diagnosis is easy when the disease is advanced, but it certainly is not easy when the tumour is still well within the parotid gland. This is one of the points to which attention must be directed in future.

Now, gentlemen, I am conscious that this lecture is very defective. It is defective in knowledge of the diseases of which I have been treating and it is defective in knowledge of how to deal with them best by surgery, particularly the malignant diseases; but I chose this subject because every now and again I like to lecture on something which I do not know well, in order to review the subject and to see what new lights it presents, and if I am asked by any one of my past house surgeons or by somebody who is about the hospital to recommend them a piece of special work I am sure that nobody could do better work or work which is more likely to bring credit to himself and to surgery than he who engages in work upon these tumours. Let him take the whole subject up afresh and work from both a clinical and a pathological standpoint. The material in this hospital is very rich. He will find here a most interesting series of tumours, including one melanotic tumour of the parotid and one partly melanotic tumour of the same region. He will find also sections of a certain number of these tumours in the microscope box upstairs, and he will find a much better account of operations and the connexions of the tumour than he would have done years ago, particularly in my own wards, where the notes have been taken with considerable care by my dressers. He can search out patients and can trace them, and he can also use my private notes and drawings of parotid tumours removed in this hospital many years ago when I was surgical registrar. I wish that I could persuade somebody to take this up and to give some months to it. It is worthy of being the subject of a treatise for a degree at one of our universities; but I think it is worthy of something more than that: it might make a very good monograph—a monograph founded, I think, on extraordinarily rich material.

DEVELOPMENTAL (MYELOGENETIC) LOCALISATION OF THE CEREBRAL CORTEX IN THE HUMAN SUBJECT.[1]

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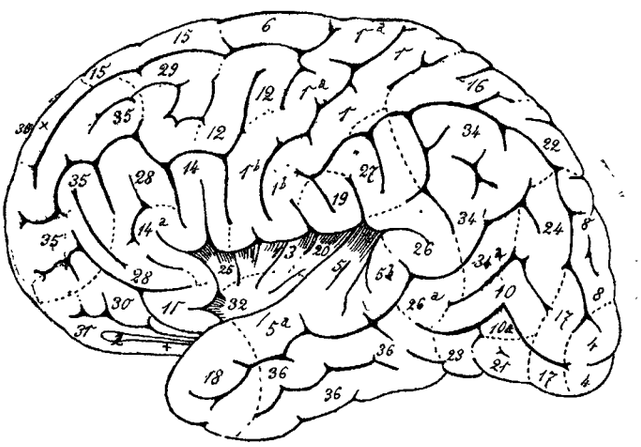
(*Translated for* THE LANCET.)

I.

THE following remarks are founded partly upon researches carried out some time ago and partly upon unpublished new researches undertaken on the human subject exclusively, and therefore of especial value in this respect.

In the cerebral convolutions, as in all other parts of the central nervous system, the nerve-fibres do not develop everywhere simultaneously, but step by step in a definite succession, this order of events being particularly maintained in regard to the appearance of the medullary substance. In the convolutions of the cerebrum the investment with medullary substance (myelinisation) has already begun in some places three months before the maturity of the fœtus, whilst in other places numerous fibres are devoid of medullary substance even three months after birth. The order of succession in the convolutions is governed by a law identical with the law which I have shown holds good for the spinal cord, the medulla oblongata, and the mesocephalon, and which may be stated somewhat in this way—that, speaking approximately, equally important nerve-fibres are developed simultaneously, but those of dissimilar importance are developed one after another in a succession defined by an imperative law (Fundamental Law of Myelogenesis). The formation of medullary substance is almost completed in certain convolutions at a time when in some it is not even begun and in others has made only slight progress, so that the convolutions are divided at certain periods of age into regions which are (1) well provided with medullary substance, (2) scantily provided with medullary substance, and (3) altogether devoid of medullary substance. Thus there come into existence sharply circumscribed areas differing in the stages of development of their elements[2] which I call myelogenetic cortical areas. These fields are constant in arrangement; they repeat themselves in essentially the same position and extent in all individuals of approximately the same age. The contours do not change perpetually with the progress of the medullary investment, but show during a certain period the same type, a fact which obviously depends upon the general character of the myelogenetic differences. It has been said (1) that the formation of medullary substance spreads from certain points in the cortex—to some extent in concentric rings—over the surface (Vogt), or that the order of succession in which the nerve-fibres receive medullary substance is in relation to the diameter of the fibres (Vogt), or (3) that this order of succession is in relation to the position of the blood-vessels (von Monakow). These opinions, however, are generalisations from accidental phenomena, and when treated as a whole they are found to be ill-supported and totally useless from a scientific point of view. (Fig. 1 and Fig. 2.)

