to Swanson the choice of the uterus is the most difficult part of the method. Braun called attention to the time factor and suggested that the product of concentration of the alkaloid into the time of its action is constant; on this assumption he attempted to shorten the assay by not washing out; he has been criticised by Langecker and by Mendez. The complete washing out of the complex ergot alkaloids takes two to four hours, but is not so extremely slow as Braun imagined. Pattee and Nelson wash out after the alkaloid has acted for five minutes, refill with saline, and then test the final response to adrenaline. This technique was adopted by Thompson and is desirable in order to avoid the interference of histamine.

3. **Partial abolition of the motor action of adrenaline on the blood-vessels of the frog**, detected by perfusing the hind limb with Ringer's solution; Masuda [1925]. This method was used for ergot preparations by Mahn and Reinert [1925], and for total purified alkaloid in a simpler form by Forst [1926]. In a large frog both hind limbs can be used comparatively; adrenaline lowers the number of drops per minute, *e.g.* from 35 to 4, but after adding ergot alkaloids, the lowering was only to 18 and a second time to 21. No great accuracy seems possible by this method.

4. **Abolition of the inhibition by adrenaline** of the peristalsis or pendulum movements of the *small intestine* of the guinea-pig or rabbit. The principle of the method was discovered

by Planelles (see the section on pharmacology of ergot alkaloids). Leinzinger and Kelemen [1928] have used this method with the isolated rabbit's intestine to assay the total alkaloid from samples of ergot obtained by the Keller-Fromme method. They found all specimens of crude alkaloid to be as active as ergotamine; the error of assay in this special case was mostly less than 10 per cent. The method is, however, not applicable to ergot extracts containing histamine, which has a disturbing effect on the gut.

The above methods all utilise the antagonism between ergot alkaloids and adrenaline and other similar methods are conceivable. Thus the motor effect of adrenaline is also abolished by ergot alkaloids in the isolated seminal vesicle of the guinea-pig [Rothlin 1929] and in the physiologically isolated melanophores of *Fundulus* [Spaeth and Barbour 1917]. In the delicate amnion of the fowl and goose [Baur 1928] it is the inhibitor effect of adrenaline which is abolished.

5. **Reversal of the motor effect of histamine on the isolated guinea-pig's uterus.**—Thompson [1929] found that this effect is abolished by ergot alkaloids in a special type of uterus (guinea-pig of 500 to 800 grm., several weeks *post-partum*). The uterus is divided into eight to twelve strips, two of which are used simultaneously in different baths, to which the drugs are added at the same intervals of time. This method has some resemblance to that of Broom and Clark; the two were compared by Thompson on a series of ten ergot samples (see table, p. 201) and showed good agreement; the histamine method gave results on the average 8 per cent. below that with adrenaline. The former is not sufficiently sensitive for very small concentrations of the alkaloids; Thompson assigns to his own method a discrimination of 20 per cent., and one of 10 per cent. to that of Broom and Clark.

All the methods so far mentioned depend on the antagonism of two drugs and are zero methods. The remaining ones depend on the direct comparison of the action of ergot on an organ or tissue.

6. **Cock's-comb method.**—After the cyanosis of the cock's-comb had been used qualitatively by many European investigators, particularly German, it was adopted some thirty years ago by American manufacturers for the routine testing of ergot in a more quantitative fashion [Houghton 1898, 1903]. Doubts

were expressed by Santesson [1902] whether the cock's-comb reaction was a measure of the therapeutic value. Dohme and Crawford [1902] compared the alkaloidal content of ergot preparations with the action of these preparations on the cock's-comb and found that after the alkaloid had been extracted, the residual marc did not produce cyanosis. Later Dohme [1907] found that samples of ergot with very low alkaloidal content were quite active physiologically, and abandoned the cock's-comb method. Its extensive use by manufacturers, nevertheless, led to its detailed examination by Edmunds and Hale [1911; this publication contains a full account of the earlier work on the physiological testing of ergot]. Edmunds and Hale compared the cock's-comb method with the action on the cat's uterus, *in situ* and isolated, and with that on the blood-pressure (method 7, below). They found a close agreement between the cock's-comb and the uterine method, a less close agreement of these with the blood-pressure method, and little relation to the results of the chemical assay of alkaloids. They recommended injection into the breast muscles and observation of the comb one hour afterwards; 5 mgm. of ergotoxine phosphate produced a suitable effect (this is something like twelve times the dose later recommended by the U.S.P.). After a few days the animals were used again for another test, and by interchanging them the effect of individual variations was so far reduced that the error was considered not to exceed 10 to 15 per cent. The work of Edmunds and Hale seems to have led to the inclusion of the cock's-comb test in the United States Pharmacopœia, tenth revision, 1926, as follows: "Assay. Use single-comb, white Leghorn cocks, which are less than eighteen months of age, and weigh approximately 2 kilograms. Injections are made deeply into the breast muscles, and the effects are observed within one hour to one hour and a half after the administration of the drug. The same cock must not be used for testing purposes at shorter intervals than two weeks."

The standard is a composite fluid extract prepared from at least ten different samples of ergot. The dose should not exceed 0·5 c.c. of this extract per kilogram of body weight, *i.e.*, about 1 c.c. per animal. A standard extract examined by Pattee and Nelson had an action equal to 0·4 mgm. of ergotoxine per c.c.: one employed by Thompson corresponded

to about 0·3 mgm. per c.c. on the average, therefore to about 0·4 mgm. of ergotoxine phosphate, instead of 5 mgm. originally recommended by Edmunds and Hale.

The official recognition given to the cock's-comb method has led to its repeated examination by American workers. Gittinger and Munch [1927] emphasised the individual variations in cocks and the necessity of standardising them by a sufficient number of tests; they further attempted to record the degree of cyanosis by a series of numbers, and declared the method to be satisfactory. Pattee and Nelson [1929] instituted a careful comparison between the cock's-comb method and that of Broom and Clark (which latter is certainly more specific for the alkaloids). They found a close agreement between the two methods, as is shown by the following relative values:—

Cock's-comb . .	100	200	150	100	100	100	125
Broom and Clark .	100	190	175-200	100	100	100	130

The first pair of figures refers to an official standard (composite) extract, the others to laboratory and commercial fluid extracts. In two further cases, that of an ampoule preparation and of an ergotin-Bonjean, the Broom and Clark method indicated a mere trace of alkaloidal activity (6 to 2 per cent. and 1 per cent. of the standard extract) and these preparations could not be tested by the U.S.P. method.

Incidentally Pattee and Nelson found that 1 c.c. of their U.S.P. standard extract had an action on the cock's-comb between that of 0·40 and 0·50 mgm. of ergotamine, on the average therefore = 0·45 mgm., and an action equal to 0·40 mgm. of ergotoxine, which they consider to be slightly but distinctly the more active.

Swanson also found a good agreement between Broom and Clark's and the cock's-comb methods, and as the average of more than a hundred tests concluded that 1 mgm. ergotoxine base has the same activity as 1·3 mgm. ergotamine base, a somewhat larger difference than that found by Pattee and Nelson (*cf.* p. 156). Holdermann [1928] found by chemical assay 0·048 per cent. of alkaloid in a U.S.P. standard extract, in good agreement with Pattee and Nelson's results. Nevertheless the cock's-comb method has been subjected to some adverse criticism. Rusby [1929] had the same sample of

ergot assayed by a number of analysts who found relative figures ranging from 91 to 167 per cent. of the standard; this, however, merely shows that a concordant technique is not easily acquired. Smith and Stohlman [1930] found their chemical assay to agree quite well with Broom and Clark's method, but not with the official cock's-comb test. A. C. and J. P. Crawford [1913] encountered a fundamental objection when they discovered that 8 to 16 mgm. of histamine soon produces a blue coloration of the cock's-comb, lasting for one and a half to two hours. Thompson, in his recent careful examination of the U.S.P. method, has confirmed this, and states that 1·5 mgm. of histamine per kilo may cause maximal blueing in forty-five minutes. Since, according to him crude ergot often contains 1 mgm. of histamine per gram of drug, this amine may contribute to the cyanosis. On the other hand, Thompson found with mixtures of ergotamine and histamine that in some cocks much smaller quantities of the amine may interfere in an opposite direction, by partially neutralising the effect of the alkaloid. Hence he concludes that if the cock's-comb results are not found to be consistent within ± 20 per cent., the interference of histamine may be suspected. Thompson, moreover, finds that crude ergot varies enormously in its amine content, and that extracts may show an appreciable activity by the cock's-comb test, although they contain no alkaloid. In about two-fifths of the number of extracts examined by him, there was a considerable discrepancy between the U.S.P. and the Broom and Clark methods, due to the interference of histamine. As Kehrer [1908] had already noticed, the histamine disappears on aging more rapidly than the alkaloids; thus in one case the percentage of the former declined in nine months from 0·15 per cent. to 0·012 per cent., while the alkaloid activity, as measured according to Broom and Clark, declined only by one-third (from 425-450 per cent. of the standard extract to 280-300 per cent.). The activity measured by the cock's-comb was at first indeterminate (100 to 350 per cent.) and ended by being 250 to 275 per cent. It will be seen that in Thompson's investigation the cock's-comb method only became precise, and only agreed with Broom and Clark's method, after the histamine had almost entirely disappeared.