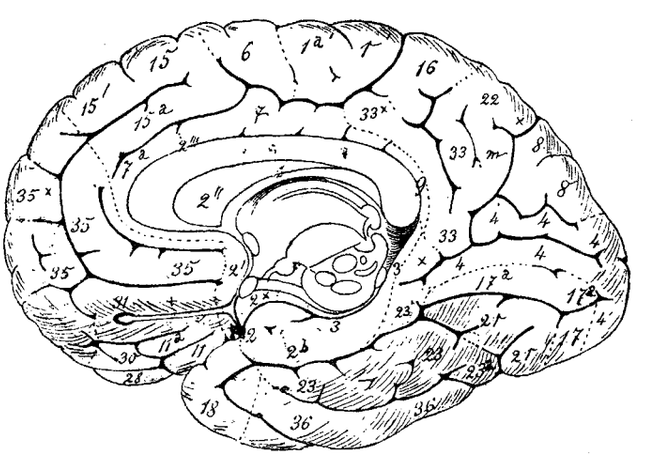
FIG. 1.



Cortical areas on the external surface of a cerebral hemisphere.

In my first memoir on the subject[3] I estimated the number of the myelogenetic cortical areas at 40. Further researches have shown that some of these must be combined into one, so that I at present distinguish only 36.[4] I find

FIG. 2.



Cortical areas on the internal surface of a cerebral hemisphere.

[1] A paper read at the International Congress of Physiology at Turin. Owing to the operation of a time limit in the delivery of the address some passages here shown had to be omitted from the paper as originally written.

[2] The protoplasmic processes of the ganglion cells are also formed in different areas at different times. This is another instance of periods of time arranged in conformity with a natural law.

[3] 1898. Neurologisches Centralblatt, No. 21.

[4] In my report to the Paris Congress held in 1900 I pointed out that the number 40 must be taken as a provisional estimate. The diagrams of my cortical areas which Hitzig gave in the Comptes Rendus of the Section for Neurology (Pl. II.) are useless. They are neither copies of my drawings of 1898 (for here the areas nowhere show contours) nor of any other illustrations whatever that have been published by me. They are simply of the nature of misconceptions, enlarged reproductions of private communications (rough sketches) which being incomplete were not intended for publication and which in the form given to them by Hitzig can only lead to confusion.

it useful to denote the areas simply by numbers (1 to 36) corresponding to their respective places in order of development, and therefore wholly chronological. In order to present a comprehensive view, and having regard to differences of a general nature, I have classified them in the three following chronological groups: (1) regions of early development (primordial zones); (2) regions of intermediate development (intermediary zones); and (3) regions of late development (terminal zones).

As the process of myelinisation presents no distinct intervals, the fixing of the limits of these groups is to some extent a matter of individual opinion; there are not as yet any definite landmarks to go upon. In my first memoir I assigned to Group 1 the areas which showed a comparative preponderance of medullary substance at birth at full term—i.e., the areas numbered 1 to 8. Further investigations have convinced me that as a rule the number of areas in which myeline formation has at least commenced before birth at full time is greater than this, including as a maximum the areas as far as No. 20, but sometimes only those as far as No. 12. The extent to which the medullary substance has spread at the time of full development of the fœtus is therefore not available in all cases as a principle of classification. Nevertheless, the areas numbered from 1 to 10 have this in common, that in full-term fœtuses the formation of medullary substance has, as a rule, not only begun in these areas but has advanced so far that it is perceptible to the naked eye. I accordingly reckon Group 2 from area No. 11 onwards. Under Group 3 I some time ago included those areas in which the formation of medullary substance (birth at full time being taken for granted) does not begin until after the completion of the first month of the child's age. This applies, as a rule, to the areas numbered from 32 to 36, occasionally, also, to No. 31; but this last-mentioned area appears to me to present individual variations of a special kind.

II.

The general significance of the myelogenetic localisation of the cortex may be put into words as follows. Every area possesses a special anatomical position and, therefore, also a special functional importance. For a great number of the areas this can now be absolutely proved. [The objection that the recognition of 36 different "organs" in the cortex means a falling-back to the phrenology of Gall, and other objections of a like kind, may be met by a simple reference to the fact that it was the myelogenetic parcelling-out of the surface of the brain which for the first time provided tangible and comprehensive anatomical data for the scientific solution of the questions involved, and which revealed points of difference that had not up to that time been even suspected.] The average size of a cortical area (about 20 square centimetres = three and a quarter square inches) is very considerable when compared to the much smaller dimensions of the medulla oblongata with its many centres.

Anatomically, the areas forming Group 1 (primordial zones) are distinguished above all by their great richness in projection fibres (fibres leading to and from sub-cortical centres). This group contains the points of entrance of all the channels conveying sensory impressions to the cortex. Every sensory peripheral end-organ has corresponding to it in the cortex a well-defined region of early development (primordial zone)—the cortical sensory centre or sensory area. Area No. 2 is the olfactory centre, No. 4 is the visual centre, No. 5 is the acoustic (cochlearis) centre, and so on. From pathological and other phenomena area No. 1 may be regarded as the end-organ, especially of the posterior columns of the spinal cord and consequently of the posterior roots; the nerves of the skin and muscles seem to be represented here side by side. For many primordial zones (as for instance the gyrus subangularis No. 10) it is for the present unknown whether they are in relation with any peripheral end-organ at all.

The individual sensory areas are separated from one another by wide tracts of cortex (intermediary and terminal zones) in which sensory fibres cannot be followed up. Moreover, the known motor fibres originate in and immediately beside the regions of early development (primordial zones), such as the pyramidal tract in No. 1, the motor part of the inferior fornix in Nos. 2 and 3, the inner fasciculi of the ventral part of the cerebral peduncle (pes or basis or crusta pedunculi) in Nos. 1*b*, 6, 12, 14, and 15. Only with respect to the external fifth of the pes pedunculi (column of Türk) is there a controversy as to the cortical regions of origin (Nos. 5 and 36). From No. 4 a set of fibres can be followed (in secondary degenerations and in newly-born infants) up to the central medullary substance of the anterior corpora quadrigemina; these fibres are lost in the "secondary" visual radiation (Flechsig). Therefore to every sensory path there corresponds a motor (corticofugal) tract. One may speak, therefore, of conjugate tracts or columns (Strangpaaren). With regard to their position within the corona radiata, they in general follow the law that corticopetal lines of communication are placed laterally with respect to the centrifugal ones.

In the primordial zones the corticopetal and corticofugal fibres do not mingle uniformly. It may be specially remarked with reference to No. 1 that the tactile radiation passes over for the most part into the posterior central ascending parietal convolution and only with a few fibres into the anterior central, whilst the undoubtedly motor pyramidal tract originates to a great extent from the anterior central ascending frontal convolution and to a less extent from the posterior one. Area No. 1 is therefore composed of a preponderating sensory and a preponderating motor division. A purely sensory or a purely motor area cannot be outlined anywhere. The auditory sphere (No. 5) to which fibres lead from the internal corpus geniculatum and thalamus, which may be denoted as the auditory radiation (and eventually as the cochlearis radiation)[5] according to my researches (in cases of secondary degeneration), sends fibres into the column of Türk—fibres which to all appearance terminate in the pons and convey corticofugal impressions. Whether they are to be considered as motor fibres is not quite decided. To all appearance their origin projects somewhat beyond the region of the auditory radiation and extends also to the part of the second temporal convolution hidden in the first temporal furrow; it is therefore a cortical region immediately adjacent to the auditory sphere. It is very questionable whether the convex part of the second and third temporal convolutions belong to this zone. In the cortex they lose the arrangement of the fibres which is characteristic of motor regions, whilst this type is very prominent in the auditory sphere and immediately beside it in the second temporal convolution. Therefore in the event of the columns of Türk fulfilling motor functions (motions of the body and head in consequence of auditory impressions?), it will have to be admitted with respect to the auditory sphere that here a motor and sensory area are united in such a way that they partly coincide and partly perhaps do not coincide. Here, as in the cortex generally, an entirely motor or entirely sensory area is not recognisable.