The effect of histamine on the cock's-comb test is further

shown by the following table of Thompson's results, which may also serve to illustrate the comparative accuracy of what are perhaps the three most accurate methods for the biological assay of ergot alkaloids. Column I. gives the effect on old cockerels, column II. the same on new cockerels, both in percentages of the activity of a standard extract, column III. the percentage of ergotamine by Broom and Clark's method, column IV. the same by Thompson's histamine reversal method, column V. the percentage of histamine in the ergot:—

	I.	II.	III.	IV.	V.
1. Russian . . .	130–150	160–170	0·05	0·04	0·035
2. Polish . . .	175–200	175–200	0·067	0·06	0·015
3. Russian . . .	25–80	100	0·036	0·03	0·045
4. Russian . . .	200–225	200–225	0·075	0·07	0·033
5. Spanish . . .	300–450	500	0·150	0·15	0·052
6. Spanish . . .	400–450	400–450	0·133	0·12	0·027
7. Portuguese . . .	250–275	250–275	0·080	0·08	0·012
8. Portuguese . . .	150–250	350–400	0·120	0·11	0·087
9. Spanish . . .	100–350	200–300	0·125	0·12	0·125
10. Spanish . . .	100–350	200–300	0·133	0·13	0·150

It will be seen that with the last three samples, which have the highest histamine content, the cock's-comb test does not give precise results. The figures of column III., divided by the average figures of column II., should indicate the percentage of alkaloid in the standard extract employed; this quotient ranges for the first eight samples from 0·03 to 0·036, but rises to 0·05 and 0·053 in the last two containing much histamine, which partly neutralises the effect of the alkaloid on the cock's-comb. The table further illustrates the superiority of Spanish and Portuguese ergots, and the advantage of employing new cockerels instead of those on which several tests have been made.

In the case of ergots which contain so much histamine as to render their assay difficult, Thompson suggests removing the amines from the defatted drug by means of 5 per cent. aqueous sodium bicarbonate, until no histamine can be detected by physiological means, and then preparing a fluid extract U.S.P. X. A purified "deaminised" extract so prepared contained 0·075 per cent. alkaloid, no amines and 2·75 per cent. total solids, as compared with 0·085 per cent. alkaloid, 0·097 per cent. histamine and 10·2 per cent. total solids in a liquid extract made

from the same ergot in the ordinary way. In an extract free from histamine, the alkaloids can be determined, according to Thompson, with an accuracy of ± 10 per cent. by Broom and Clark's method, and with one of ± 20 per cent. by the cock's-comb method and by his own.

7. **The blood-pressure method of assay** (by observing the absolute or relative rise instead of the vasomotor reversal) was particularly advocated by Dixon [1905, 1906; Dixon and Haynes 1905], who was one of the first to discuss the general principles of the biological assay of ergot. He believed the pressor effect to be proportional to the action on the uterus, used rabbits under urethane, and had only crude ergot extracts at his disposal. A year later Dale [1906, *loc. cit.*, p. 193] working with alkaloidal preparations wrote: "Some cats, in which the blood-pressure effect was comparatively small, showed marked uterine effects, and *vice versa*. Probably, therefore, vascular changes are but little, if at all, concerned in the production of increased uterine activity." Ergotoxine, indeed, causes a considerable rise of blood-pressure in pithed cats, but the effect is prolonged, and of a different type from that given by aqueous extracts, which owe such pressor activity as they may possess mainly to tyramine [Barger and Dale 1909, ii.]. It has been shown chemically and pharmacologically that most of these extracts contain very little alkaloid; they may, however, also contain histamine, which generally lowers the blood-pressure. It is not surprising, therefore, that Edmunds and Hale found the blood-pressure method to disagree with the cock's-comb and uterine methods. They severely criticise the blood-pressure technique of Goodall [1909] and his dictum that "broad effects were more desirable than nicety of detail," and point out that "errors of the same kind have cost some manufacturing houses large sums of money, to say nothing of damaged reputation." Attempts to utilise the pressor effect were also made about this time by Wood and Hofer, and by Cronyn and Henderson. The latter authors concluded after an exhaustive inquiry, that no reliable method of assay was available. Rothlin and Schegg [1925] also reject this blood-pressure method.

8. **The isolated virgin guinea-pig's uterus.**—Contraction of the uterus seems *a priori* to be the ideal reaction for testing ergot preparations, and a century ago experiments were already

made with pregnant animals, with a view to inducing abortion. Later the exposed uterus was observed directly *in situ*, or made to record its contractions. The isolated uterus was first used by Kobert, whose pupil Krysinski [1888] discussed the difficulties of the method. Kurdinowski [1904] found the isolated rabbit's uterus, perfused with Locke's solution, unsatisfactory. Cushny [1906] could find no concordance between the action of ergot on the uterus and on the sympathetic system. Jaquet (see Kraft 1906, p. 357) was led by the uterine method to the conclusion "dasz den Alkaloiden die therapeutisch verwertete Wirkung des Mutterkorns, den Uterus zu Kontraktionen anzuregen . . . durchaus abgeht," and Vahlen [1906] was induced, by the same method, to believe in the therapeutic value of "clavin," a mixture of amino acids and potassium salts.

Thus, in the same year, by experiments on the uterus, the therapeutic activity of the specific active principle was denied and that of non-specific substances asserted. This might well have discredited the uterine method altogether, had Kehrer [1907] not soon afterwards employed a convenient process of recording the movements of the isolated uterus in a bath of warm oxygenated Ringer's solution [*cf.* Magnus 1905]. Kehrer called attention to the different reactions of non-pregnant, pregnant and puerperal uteri in the cat; he preferred the cat's non-pregnant uterus and also used that of the bitch and guinea-pig. "When everything is considered it is seen that Kehrer contributed one of the most important chapters to the physiological standardisation of ergot" (Edmunds and Hale). Kehrer was soon followed in the use of the isolated uterus by Edmunds and Roth, and by Cronyn and Henderson; but since the powerful action of histamine on this organ was not yet known, no satisfactory conclusions were reached. The effect of certain ergot extracts, particularly of Wernich's *ergotinum dialysatum*, on the isolated guinea-pig's uterus then led Barger and Dale [1910, ii.] to the isolation of histamine from such extracts and the recognition of its physiological activity. Since then the isolated uterus of the virgin guinea-pig came into frequent use in pharmacological laboratories and has been recommended for the assay of ergot preparations. The method has been prescribed in the Russian Pharmacopœia [1929], where a detailed account of the technique and apparatus

is given. It should, however, be emphasised that since histamine, tyramine and the alkaloids all act differently on the isolated uterus, this organ can, strictly speaking, only be used for the estimation of one of these constituents, when separated from the others. (The effect of acetyl choline, occasionally present, is at once abolished by atropine.) Histamine, mixed with the alkaloids, is best assayed by means of the isolated intestine, on which the alkaloids have little effect [Forst and Weese]. According to Thompson (see the table, p. 201) the amount of histamine in ergot itself varies enormously, and may be much larger than has hitherto been supposed; in aqueous extracts the amount may be greatly increased. Thus Forst and Weese [1926] found most histamine in ergotitrin [Kahlbaum], a preparation made, according to Wiechowski's directions, by allowing ergot to ferment at 37° for some days. It is under the latter's influence that papers have still appeared of late years, advocating assay by means of the isolated guinea-pig's uterus [Halphen 1922; Langecker 1928]. Such papers, in company with the Russian Pharmacopœia, overlook the fact that by this method the specific and desirable constituents, the alkaloids, are not assayed.

It follows from the above review that the first method (vasomotor reversal) is the most specific; the second (Broom and Clark) the most accurate; the sixth (cock's-comb) probably requires least skill; the seventh (blood pressure) is wholly unreliable; the eighth (isolated guinea-pig's uterus) is non-specific. For a comparison of these methods, see Rothlin and Schegg, [1925] Pattee and Nelson, Swanson, Thompson [1929]. See further the report on international conferences by Knaffl Lenz [1928].

The Alkaloidal Content of Ergot.