In the regions of late development and in most of those of intermediate development the corona radiata is not represented. The projection fibres therefore undoubtedly diminish in number here in comparison with the primordial zones. This is the case not only in newly-born children, but also in children of the age of four, five, seven, and eight months. It has been said that the scanty occurrence or complete absence of the projection system in the cortical areas of late development is quite an illusion, and that the corona radiata appears here only at a later stage, but this objection has little to support it. At no period of age do I find clearly differentiated fasciculi of the corona radiata. Some projection fibres may be recognised in the intermediary zones and occasionally also in the terminal zones, but they sink into insignificance in presence of fibres of a different kind.

The normal adult brain presents conditions too complicated to permit of positive opinions being arrived at. But two of the most important *projection* systems (the fasciculus longitudinalis inferior and the cingulum) have been declared to be *association* systems, and the descriptions of the brain in the most recent articles by von Monakow, Déjerine, and others propagate these quite incomprehensible errors as if they were established facts. Nowhere in adults do I find fasciculi of the corona radiata which might not occur in children aged three and a half months, the children having been born at full time. In them the extension of the corona radiata can be clearly seen, and it is plain that the convolutions which contain abundance of projection fasciculi have others opposite to them in which it is hardly possible to find one such fasciculus.

It is also a complete mistake to assert that secondary

[5] The position of the vestibularis conducting fibres in the corona radiata is not yet determined; indeed it is by no means proved that the semicircular canals are in connexion with the cortex of the cerebrum although it is extremely probable.

degenerations in the adult human subject prove the contrary. If everything that has hitherto been published in support of this view is brought together it will be found that not even half a dozen cases are recorded which supply incontestable data, and of these the majority are referable to two areas, No. 1 and No. 4. For the other areas neither von Monakow nor Déjerine has quoted cases which could really decide the question in terms of the corona radiata. I wish here to make this statement only for the last three terminal zones, since Déjerine has said that he has specially investigated uncomplicated cortical lesions, even quite superficial ones, of these regions, and has always found fasciculi of the corona radiata in a state of secondary degeneration. But taking the case of area No. 36, in the alleged uncomplicated lesions of this area there is always accompanying derangement of either the first temporal convolution (acoustic sphere) or of the visual radiation. With regard to area No. 35, Déjerine describes what he calls an uncomplicated superficial lesion and deserves our thanks for having given a drawing which enables an idea to be formed of its extension in the direction of depth. From this it is evident that in reality the primary softening of the first and second frontal convolutions has not only reached the corona radiata of the gyrus fornicatus traversing the frontal medullary substance but has partially disorganised it, and it is anything but surprising that secondary degeneration of the anterior pedicle of the optic thalamus should be transmitted in the thalamus to regions the connexion of which with the gyrus fornicatus can be recognised from a study of the history of their development. How little all these drawings prove is abundantly plain from the fact that in the same case an identical degeneration is found in the optic thalamus on the opposite side, but is here due to a focus of disease "in the third frontal convolution."

Finally, the case of superficial disorganisation of the gyrus angularis (area No. 34), a lesion which is in this instance alleged to be uncomplicated, is in reality not concerned with this convolution exclusively, for areas No. 26, No. 27, and No. 5*a* are also disorganised. Neither is the softening limited to the cortex; on the contrary, it has penetrated to the optic radiation (corona radiata), so that on every sound principle there is no reason for bringing the secondary degeneration found in the corona radiata and optic thalamus specially into relation with the degeneration of the cortex of area No. 34.