The amount of total alkaloid varies greatly with the year and the locality. Cæsar and Loretz [1905] reported for that year a range of 0·013 to 0·38, in 1896 one of 0·1 to 0·26, in 1904 one of 0·025 to 0·414 per cent. The biological assay never gives a content in excess of 0·3 per cent. of active alkaloid. Most alkaloid is contained in Spanish and Portuguese ergot; Thompson [1930] who has evidently had a large official experience during recent years, found 0·05 to 0·30 per cent. in Spanish and Portuguese, and only 0·02 to 0·10 per cent. in Russian and

Polish ergot. See also the table on p. 201. Gittinger and Munch [1927, ii.], state that 26 out of 27 Spanish and 6 out of 6 Portuguese ergots satisfied the standard of the United States Pharmacopœia, but only 2 out of 9 Russian and 3 out of 5 Polish samples. The superiority of Spanish and Portuguese ergot also follows from the (less numerous) assays of Burn and Ellis, Garner, Holdermann and Schilske; the last two authors employed the Keller-Fromme method. German ergot approximates to the Russian, rather than to the Spanish. König found in it 0·032 to 0·14 per cent., Meulenhoff [1902] 0·12 to 0·14 per cent., Harmsma exceptionally in an ergot picked near Leipzig 0·26 per cent. (all these by chemical means). According to König, the standard of 0·2 per cent. at one time suggested by Cæsar and Loretz could not be satisfied by German ergot, and the German Pharmacopœia [1926] has adopted a minimum of only 0·05 per cent.

The high alkaloidal content of Spanish ergot is probably due to the warmer climate, and a high content in other places to an exceptionally warm summer; according to Vatter, Swiss ergot grown in the hot summer of 1911 was unusually rich in alkaloid (up to 0·22 per cent.). The great variation in quality in different years must have been as much a cause of the fitful appearance of ergotism as variations in the quantity of ergot.

General properties of a good ergot.—It has been suggested that ergot is most potent a few weeks before the harvest (Dierbach [1837] already quotes experiments to this effect), and the Norwegian Pharmacopœia directs that it shall be collected before the rye is fully ripe; this point deserves investigation by modern assay methods. There is little doubt that large sclerotia contain, weight for weight, less alkaloid than smaller ones of the same sample [Beckurts and Grothe 1896; König 1912]. According to Hartwich [1912] sclerotia over 25 mm. in length were rejected by the Swiss Pharmacopœia on account of their small alkaloidal content; he figures sclerotia up to 77 mm. in length. Rojdestvensky [1928, *loc. cit.*, p. 153] states that the greater toxicity of small sclerotia is mentioned in most descriptions of Russian epidemics of ergotism. The common preference for "bold" ergot is perhaps based on the larger average size of the Spanish product, but is probably not justified where samples from the same country are compared. Thompson, in giving his general impressions of the pharmacognosy of a

good ergot, *i.e.*, one rich in alkaloid, is doubtful whether the size has any effect and mentions that large and small sized samples are often mixed by dealers. He states that the shape and colour of the sclerotia are without effect, but later suggests that in ground ergot, which varies from a light purplish grey to a greyish brown, the predominance of brown is to be preferred. Russian and Polish ergots have a more purplish colour and contain little alkaloid, and further, according to Thompson, the fresh percolate of potent samples is of a rich brown colour rather than a relatively transparent red, which is apt to be given by weaker ergots. Rojdestvensky [1927, *loc. cit.*, p. 152], states that in the recent Russian epidemic dark ergot was found to be the most toxic. Hence it would seem that colour, or at least the amount of colouring matter in the sample, is connected with the alkaloidal content. (Small sclerotia of course have a larger relative surface and hence more colouring matter, and they are also richer in alkaloid, as has been pointed out.) According to Thompson, a pleasant, fruity, aromatic odour is usually better than a soapy unpleasant one, or absence of odour. According to him the fracture is most significant; it should be short and corky; a tough horny fracture is less good. When damp, all varieties have a rubbery fracture and cannot be distinguished by this test. The colour of the broken surface should be white, or yellowish white; a bluish, purplish or brownish tint is unsatisfactory; age usually darkens the colour. Good samples are ground easily; a soft mealy texture of the coarsely powdered drug is best; when it feels sharp or angular on rubbing between the fingers, it is likely to be less satisfactory. A high content of oil is good; the amount varies from 10 to 35 per cent. A deep colour of the oil indicates rancidity (and probably decomposition of alkaloid). It is an indication of the past history of the sample rather than of its original quality. Mites and lice do not necessarily lower the alkaloidal content [see also Burn and Ellis, 1927].

Burn concludes from the examination of his specimens by Wallis, that pharmacognosy gives no certain clue to the amount of alkaloid present; apparently, however, the right criteria were not applied. The fractured surface of the inferior Polish and Russian ergots was purplish, in the better Spanish and Portuguese it was white, which agrees with Thompson's impressions. Wallis seems to have assumed that a fresh-looking

clean ergot is better than an old dirty one, which is not necessarily the case.

The superiority of Spanish and Portuguese ergots is partly due to careful drying. The Russian peasant does not use artificial drying, and his ergot may become mouldy. Rusby [1928] states that a regular business has grown up in New York of "re-conditioning" ergot by removal of mould. Mould means moisture, and according to Thompson the latter greatly increases the amount of non-specific amines; thus after keeping entire ergot in a humid container at room temperature for two years, the amount of histamine rose from 0·005 per cent. to 0·12 or 0·13 per cent. and the alkaloidal content declined from 0·133 to 0·01 or 0·02 per cent. In a sample of the same ergot kept dry in a sealed jar, there was still 0·10 or 0·11 per cent. of alkaloid. Evidently ergot deteriorates much more through moisture than through age, and on that account mould is a suspicious sign.

Liptak has suggested that the increase in the acid number of the oil is a direct measure of the decline in alkaloidal content. Thompson defines it as the number of cubic centimetres of decinormal alkali required to neutralise the fatty acid in 10 grm. of the oil, and found it to vary from 2·6 to 42·5 in fifty samples of Spanish and Russian ergot. On keeping it may certainly rise to many times its original value, but the rise bears no relation to the destruction of alkaloid. Yet according to Thompson an acid number over 15 indicates that the ergot is old, and therefore suspect (although by no means necessarily bad).

Some non-official ergots.—That of wheat has been the subject of favourable clinical reports by Carbonneaux le Perdriel [1862; figure] and Grandclément [1863], but its alkaloidal content does not appear to have been recorded. G. Tanret [1922] found a rather high content in ergot of oats, but only very little (0·01 per cent.) in Algerian ergot of Diss (on *Ampelodesma tenax*). In both cases crystalline ergotinine was isolated. An ergot on *Elymus arenarius* contained 0·105 per cent. of alkaloid (Amberg) and one on *Festuca elatior* from New Zealand 0·3 per cent. (Carr and Dale 1913, see also p. 136). An ergot on rye grass (*Lolium perenne*) was found by Bredemann to contain 0·29 per cent. of alkaloid, as compared with 0·028 per cent. in ergot of rye grown at the same time only 500 metres

away. The sclerotia on *Lolium* weighed on the average 9 mgm. (see Fig. 18, p. 86), those on rye 55 mgm. Bredemann thought that both ergots contained the same alkaloid. An ergot "on grass" [Cæsar and Loretz 1896] contained 0·37 per cent. of alkaloid. In general the alkaloidal content of the smaller

FIG. 40.—Various Ergots.

Ergot (?) on *Andropogon sorghum*. (Burmah).
Rye.
Ampelodesma tenax.
Oats.
Artificial Ergot.

grass ergots seems to be high (this is also the impression of Rojdestvensky [1927], *loc. cit.*, p. 153).

All the above ergots are *C. purpurea;* the only analysis of *C. microcephala* (on *Molinia cærulea*) is due to Hartwich [1895] and yielded the very high proportion of 0·8 per cent. of a definitely crystalline alkaloid. For illustrations of ergots on various grasses see Carruthers, John (*Molinia* and wheat), Warburton (oats), and Williams (grasses of S. Dakota). Fig. 40

represents a small portion of an inflorescence of *Andropogon sorghum* bearing sclerotia (?) derived from *Sphacelia sorghi* McRae (*cf.* p. 112). It was taken from a specimen in the Imperial Bureau of Mycology, Kew, collected in 1927 on "Mandelay Farm, Burmah, by D. Rhind." I am greatly indebted to Mr J. H. Gaddum of the National Institute for Medical Research for a biological assay of the sclerotia in Fig. 40, of a total weight of 0·6 grm. By the Broom and Clark method no active alkaloid could be detected (there was certainly less than 0·007 per cent. of ergotoxine). It is hardly likely that by four years' keeping in a herbarium, the whole of the alkaloid would be destroyed, so that this parasite is very different from ordinary *Claviceps*. Fig. 40 further shows ergot of Diss (top right), ergot of oats (below), ergot of rye (bottom left) and an artificial ergot made from dough and present as an adulterant to the extent of 15 per cent. in a commercial specimen of Spanish ergot (bottom right). I owe the Diss, oats and artificial ergots to the kindness of Dr G. Tanret who has described them [1922, 1923]. Diss ergot has also been described by Lallemant, by Germaix and by E. M. Holmes.

Proprietary Preparations.