Moreover, the cases of foci of subcortical softening, which have served for investigations of secondary degeneration in the corona radiata, entirely fail to support the opinion that the terminal zones No. 34 and No. 35 are provided with a corona radiata. In a case described by von Monakow, in which there was a focus of softening in the thalamus opticus with fibres of the corona radiata in an alleged state of secondary degeneration present in the whole of the upper part of the cerebrum, not only was the examination made by a quite inadequate method (the use of carmine) but the case was, moreover, so greatly complicated by the occurrence of numerous miliary foci in the parieto-occipital lobe that definite conclusions seem to be impossible. Everyone who has been to some extent engaged in the investigation of miliary foci of softening knows that secondary degenerations may proceed from each one of them. The account of the finding of degenerated fibres (and cells) in area No. 34 (?) given by von Monakow says nothing as to the origin of these fibres. In like manner a case recently described by Proft (discovery of Marchi's strata in all three frontal convolutions, &c., in a case of hæmorrhage in the thalamus) is so ambiguous that it cannot serve as a proof of the presence of a corona radiata in area No. 35. For instance, in it both pyramids showed degeneration. If Proft's interpretation is accepted it would therefore have also to be inferred from this observation that both pyramids of the medulla oblongata are in relation with the thalamus opticus of the right side—a thing which is most improbable.

In the present state of knowledge on the subject of secondary degenerations I think that it is extremely unscientific to attempt to infer that "the pathological method" has absolutely proved that all the convolutions of the cerebrum are equally provided with a corona radiata. In conclusion I ask, Why is there no doubt as to the central convolutions and the visual sphere possessing an exceedingly effective corona radiata? Why cannot it be demonstrated in the terminal zones?

III.

Clinical observations of the symptoms produced by lesions of various cortical areas give results which agree very satisfactorily with those obtained by a study of the developmental conditions of those areas. Disorders of the motor and sensory functions are observed only in lesions of the primordial zones. The motor zone delimited by Charcot coincides with area No. 1; the zone defined by Henschen (the most reliable worker in this field), lesions of which always interfere with vision, coincides with No. 4, and so on. Of localised symptoms which occur in lesions of the intermediary and terminal zones the only known forms are some that involve (1) interference with speech (alexia, optic aphasia, sensory amnesic aphasia, &c.), and (2) partial amnesia (optic, for example). The time to localise these symptoms more definitely has not yet arrived. The question will ultimately reduce itself to this—whether the structures concerned in these obviously preponderating association disorders are the intermediary and terminal cortical zones (i.e., their ganglion cells), or are only deep-seated association systems (i.e., nerve-fibres), as Wernicke and others suppose. I consider it, however, to be extremely unsettled, and it will be impossible to come to a satisfactory decision without a more intimate acquaintance with the whole mechanism of association—namely, of the nerve-fibres and the connexions which they form between the different areas.

From my observations on the child I am led to believe that the opinions which have hitherto been held regarding this mechanism are erroneous, at least so far as concerns the so-called long association system. The fibræ arcuatæ which unite every two neighbouring convolutions are found between all the areas which immediately adjoin one another. Areas which lie further apart are united by long tracts, and it is to be observed that their anatomy is as yet incomplete in the highest degree. All the areas with long tracts are by no means in effective connexion. The areas differ with respect to the corona radiata and they also differ in a most extraordinary manner with respect to the long association systems. The terminal zones are the richest in them; they are the endings of the long association systems. On the other hand, no long association system is known which connects two primordial zones that are to be regarded as sensory centres. The fasciculus longitudinalis inferior, which is always quoted as an example of this, is in actual fact a projection system, the real optic radiation, the line of transmission of optic stimuli from the external corpus geniculatum to the visual centre in the cortex, and this can be demonstrated in the newly-born so conclusively that all objections to it must fail. If a visual and an auditory impression meet one another anywhere in the cortex of the cerebrum, this can only happen through the instrumentality of the intermediary and terminal zones. If the mutual interference of the stimuli is a preliminary condition of the association of their mnemonic impressions, the cortex of the intermediary and the terminal zones will be indispensable for this purpose also. They are therefore association centres; and this view is strongly confirmed by the clinical observation that in lesions of the region lying between the visual and tactile spheres it is association troubles that occur, the best known of which is sensory alexia.