Whilst the United States Pharmacopœia aims at a constant and the German at a minimum amount of alkaloid in the fluid extract, some approach to uniformity is secured in these official preparations, at least when freshly prepared. This is far from being the case with the proprietary preparations of manufacturers. A number of American ones were examined and discussed by Edmunds and Hale [1911] and showed a considerable range of activity, but since the cock's-comb test, first used extensively by the manufacturers themselves, has been adopted in the U.S.P., it is probable that greater uniformity will be achieved. Increased knowledge and better assay methods will perhaps also prevent the putting forward of the unwarranted claims, quoted twenty years ago by Edmunds and Hale, as, for instance, that a preparation is a "permanent solution" and that "it does not change with age." On the Continent of Europe the position is still rather different. Most German and Swiss proprietary preparations contain very little alkaloid; some, by accident or by design, contain a rather high proportion of histamine

[*cf.* Rothlin and Schegg 1925]. Schübel and Straub [1929] examined a number of these preparations for alkaloids by the vasomotor reversal, and in some cases chemically, according to the German Pharmacopœia (column III.).

	Vasomotor Reversal.	Percentage of Histamine.	Percentage of Alkaloid.	
Clavipurin. Gehe. . . .	+	traces	0·018	0·06
Cornut. Ergot. Bombelon .	0	0·003	0·002	0·0075
Ergopan. Temmler . . .	0	...	0	...
Ergotin. Denzel	0	...	0	...
„ Fromme . . .	0	...	0·003	...
„ Merck	0	0·01	< 0·002	...
Ergotitrin. Kahlbaum . . .	0	0·02-0·4	0	...
Secacornin. Cewega and Grenzach	0	0·009	< 0·002	0·0054
Secalysat. Bürger . . .	0	0·001	0·008	0·054
Secalan. Golaz	0	0·001	...	...
Gynergen. Sandoz. Ampoules .	+	...	...	...
Ergotamine methane sulphonate. Sandoz	+	...	...	...
Fluid extract. Merck . . .	0	...	...	...
„ „ Gehe . . .	+	...	...	...
„ „ from pharmacy .	0	...	...	...

The second column refers to a biological estimation of histamine by Forst and Weese, the fourth to an alkaloidal assay by Mahn and Reinert, on other samples of different age, so that the results are not strictly comparable.

Apart from the two Sandoz products, which are professedly pure ergotamine salts (gynergen ampoules contain 0·5 mgm. of the tartrate per c.c.), the only alkaloidal preparation is Clavipurin Gehe, in which a less purified mixture of alkaloids is presumably used. The last three are official extracts of the German Pharmacopœia, of which the first and third had become inactive through age. Secalysat Bürger contained 0·01 per cent. of histamine, and would appear to be analogous to *ergotinum dialysatum* of Wernich. Ergotitrin Kahlbaum is also rich in histamine (Forst and Weese). Thus, although the German Pharmacopœia has declared in favour of alkaloids, German manufacturers are less definite. The first ampoule preparation made from pure active principles, was ernutin of Burroughs, Wellcome & Co., a solution containing ergotoxine, histamine and tyramine.

Deterioration of Ergot and of its Preparations on Keeping.

For *ergot itself*, a rapid loss of activity (as tested on the cock) was alleged by Kobert's pupil Grünfeld [1892]. He came to the conclusion that samples lose all their activity within eight months of the harvest ("absolut keine Wirkung mehr haben"). This is a gross exaggeration. Grünfeld's experiments and reasoning were severely criticised by Meulenhoff [1900]; for instance, Grünfeld contented himself with small commercial samples of unknown history, and did not test one and the same sample at different times; his conclusions, moreover, conflict with his protocols. Meulenhoff himself experimented with more cocks than did Grünfeld and found hardly any loss of activity after two years; his most active specimen was at least five years old and had a lethal dose of about 20 grm. per kilo body-weight. Burn and Ellis [1927] found 0·075 per cent. of active alkaloid (by Broom and Clark's method), in a specimen of Spanish ergot, at least fourteen years old (this is one and a half times the minimum content required by the German Pharmacopœia and one and a half times the standard content demanded by the U.S.P.). They found that another specimen, about twenty-five years old, which had been reduced by insects to an evil-smelling powder, still contained as much alkaloid as the recent Russian ergots they examined. Thompson kept samples of an ergot originally containing 0·133 per cent. of active alkaloid, for two years at room temperature (*a*) entire in a paper bag (*b*) entire in a sealed jar (*c*) entire in a moist container (*d*) ground and stored in a loosely covered jar, and found after this period that the alkaloidal content had fallen respectively to 0·11 to 0·12, 0·10 to 0·11, 0·01 to 0·02 and 0·06 to 0·07 per cent. Entire ergot, kept dry, deteriorates only very slowly. The stipulation which most pharmacopœias contain as the result of an international agreement, that ergot should not be kept for longer than one year, seems to be most wasteful [*cf.* also Schilske, 1925].

Even powdered ergot does not deteriorate quite so rapidly as Grünfeld suggested. Meulenhoff did not detect any serious deterioration in a powder kept for two years (cock fed with ergot powder), but Forst [1926] found that the alkaloidal content of a powdered ergot declined from 0·08 per cent. to

0·036 per cent. in the course of six months. The decline in Thompson's experiment was much less rapid.

It has been suggested, without experimental evidence, that the oxidation of the alkaloids is catalysed by that of the unsaturated fatty acids, but the acid number of the oil is of no great importance (see p. 207). Defatting has been suggested by Perret as a means of preservation, and Thompson reports that in a powdered defatted ergot the alkaloid declined only from 0·05-0·06 to 0·045-0·05 per cent. Meulenhoff [1899] gives a different explanation of the action of rancid oil. Freshly powdered ergot, whether old or new, furnishes with petrol a pale oil containing practically no alkaloid, but an old powder gives a much darker oil, strongly acid and containing a distinct amount of alkaloid, which escapes detection by the Keller-Fromme method and is also lost in defatting before preparing a liquid extract. The disappearance of alkaloid (due to transformation into ergotinine?) is therefore more apparent than real.

Deterioration of fluid extracts.—This is much more rapid than that of the powdered drug, and raises a pharmaceutical problem of considerable importance and difficulty, not foreseen by those who introduced into the German Pharmacopœia of 1926 a fluid extract designed to contain a minimum content of alkaloid [Schübel and Straub 1929]. This deterioration has only been studied since 1928, most fully by Thompson [1930].

	Half-life period in months.
1. Clear glass, filled, cork stopper, room	7
2. Amber glass, filled, cork stopper, room	8
3. Amber glass, half-filled, cork stopper, room	3
4. Amber glass, half-filled, cork stopper, ice-chest	5
5. Amber glass, filled, cork stopper, ice-chest	19
6. Amber glass, unstoppered, room	<1
7. Amber glass, unstoppered, ice-chest	$1\frac{1}{2}$
8. Sealed ampoule *in vacuo*, ice-chest	60
Wokes, sealed ampoule *in vacuo*, ice-chest (calculated from data in a private communication by Dr J. H. Burn)	17
Prybill and Maurer [1928] by Keller-Fromme, cellar	4 to 10
Harmsma [1928], by spectrophotometry, room	<6
Wokes [1929], by Broom and Clark, room	$1\frac{1}{2}$ to 3

In order to facilitate comparison between the latter's results and those of other workers, it is convenient to consider the

period during which the activity of an extract is reduced to half its original value. This "half-life" period can be obtained by graphical interpolation from most of Thompson's experiments, for he assayed the same extract as many as eight times. Other investigators have generally made only two or three assays on the same extract; in such cases, and where exterpolation is necessary, the half-life period is probably best calculated on the assumption that the decay takes place according to a unimolecular reaction. The results are necessarily very rough. The first eight results were obtained by Thompson with one and the same U.S.P. extract; it is at once evident that access of air is the most important cause of deterioration. Comparison of his results with those of the other authors is difficult, for several reasons. In the first place the others used, in addition to U.S.P. extracts, some which are much less acid, like the 1926 German. Now Swanson [1929] claims that a sufficient degree of acidity (already nearly possessed by the U.S.P. extract) increases the stability. This is doubtless the reason why Wokes' extracts, made with citric and with tartaric acids, showed the extraordinarily short half-life period of ten weeks and six weeks respectively, *in an ice-chest*, which would be something like one to one and a half months at room temperature; for his U.S.P. extracts the corresponding period was about three and a half months. In any case, Wokes found a much more rapid decay than Thompson did, when the access of air was prevented.

A second reason which makes comparison difficult is that workers, other than Thompson, did not specify accurately their conditions of storage. Prybill and Maurer were apparently the first to call attention to the great instability of liquid extracts; their biological assays do not agree well with their chemical results by the Keller-Fromme method; the latter when plotted allow some sort of half-life period to be deduced (five to ten months for the U.S.P., four to eight months for the German extracts), but even these chemical results are not so regular as Thompson's biological assays. Harmsma's results are few and were obtained by a very different method, with the Dutch extract (containing tartaric acid). Wokes found the rate of decay at 37° to be about three times that at 0°, which implies a low temperature coefficient (about 1·4 per 10°) of the same order as that indicated by Thompson's experiments.

The effect of P_H, reported by Swanson [1929], is very pronounced. He added varying amounts of concentrated hydrochloric acid to identical samples of a fluid extract. After two years the activity at P_H 5·35 had fallen to 2 per cent. of the original, but at P_H 2·7 it was fully maintained. The sample which contained the same amount of acid as that required by the U.S.P. had a P_H of 3·21 and still retained after two years 80 per cent. of its original activity. (According to Wokes and Elphick [1930], the P_H of U.S.P. extracts may vary from 3·0 to 5·0.) This very slow rate of decay of the official extracts is not in accordance with the results of other investigators. Nevertheless the hydrogen-ion concentration will have to be considered in future work[1]; Swanson reports, for instance, that (neutral) solutions for hypodermic use deteriorate rapidly. Wokes found that concentrated (soft) extracts were rather more stable than his ordinary official ones, retaining half their activity in an ice-chest for four to nine months; the greater stability may well have been the result of a greater acidity of the concentrated extracts.

Kehrer [1908] found that the action of an extract on the isolated uterus declined even more rapidly than that on the cock's-comb, which implies that histamine disappears even faster than the alkaloids; the same was found by Thompson (see p. 200).

The great instability of the liquid extract of ergot is a serious disadvantage. Even when the pharmacopœia contains a good method for its preparation, this method will usually not be applied in dispensing, but chiefly for its preparation in bulk by manufacturers. Hence it has been repeatedly suggested [*e.g.* by van Itallie 1928] that the liquid extract should be replaced by pure alkaloidal salts, which, in the absence of oxygen and light, keep well for years.

Standards for biological assay.—The standard extract of the U.S. Department of Agriculture is a composite one made from ten ergots; it is aged for six months, is then standardised, and is kept *in vacuo*. Like a Christmas pudding, many ingredients go to its making, but unlike the pudding, it does not improve on keeping. Pattee and Nelson found lot No. 635

[1] Since this sentence was written, a paper by Wokes and Elphick [1930] has appeared, in which the effect of the P_H of the ergot is for the first time fully considered; this paper is referred to above, p. 184.

to contain 0·045 per cent. of active alkaloid, but after four years only 0·02 per cent. Lot No. 636 seems originally to have also contained about 0·04 to 0·05 per cent. of alkaloid (Swanson), but examined by J. H. Burn and by M. I. Smith, contained no more than 0·03 per cent., perhaps only 0·025 per cent., which, as Thompson points out, is too little to give a pure effect on the cock's-comb in the prescribed dose of 0·5 c.c. per kilo. The U.S. Department of Agriculture puts out new standard extracts every eight to ten months. As Thompson suggests, a pure alkaloidal salt would be a far better biological standard. Solid ergotamine tartrate and methane sulphonate have been found stable for five years, if kept in the dark, in the absence of oxygen. Ergotoxine salts, similarly kept, appear also to be stable. The deterioration of the phosphate, which has been mentioned from time to time, is due to exposure to the air; at first the need of special conditions of storage was not appreciated. Thompson refers to the results of Pattee and Nelson, and of Swanson, who agree that ergotoxine is slightly more active than ergotamine, but he considers the difference to be no greater than the error of the Broom and Clark method, and recommends a standard fluid extract containing 0·05 per cent. of alkaloid, whether ergotoxine or ergotamine; 0·5 per cent. of ergotoxine phosphate has been adopted by the Pharmaceutical Society of Great Britain for liquid extracts. Ergotamine salts are indeed more soluble than those of ergotoxine, but are proprietary preparations.

Ergot in Commerce.

For the information contained in this section, I am largely indebted to Mr N. A. Johns, of the firm of Messrs F. W. Berk & Co., Ltd., London, who has spared no pains in collecting data about shipping, prices, etc. I am further indebted to the Buying Department of Messrs Burroughs, Wellcome & Co. for information about London prices before 1923. Other information, of a fragmentary kind, has been obtained from various published sources. A complete utilisation of official data was outside the scope of this book.

The two most important *sources of ergot* are a large region in Eastern Europe (chiefly Russia and Poland) and a much smaller one, the moist north-western corner of the Iberian Peninsula, comprising parts of Spain and Portugal. Russian

ergot is almost entirely shipped from Leningrad, Polish from Danzig, Spanish chiefly from Vigo, Portuguese from Lisbon, but some ergot grown in Portugal is bought up by Spanish shippers and then figures in the market as Spanish. Minor sources are Esthonia, Latvia and Lithuania; Germany and Austria also produce some ergot, shipped overseas from Hamburg, but nothing is heard of these crops when the price of Russian ergot is low. Sweden produces enough for her own consumption and sometimes exports a few hundred kilos, when prices are high. Occasionally ergot is offered from Rumania and Bulgaria, but it is not known whether this is native grown or really comes from Russia.

Amount produced.—The size of the crop varies greatly from year to year. In addition to meteorological conditions which affect the degree of infection (see p. 98), an important factor may be the occurrence of strong winds or heavy rain just before the rye harvest, so that much ergot falls to the ground. Estimates of Spanish crops have been reduced from 100 tons to 30 tons in the course of a day or two, on this account. In Eastern Europe, which, unlike Spain, does not specialise in the production of ergot, very low prices may reduce production, for instance in Germany and Austria. In Russia economic conditions are peculiar. The total Iberian crop for the ten years 1920 to 1929 is estimated at 725 tons. In each of the years 1919 and 1920 the crop exceeded 100 tons, in 1929 and 1930 it was only about 35 tons each, in 1928 there was a normal crop of 70 to 80 tons (Johns); yet, according to Rusby, the latter crop was at one time estimated by the United States Consul at Vigo at 100 tons Spanish and 60 tons Portuguese. The Russian crop varies perhaps even to a greater extent; for instance, the wet summers of 1897 to 1899 produced an exceptionally large amount of ergot; the average pre-war export from Russia has been placed at 150 tons, or about double that from the Iberian Peninsula (in 1906, 190 tons according to *U.S. Dispensatory*, 20th ed., p. 424; in 1913, 100 tons, according to a recent Russian official pamphlet). The "Handelsvertretung der U. d. S.S.R. in Deutschland" at Berlin have kindly informed me that the present average Russian export is about 100 tons, which goes principally to Germany, in the second place to America, and in small quantity to England. The Spanish crop becomes available in London

about the middle of August, that from the Baltic States and Germany in September and October, that from Russia in November.

Centres of distribution.—Ergot destined for consumption in Britain goes mostly to London, either direct, or in the case of Spanish ergot, often via Southampton. Hamburg is the chief centre of German and Austrian ergot, a very important sub-centre for Russian ergot, and also an important market for the Spanish, Polish and Baltic products. New York is the chief centre in the United States, which country consumes much more ergot than any other. According to Bonns, the amount imported into the U.S.A. during the years 1913 to 1919 varied from 58 to 112 tons per annum, with a value as high as $208,000. The following table is based on data in the *Oil Paint and Drug Reporter* and in *Drug Markets* (especially December 1930 for Spanish ergot):—

Importation of Ergot into U.S.A. in Tons (of 2240 lbs.).

	Total.	Spanish.
1919-1921	average 78	...
1922		...
1923		...
1924	average 89	...
1925		21
1926		34
1927	80	57
1928	134	76
1929	102	24

It would appear that the U.S.A. consume something like one-half of the world's production; in 1929 and probably also in 1927 they secured two-thirds of the Spanish crop. The great American demand for Spanish ergot in 1927 was due to the U.S.P. of 1926, and the policy of insisting on a definite alkaloidal content of the liquid extract has resulted in considerable quantities of ergot (mostly Russian) being refused entry into the U.S.A., and being probably shipped back to Europe. Thus, of the 328,000 lbs. imported during the twelve months ending 31st July 1929, 73,787 lbs. were detained.

Fluctuation in price.—The price of ergot, like the size of the crop, varies greatly from year to year, and is further influenced by the rate of exchange and other economic con-

ditions; thus in 1919 Russian ergot commanded 20s. per lb., whilst in 1907 and in 1930 the price was below 1s. A feature of greater scientific interest is the progressive change in the relationship between the prices of Eastern (Russian, Polish) and Iberian (Spanish, Portuguese) ergot, due to the recognition of alkaloids as the important constituents of the drug. As pointed out earlier in this chapter, Iberian ergot generally contains much more alkaloid than does Eastern. For the following table of London prices, I am indebted to Messrs Burroughs, Wellcome & Co.