The objections which have been raised against these views on the grounds of comparative anatomy, experimental observation, and the study of the successive phases of development are not very weighty. If the development of the medullary substance is studied in the lower animals it must not be forgotten that they are without exception much less favourable for the purpose than the human subject is. Here it is a fact of primary importance that in the lower animals the process passes through its stages much more quickly than in man—in the cat, for instance, in about one-fifth of the time. All the phases of the development are brought much closer together. The number of the areas in the cortex is considerably less (in the dog Dr. Döllken could hardly reckon 20), and the size of the areas of late development is much greater in the human subject than in the lower mammals, so that in the human subject not only do all the points of difference continue unchanged over far larger spaces of time, but they also take much clearer and more distinct shape. The fundamental laws of development come better into view in the human subject, in like manner to the degree in which the human intellect excels that of the lower animals.

ON THE PROTECTIVE SUBSTANCES OF IMMUNE SERA.

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PRELIMINARY COMMUNICATION.

THE experiments on which the following arguments are based were made originally in the Bacteriological Institute at Berne during the early months of the present year.

1. If the M. L. D. (minimum lethal dose) of a given bacterial culture be determined and the dose of immune serum necessary to protect against this M. L. D. be called its serum equivalent, it has been observed that if an animal be now given two M. L. D. and two serum equivalents it is not protected but dies from the infection. This has been explained as due to a deficiency of addiment in the animal concerned, but in reality it is only due to a deficiency in the amount of immune body given in the immune serum.

For if d be the M. L. D. and e the largest dose of the bacterium found not fatal, s the dose of serum necessary for protection in the first experiment with one M. L. D., it follows that since the animal can itself protect against a dose of e the serum s was protecting only against $(d-e)$ of the bacterium when one M. L. D. was given. When, therefore, we proceed to give two M. L. D. we require serum protection against a dose of $2d-e$ and this requires $\frac{2d-e}{d-e}s$ of the serum. Similarly three M. L. D. require $\frac{3d-e}{d-e}s$ serum and four M. L. D. require $\frac{4d-e}{d-e}s$ serum. Experimentally, if serum be given according to this formula the animals are found with the bacillus used—the bacillus typhosus—to be completely protected up to and including the fourth M. L. D., and only after this point is passed does a deficiency of addiment appear, as may be seen below, where the serum-equivalent of one M. L. D. is called the serum unit, d being 0·075 of a given culture, e 0·05 of the same culture, and s 0·025 cubic centimetre of immune serum per 100 grammes of guinea-pig.

Guinea-pig	1,	given	1	M.L.D. and	1	serum unit;	recovered.
,,	2,	,,	1	,,	½	,, ,,	died in 16–18 hours.
,,	3,	,,	2	,,	4	units;	recovered.
,,	4,	,,	2	,,	3	,, ,,	died in 18 hours.
,,	5,	,,	3	,,	7	,, ,,	recovered.
,,	6,	,,	3	,,	6	,, ,,	died in 14–16 hours.
,,	7,	,,	4	,,	10	,, ,,	recovered.
,,	8,	,,	4	,,	9	,, ,,	died in 18–20 hours.
,,	9,	,,	5	,,	13	,, ,,	died in 14 hours.
,,	10,	,,	5	,,	12	,, ,,	,, ,,
,,	11,	,,	6	,,	16	,, ,,	,, ,,
,,	12,	,,	6	,,	15	,, ,,	,, ,,

In another series of experiments made in Oxford with a more virulent variety of the bacillus typhosus the deficiency of addiment appeared at the fourth M. L. D. In working with the immune sera it is therefore necessary to employ the formula above arrived at in order to determine accurately the amount of serum which contains the quantity of immune body required for any given multiple of the M. L. D. of the bacterium concerned.