	Russian.	Spanish.
1871	3s. 4d. to 3s. 6d.	...
1881	2s. 6d. ,, 2s. 8d.	...
1891	1s. 7d. ,, 1s. 8d.	1s. 5d. to 1s. 7d.
1901	1s. 9d.	1s. 6d. ,, 1s. 8d.
1906	2s.	1s. 6d. ,, 2s.
1907	7d. to 1s.	...
1908	1s. 0d. ,, 1s. 1d.	...
1909	1s. 1d. ,, 1s. 3d.	...
1910	1s. 4d. ,, 1s. 9d.	...
1911	5s. 3d.	3s. 3d. to 5s. 3d.
1912	...	4s. 0d. ,, 4s. 9d.
1913	...	2s. 0d. ,, 3s. 8d.
1914	1s. 8d.	1s. 9d. ,, 2s. 7½d.
1915	...	2s. 6d. ,, 2s. 9d.
1916	1s. 10d. to 2s.	2s. 4d. ,, 2s. 6d.
1917	...	2s. 6d. ,, 3s. 0d.
1918	...	3s. 9d. ,, 5s. 6d.
1919-20	No record	...
1921	...	5s. 0d. to 6s. 0d.
1922	...	1s. 10½d. ,, 4s. 3d.
1923	...	1s. 1d. ,, 2s. 1d.

The monthly prices from 1923 onwards were supplied to me by Mr N. A. Johns, and are represented in the diagram (Fig. 41) (from which transitory minor oscillations have been eliminated).

The table and the diagram show that until about 1906 the price of Russian ergot was actually a little higher than that of Spanish; from then until 1926 there was very little difference between the two, but in that year the American Pharmacopœia prescribed an alkaloidal content of 0·05 per cent. for the liquid extract, which caused the American consumption of Spanish ergot to rise suddenly, and with it the price rose to double or occasionally treble that of Russian

(dotted curve in the diagram).[1] A result of this has been that the importation of ergot into Spain was prohibited by royal decree of 17th January 1929 [*Pharm. Zentralhalle*, 1929, **70**, 383] in order that Eastern ergot shall not be re-exported as Spanish. Another result of high prices is the remarkable adulteration of Spanish ergot with artificial "sclerotia" made from dough (G. Tanret [1923]; illustrated in Fig. 40, p. 208). The diagram also shows a seasonal fall in the price of Spanish ergot in the middle of the year (June, July), partly due to the proximity of the harvest, and still more to a depression of

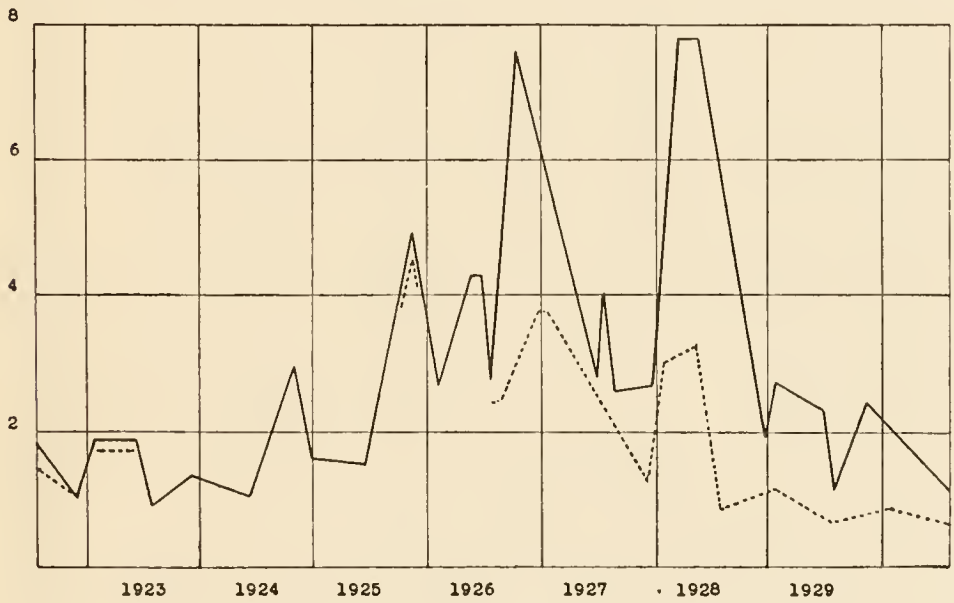


FIG. 41.—Prices of Ergot in shillings per lb. in London.

Upper line, Spanish; lower line, Russian.

the market by Spanish shippers, so that they may buy the new crop at a low figure from peasant collectors.

According to Mr Johns the small manufacturers of ergot preparations in the United States are finding it more and more difficult to compete, owing to the strict control of the Board of Agriculture, so that the manufacture of these preparations is becoming concentrated in the hands of a few large firms (who incidentally, by their introduction of biological standardisation thirty years ago, were the primary cause of this result). The new British Pharmacopœia may produce a

[1] For the fourth quarter in each of the years 1925 to 1929 in London the ratio was 1·09, 2·0, 1·9, 2·3, 2·9 respectively.

similar situation in this country. The deterioration of ergot (much exaggerated) and of the liquid extract has also an economic bearing; it is a question whether better use could not be made of exceptionally good crops by extracting the alkaloid and keeping this in solid form. Attempts are being made to counter the deterioration of the liquid extract by using only small sealed containers, but even then a liquid preparation is much less stable than a solid one.

Crude Spanish ergot is usually packed in double bags of 75 kilos net weight, Eastern in double bags containing 50 kilos net. During storage ergot is liable to attack by mites, which during one year often reduce the weight by as much as 10 per cent. The mites eat principally the interior of the sclerotium and finally leave only a shell. In addition there is an attack, especially on "bold" ergot, by a parasite invisible to the naked eye, which attack results in the formation of a fine, light brown dust. Very thin ergot of poor quality from Russia does not suffer this kind of deterioration, nor is properly disinfected Spanish ergot subject to it. The best Spanish shippers disinfect before shipping, but this is apparently not done in Russia. Rats and mice gnaw through bags and wooden cases containing ergot and carry it all over a warehouse floor, but it is not clear how much they actually eat. Attack by mites, however, by no means necessarily implies diminution of alkaloidal content in the remainder (see p. 211, concerning this, and p. 205, where the appearance of a good ergot is discussed).

Attempts to grow ergot as a saprophyte, the artificial inoculation of rye, and some non-official ergots, possibly of commercial value, are mentioned in the Botanical chapter.

Ergot and Public Health.

Attempts by public authorities to prevent ergotisms were made in Germany much earlier than in France. Already in the epidemic of 1722 in the Prignitz district (see *Acta medicorum Berolinensium*), the Prussian Government exchanged ergotised rye for sound grain, and the Hanoverian authorities likewise supplied corn during the 1770 outbreak near Celle. On 24th September 1770, the Hessen Government issued a warning against ergot, with orders to clean the grain and punishments

for neglecting to do so, to be promulgated by public crier (Nebel). Towards the end of the eighteenth century ergot is referred to at some length in works on medical jurisprudence, for instance by Frank [1783] and von Haller [1784]. Rössig [1786] advocated land drainage and cleaning of the grain; he relates that punishments for selling ergotised grain were enacted in Chur-Hessen in 1768 and at Leipzig in 1785. Hebenstreit [1791] mentions preventive ordinances issued in Saxony (Churfürstlich Sächsische Verordnungen, die Verhütung der Gefahren vom Genuss des Mutterkorns betreffend, vom 20 August 1764) [*cf.* Schroeter, 1792]. A full account of enactments against ergot, up to 1832, is given by Galama; the best laws are said to have been those of Saxony. Later when ergotism became rare, these regulations appear to have lapsed; they are not mentioned by Thieme [1930] in a paper written under official auspices; according to him there are no specific laws for the prevention of ergotism in Germany or in any civilised country, and he merely mentions German notifications of 1882 and 1884, which pointed out that the sale of ergotised rye is punishable under a general law prohibiting the sale of poisonous food. In recent years we are only concerned with statements, private and official, of the maximum amount of ergot permissible in grain and flour.

It is impossible to determine this limit exactly. The experience in the older epidemics is not very helpful; such data as are available (see Chapter II., p. 26) refer to an ergot content of grain, which produced more or less severe poisoning and was far above the amount permissible in relation to public health. We may however, for instance, utilise the data of the Manchester epidemic of 1927 (see p. 64) where 0·18 to 0·3 per cent. in flour produced mild ergotism. Thus it is not surprising that (according to Thieme) a semi-official publication of the Verband der Nahrungsmittelchemiker [1897] considered 0·5 per cent. of ergot in flour absolutely objectionable. The official Codex Alimentarius Austriacus [1911] states that 0·2 per cent. is harmful to health, whereas the Russian provincial authorities in the Ural district in 1926 declared the same amount (in flour) to be harmless. According to Rojdestvensky the U.S.S.R. has now however fixed this limit at 0·15 per cent. as the result of the epidemic of 1926. The Institut für Getreideverwertung at Berlin considers 0·1 per cent. in flour

as the maximum allowable (Thieme). It might seem possible to fix an even lower limit but this is not practicable; rural mills in Germany are said constantly to produce flour with this amount of ergot, or more; in America 0·1 per cent. is also often present in the flour, and its producers state that it is not objected to.

The limit would therefore appear to be 0·1 to 0·15 per cent., and as shown in the following section, this amount can indeed be recognised by the better chemical and histological methods (but not by the others). With a consumption of 0·5 kilo of flour per day, this means a daily dose of 0·5 to 0·75 grm. of ergot, which is well below that usually prescribed, but is continued over a long period. Seeing that the alkaloidal content of ergot varies considerably, it would of course be more scientific to fix a limit for the amount of alkaloid in flour, rather than for that of ergot (the difficulties and possibilities which this problem presents, are indicated in the next section).

The amount of ergot in threshed grain may be considerably larger than in flour, for before milling a very large part of the ergot can be eliminated by mechanical means. Tessier [1776, iii.] already pointed out that the larger sclerotia can be removed by sieves, and the smaller ones by stirring the grain into water. Weinzierl, who specially studied this question on behalf of the Austrian Government, found that with up-to-date machinery the ergot content could be lowered from 1 to 0·06 and from 3 to 0·10 to 0·17 per cent.; nearly all the ergot was concentrated, with other impurities, in one quarter of the grain. In modern roller mills the amount of ergot in the flour would be reduced still further, but when the grain is not cleaned or screened, and is merely ground to coarse meal in a primitive stone mill, no purification is effected. This was a most significant feature of the recent outbreak of ergotism in Manchester (Morgan). Apart from such exceptional conditions there is now no danger of ergotism in civilised countries. The conditions in the Ural district in 1926 were also exceptional; in order to prevent a recurrence of the outbreak the local Soviet issued an ordinance aiming at the enlightenment of the people concerning ergot, the supply of modern machinery for cleaning the grain, the buying up of ergot by the State, and the exchange of ergotised for sound grain. The main difficulty lies in rustic

obstinacy; in order to prove its harmlessness, a peasant near Perm consumed a glass full of ergot; he died next day (Thieme).

Detection and Estimation of Ergot in Flour and in Bread.

The numerous methods may be classified as follows:—

1. Rough preliminary tests, by flotation and by chemical means.
2. More exact chemical methods, depending on the presence of sclererythrin.
3. Spectroscopic methods, also involving sclererythrin.
4. Histological methods, under the microscope.
5. Chemical and pharmacological methods of estimating the alkaloids.
6. Serological methods.

The chemical methods are the oldest, and until 1895 were preferred to the histological, when Gruber emphasised the convenience and delicacy of the latter. With his conclusion most subsequent investigators have agreed: in the case of flour the histological method is several times as delicate as the chemical, and when applied to bread, its superiority is even more evident. The histological method is, moreover, quite effective with small quantities of material, whereas the best results cannot be obtained with the chemical methods unless 10 grm. of flour, or even more, is used. Spectroscopy is troublesome and less delicate than the simpler chemical methods: it is only desirable, when the identity of the red colouring matter is in doubt. On the other hand, Moeller [1928, revised by Griebel] considers the chemical spectroscopic method more delicate than the microscopic.

1. The *flotation methods* depend on the fact that the particles of ergot are lighter than those of rye. By stirring up the flour with acidulated water the darker ergot particles mostly remain on the surface. A better separation is achieved by centrifuging with 6 to 8 parts of chloroform (Wittmack, Spaeth, Thieme). Adwujewski recommended a mixture of 24 parts of chloroform and 7 parts of 95 per cent. alcohol, and after shaking measured the volume of the upper ergot layer; Mitlacher suggested a similar volumetric method. Musset adjusted the density of a

chloroform-alcohol mixture (about 10 : 1) with dry alcohol to 1·435 at the temperature of the experiment and shook 5 grm. of flour with 60 c.c. of this mixture in a cylinder; the upper layer is poured off and the ergot in it can be precipitated by addition of alcohol. *These chloroform methods are chiefly useful in order to concentrate the ergot for microscopic examination.*

The oldest attempts to recognise ergot in flour aimed at the detection of its trimethylamine, or its oil [Wittstein 1852]. A much more suitable constituent is the acidic red colouring matter *sclererythrin*, which occurs in the outer hyphæ of the sclerotium as an insoluble calcium salt. Jakoby [1865] seems to have been the first to utilise this by shaking flour with a tenfold quantity of alcohol containing a little sulphuric acid. The test is generally attributed to Vogl who used 10 c.c. of 70 per cent. alcohol, plus 0·5 c.c. concentrated hydrochloric acid for 2 grm. of flour. The supernatant liquid becomes blood red or flesh coloured, more rapidly at 50°. According to Thieme an ergot content of 1 per cent. can thus be recognised; on standing for twenty-four hours a faint red coloration is given by all flours, even when free from ergot. Vetch seeds (*Vicia*), often present in grain, produce a red colour of a more bluish tinge which interferes. *Agrostemma* seeds produce an orange, and *Melampyrum* seeds a bluish green colour. In doubtful cases the spectroscope is indicated.

2. The *chemical recognition* of ergot is rendered much more certain and delicate by utilising the fact that sclererythrin is extracted from its ethereal solution by sodium bicarbonate, giving a more deeply coloured solution of the sodium salt. Methods based on this property were reviewed by Hilger [1885] who preferred that of Hoffmann, in the following form :—

Ten grm. of flour are kept for six hours with 20 grm. of ether, to which 10 drops of 20 per cent. sulphuric acid have been added; the mixture is frequently shaken. After filtration and washing with ether, until the total filtrate weighs 20 grm., the latter is shaken with 10 to 15 drops of a cold saturated sodium bicarbonate solution. When ergot is present the aqueous layer is coloured purple. According to Hilger the extraction of the colouring matter is facilitated by letting the flour swell with a few drops of 20 per cent. sodium hydroxide before treating with ether (containing rather more acid). Extraction with alkali itself is not suitable, as the alkaline solution is difficult to filter. Schär recommends swelling the flour or bread in a concentrated solution of

chloral hydrate (1½ or 2 parts in 1 part of water) for some hours; after addition of a little water, the colouring matter can be readily extracted by acidified ether.

Hilger and Schär both state that 0·01 per cent. of ergot can be recognised by their respective modifications of the method of Hoffmann who, like Gruber and Thieme, placed the limit at 0·1 per cent. Popoff used this method during the Ural epidemic of 1926 and could detect 0·05 per cent. According to Thieme a similar process is at present widely used in Russia, where chemical methods seem always to have been preferred to the microscopic. Okoloff [1929] concentrates the ergot particles by means of 500 c.c. chloroform + 60 c.c. alcohol (as indicated above under flotation methods), extracts the sclererythrin with ether + sulphuric acid, and then with sodium bicarbonate (according to Hilger); he finally compares the colour with standard carmin solutions in a Walpole comparator, in which methyl orange is used to compensate for the yellow colouring matter of the ergot.

3. The *spectroscopic recognition* of ergot is based on the fact that sclererythrin gives two characteristic absorption bands in the green and a much weaker one in the blue. For detecting ergot in flour these bands were used by C. H. Wolff (their discoverer), by Petri, Uffelmann and Palm, who respectively claimed that 0·25, 0·2, 0·12 and 0·05 per cent. of ergot in flour can be detected. Tichomirow examined the shift of the bands towards the red in alkaline solution. Hartwich and Mjöen employed this method, and Tschirch, who determined the position of the bands more accurately (see chemical section, sclererythrin) states that 7 mgm. of ergot can be detected in alkaline solution and 14 mgm. in acid solution. With a content of 0·01 per cent. of ergot, an extract from 70 grm. of flour would therefore have to be examined. (*Cf.* also Marino-Zuco and Duccini.)

4. The *histological method*, already used by Schmid [1868], Hilger [1885], Möller, Schär and Lehmann, was later preferred to the chemical by Gruber, Spaeth, Thieme and others. Gruber simply distributed a few milligrams of flour in a few drops of water on the slide, put on a cover-slip and momentarily heated to the boiling-point over a flame, in order to gelatinise the starch, which otherwise interferes. The fragments of ergot are characteristically different from any other element in the

flour. They consist of closely-packed hyphæ, resembling polygonal cells of unequal size, 30 to 40 times smaller than those of rye (Fig. 20, p. 87). They are highly refractive on account of their oil content, or the particles may be surrounded by droplets of oil. Particles from the outside of the sclerotium which are of course relatively rare, show in addition a reddish-brown edge, containing sclererythrin. Gruber examined the samples first at a magnification of 100 to 120 and then confirmed the identification at 300 to 400. A rough quantitative estimate may be obtained by comparison with flours of known ergot content. With 0·1 per cent. one or two ergot particles were still found in every preparation, with 0·05 per cent. only in about half of them. This rapid and simple histological method can be rendered more delicate in various ways. Steenbusch used a malt extract to get rid of the starch. Lehmann, Thieme and others apply a method for isolating crude fibre which reduces the material to less than half its original weight. For instance, the flour is boiled for half an hour with 1¼ per cent. sulphuric acid, washed, boiled for the same time with 1¼ per cent. sodium hydroxide, and washed 3 to 5 times by decantation. Such a process leaves the ergot and the cellulose intact, and the residue is examined in water, glycerine, clove oil or chloral hydrate. Another elaboration of Gruber's simple method is to concentrate the ergot by flotation or centrifuging in chloroform, as described above sub. 1. Hilger placed the limit for the simple histological method at 0·01 per cent. of ergot in flour; Gruber and quite recently Thieme put it at 0·05 per cent., but after preparing the crude fibre, Thieme could detect 0·01 to 0·005 per cent., and after centrifuging in chloroform, as little as 0·005 to 0·002 per cent., *i.e.*, with 0·005 per cent. of ergot in the flour, an ergot fragment was still encountered in every microscopic preparation examined. This is the highest degree of refinement achieved in the detection of ergot in flour.