2. On the observed deficiency of addiment in experiments with multiples of the M. L. D. of a bacterium Professor Ehrlich founds a theory of the specialism of the addiment to the species of animal in question. He holds than an animal can only make use of its own addiment or of that of others of its own species, and hence endeavours to explain the fact that immune serum does not supply the lack of addiment observed. But this view is out of harmony with the experimental facts. Thus Wassermann found the addiment of fresh ox serum satisfactory to guinea-pigs and to the immune serum of dogs which was used for their protection. Ehrlich and Morgenroth have observed similar relations in their work upon the hæmolysins. The following experiments further show that the deficiency of addiment can be supplied for guinea-pigs treated against typhoid fever with immune serum of the horse by the fresh serum of the ox, the rabbit, and the pig:—

No. of guinea-pig.	Received			Result.
	M.L.D.	Serum units.	Fresh serum.	
1	10	28	—	Died within 16 hours.
2	,,	,,	Rabbit's, 1 c.c.	,, ,, ,,
3	,,	,,	,, 2 c.c.	Recovered.
4	,,	,,	Ox's, 1 c.c.	Died in from 20 to 24 hours.
5	,,	,,	,, 2 c.c.	Recovered.
6	,,	,,	Pig's, 1 c.c.	Died in from 26 to 28 hours.
7	,,	,,	,, 2 c.c.	Recovered.

Hence freshly won serum of the three different animals examined can supply the lacking addiment for guinea-pigs. The same may probably be true of other normal sera. I therefore claim that addiment is not so special to the species as Professor Ehrlich thought.

But if the sera of these animals were kept for a few days in the ice-chest they were found to lose their power of addimentary action; that is to say, their addiment disappeared and guinea-pigs which received the same and even much larger doses of the normal sera than in the above experiments were no longer protected. Further, the addiment of the fresh-won sera was found to be destroyed by their exposure to a temperature of 53° C. during an hour. On both these grounds it follows that the addiment of the bacteriolytic action here in question is extremely labile, being destroyed by a temperature of 53° C. and disappearing naturally from separated serum with considerable rapidity. And I conclude, that the reason why immune serum which supplies immune body fails to yield addiment to the infected animal is that the latter, owing to its extreme lability, is altogether absent from stored immune serum, and not that owing to its specialism it is unavailable by a species different from that of the animal which supplies the immune serum.

3. Coming next to the question of what addiment consists we have the following facts. Anti-microbic sera have *in vitro* no bacteriolytic action—they contain immune body but addiment is absent. They may be rendered active by cellular action, as, for example, by a sojourn in the peritoneal cavity of a guinea-pig. The activity thus obtained is destroyed by heating to 56° C.—destruction of addiment. It is restored by the addition of normal serum (Bordet) or of leucocytic fluids (Hahn). Moreover, an inactive immune serum which has not been subjected to the action of the peritoneal surroundings can similarly be rendered active by the addition of leucocytic fluids (Bordet's phenomenon) and a definite relation exists between the mass of the leucocytes added and the degree of bactericidal power obtained (Bordet). Again, a bacteriolytic pleural exudate has been made entirely inactive by the removal of its leucocytes, active again on their replacement (Denys and Havet). Further, it has been shown above that addiment is present in fresh normal sera from which it disappears on heating to a temperature of 53° C., or simply by keeping, and it was also found to be obtainable in other experiments from the fresh blood-clot of the animals already mentioned. It follows that the addimentary ferment is definitely associated with the leucocytes and is not a ferment circulating freely in the blood-plasma, as Ehrlich teaches. The leucocytes possess addiment even *in vitro* and can supply it to a serum from which it was previously altogether absent; and the addiment contained in the fresh sera is merely such as is set free by the destruction and breaking up of leucocytes.

4. It has been stated by von Dungern that the addiment is not increased in quantity during immunisation. If this were so it would imply that the newly-formed leucocytes of the leucocytosis, which admittedly occurs, are deficient in their characteristic and essential ferment; and this is almost inconceivable. Moreover, if new addiment is not formed it should be found impossible to immunise an animal to withstand a larger dose of the infective agent than that number of M. L. D. at which deficiency of addiment appears in unimmunised animals—e.g., in these experiments four M. L. D. of bacillus typhosus; and this is evidently not the case. Experiments, however, have shown that long after deficiency of addiment has become evident it remains possible, by giving