Differential staining has been suggested in order to make the ergot particles more obvious, but this can only make the method more rapid, not more delicate. Petri coloured the starch blue with iodine, which leaves the ergot yellow. It is, however, preferable by far to hydrolyse the starch by diastase or by boiling with dilute acid. Hilger then coloured the rye cellulose blue with iodine and sulphuric acid, which stains

the cell walls of the ergot a yellowish brown, so that 0·01 per cent. of ergot in flour could be recognised quite sharply. Lagerheim recommended staining with alcoholic dimethylamino azobenzene, thionin and safranin, which stains the cellulose violet and the ergot yellow. Wasicky [1913] states that ergot particles are readily recognised under the fluorescence microscope in ultra-violet light; they are reddish in colour, the flour particles being mostly blue.

5. *Estimation of the alkaloids.*—All the methods so far mentioned suffer from the disadvantage that the amount of ergot tissue or of sclererythrin is not proportional to that of the poisonous constituents, the alkaloids. Musset therefore recommended their estimation in the flour.

200 grm. of flour is exposed to ammonia vapour under a bell-jar for two hours, shaken with 200 c.c. of ether and percolated until 250 c.c. are collected, and then another 200 c.c. The first percolate is shaken with 30 c.c. 0.5 per cent. hydrochloric acid, which is then shaken with the second percolate. After making alkaline with ammonia and shaking into ether, then again into acid, and making once more alkaline, the alkaloids are finally shaken into ether. The completeness of the extractions is checked by Mayer's reagent. Half of the final ether extract is tested by Keller's reaction; the other half is extracted with acid, made up to 50 c.c. and treated with 3 drops of Mayer's reagent. If there is only a slight turbidity, less than 0.0002 per cent. of alkaloid is present in the flour, which for an ergot containing 0.1 per cent. of alkaloid, means 0.2 per cent. of this fungus in the sample.

This method is no doubt good in theory, but would require careful manipulation, as even the limit of the very delicate Mayer reaction is approached, which incidentally is about twice as delicate in the case of ergotoxine as in that of ergotinine. When there is only 0·0002 per cent. of alkaloid in the flour, the Keller reaction on half the total will be with 0·2 mgm., or only twice the quantity which can be readily detected in 1 c.c. of acetic acid. The much more intense colour with dimethylamino-benzaldehyde, recently described by van Urk and found by M. I. Smith to be proportional to the physiological activity of ergot extracts, reveals 0·001 mgm. of alkaloid. It develops only under the influence of light and is specific for indole derivatives. Its applicability to ergot in flour would therefore seem to be worthy of investiga-

tion. It might be possible to detect as little as 0·01 per cent. of ergot (itself containing 0·1 per cent. of alkaloid). This is in excess of practical requirements and has the advantage of estimating the constituent which matters. The only doubt is whether in an ergot, which has become inactive by age, the decomposition products of the alkaloids do not also give the reaction. Such a doubt can be resolved by pharmacological means, notably by the method of Broom and Clark (p. 195) which has, however, been applied only in the Manchester epidemic of 1928 (Morgan) when Gaddum detected 0·01 per cent. of alkaloid in the ergot by this method and by the more specific but less accurate vasomotor reversal. Of this ergot about 1 per cent. was present in the meal.

6. *Serological estimation of ergot in flour.*—This was first suggested by Ottolenghi [1903] and was worked out further by Okoloff and Akimoff [1929]. By injecting repeatedly, at intervals of two months, saline extracts of defatted ergot into rabbits, they claim to have reached eventually a titre of 1 : 20,000, so that they could clearly recognise 0·5 per cent. of ergot added to 20 grm. of wheaten flour. They do not appear to have been aware of Ottolenghi's work.

Detection of ergot in bread.—According to Thieme, bread with at least 3 per cent. of ergot can be recognised by its violet colour and by its odour of trimethylamine. Down to 0·5 per cent. the bread is darker than usual, but its ergot content is not obvious. For chemical examination the sample may be dried and powdered. Dextrin interferes to some extent, giving a yellow colour. Vogl's and Hoffmann's tests are positive down to 1 per cent., so that the latter in particular is much less delicate with bread than with flour; the spectroscopic method in the case of bread is quite inadequate. Better results are obtained by suitable histological processes. Gruber's is not suitable because clumps of starch enclose the ergot particles. The starch must be destroyed; after soaking the bread in water for twenty-four hours, it is boiled for a long time with 1 to 1·5 per cent. hydrochloric acid, when the residue may be examined directly, or washed with alcohol and centrifuged. In this way Thieme could show 0·05 per cent. of ergot with certainty, when every microscopic preparation contained several ergot fragments; there was generally still one fragment in each preparation of bread containing 0·02 per cent. of ergot. The microscopic

method is, therefore, quite adequate, especially as the toxicity in bread is reduced to some extent by baking.

Ergot in Forensic Medicine; Detection in the Viscera.

Intentional poisoning with ergot and its preparations is rare; the object is almost always to procure abortion. (For a case of attempted suicide with ergotamine, see p. 179.) The object is rarely attained, which is not surprising in view of the laboratory and clinical experiments with ergot alkaloids and the experience in epidemics (p. 37). A remarkable and exceptional case is recorded by Pouchet [1886]; a French farmer was in the habit of administering a potion to his servant, and so induced three successive abortions; she then had two children and later again three abortions; finally she developed gangrene of the hands and feet and died. In the viscera Pouchet was able to identify sclererythrin spectroscopically and ergot alkaloids by Tanret's colour reaction. The potion itself was not available, so that it is uncertain whether it contained any active constituent besides ergot.

Davidson [1882] described an unsuccessful attempt to procure abortion, which also ended fatally. Doses of liquid extract of ergot were taken for some months, and then in the fifth month of pregnancy two handfuls of ergot powder. Before death the face, eyes, neck and the upper part of the chest were intensely jaundiced; there was an anxious expression, with occasional fits of stupor; the pulse seemed to indicate its presence to the finger and disappeared before its character could be judged, so that counting was impossible. The respiration was 48 per minute and there were 150 cardiac cycles per minute. All these symptoms are typical of acute ergot poisoning, as seen in the older epidemics. The *post-mortem* examination revealed numerous small ruptured blood-vessels and hæmorrhages in the peritoneum, stomach, intestines and lungs. No attempt was made to detect ergot in the viscera.

The most recent case of which I am aware was that described in 1914 by Rosenbloom and Schildecker (who give references to several much older cases). A first attempt at procuring abortion resulted in cyanosis, a rapid pulse and the vomiting of what looked like food remnants; this attempt was mistaken for acute gastritis. Eleven days later, after another attempt

the patient became unconscious, had no control of the bowels, and the urine was suppressed. Clonic convulsions occurred; contraction of the uterus was noted by palpation and also visually. The stools were bloody and contained pieces of intestinal mucous membrane. Nine hours before death the temperature rose to 103° F. The patient died without regaining consciousness. *Post-mortem* the whole gastro-enteric tract was found to be intensely inflamed. The mucous membrane of the small and large intestines was covered with a layer of blood, and the membrane was full of punctate hæmorrhages.

The *detection* of the powdered drug in the intestinal canal can be more or less readily accomplished by the microscope; the gastric juice seems to alter the sclererythrin to some extent, so that a characteristic colour is more difficult to obtain; according to Schär, extraction with very concentrated aqueous chloral hydrate solution (see p. 224) is useful. The recognition of ergot in fæces has been specially studied by Strasburger; a single dose of 1 grm. of ergot powder could be detected microscopically. Marino-Zuco and Duccini were able to recognise 1 grm. of ergot seven days after death by the spectroscope. They extracted the viscera with alcohol containing a little tartaric acid, evaporated the alcohol *completely* in vacuo, shook many times with ether and examined the ethereal extract spectroscopically.

In cases of poisoning by ergot extracts some such method as the last mentioned has to be employed, or an attempt may be made to detect the alkaloids. In the latter Pouchet was successful, as also were Rosenbloom and Schildecker; these authors even obtained pure crystalline ergotinine from the viscera by Dragendorff's method. In order to get experience in the detection of the alkaloid (by colour reactions), Pouchet poisoned a dog with the alcohol-ether extract of 20 grm. of ergot, and obtained colour reactions for ergotinine with the crude alkaloid from the liver, the spleen and the kidneys. Its micro-chemical recognition was also studied by Bolland.

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