in other cellular structures. The nucleo-albumin is capable of preparation by either method. There is also the proteid present which coagulates at 47° to 50°. In connection with the spleen there are other points of interest to be noted. My predecessor in this lectureship, my friend Dr. Sidney Martin, stated that in certain infective diseases the spleen is a centre for the accumulation of the proteid poisons, the albumoses that cause the characteristic symptoms of diphtheria, tetanus, and so forth. Almost simultaneously with Dr. Martin's lectures, v. Jaksch⁵ stated that normal spleen is rich in "peptone." The word peptone as used includes propeptone (proteoses or albumoses). The proteoses Dr. Martin obtained from spleens in cases of disease had certain specific actions; it nevertheless appeared important to investigate the physiological action of those obtainable from normal spleens. This task has been considerably lightened by finding that the fresh spleen, like other organs and tissues, contains no peptones or proteoses at all. We have used the same methods as those adopted by v. Jaksch, except that we have taken care that the spleens were perfectly fresh and from healthy animals. Dr. Martin has been good enough to supply us with some he has had the opportunity of obtaining. If spleens are obtained from the butcher's, a small quantity of proteose is usually obtainable; but this is doubtless, as I have already stated, formed *post mortem* from the splenic cells and leucocytes.

The Thyroid.—This organ has also been investigated by Dr. Gourlay, and his general results are practically identical with those just mentioned. There is, however, this point about the thyroid: is it possible that the colloid matter in the vesicles is a nucleo-albumin, or the source of the very active nucleo-albumin which is obtainable from this organ? Here micro-chemistry, in the shape of the phosphorus reaction introduced by Lillienfeld and Monti, has come to the rescue.

We tested the method in some preliminary experiments with sections of thymus. We found the cells, and especially their nuclei, stained a brown colour; the corpuscles of Hassall were more deeply pigmented than the rest; the circumferential regions of the alveoli were more deeply stained than their interior. The muscular coats of the small vessels also stood out very prominently. Having in this way convinced ourselves of the applicability of the new method, we proceeded to a similar investigation of the thyroid. We found that the colloid matter stains as deeply as the cells, and thus it is probably a nucleo-albumin. The coloration is not due to lecithin, as the reaction is obtained after treatment of the sections with alcohol. This view is confirmed by the fact that we have been unable to get a reducing sugar by treating thyroids with sulphuric acid. The thyroid is an organ which is just now attracting much attention, and we can only hope that these investigations may throw some light on the question to which of its constituents is the wonderful curative effect of thyroid juice due?

Muscle.—This tissue has been taken up by Mr. Whitfield, Medical Registrar, King's College Hospital. He has especially investigated the question whether this tissue contains nucleo-albumin; his work is not yet complete, but I may mention that hitherto he has obtained only negative results.

PRACTICAL BEARINGS.

The practical importance of investigations on cell protoplasm seems to me chiefly to lie in the fact that it is impossible to understand the phenomena of phagocytosis and chemiotaxis until we know the chemical composition of cells. Another path into which they lead is the question of the protective proteids, and immunity generally. The alexins or protective proteids are related to if not identical with cell-globulin β (now shown to be a nucleo-albumin), and this line of research has been followed with valuable results by Hankin, Buchner, and others. But they have led me into another channel, namely, into a renewed investigation of the question of blood coagulation, and it is this subject that I propose to take up in my third lecture.

THE MILROY LECTURES

ON

CHANGES OF TYPE IN EPIDEMIC DISEASES.

Delivered at the Royal College of Physicians.

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LECTURE IV.

Accumulation of Susceptible Persons.—Varying Susceptibility of Individuals and of Classes.—Limits of Attenuation.—Unperceived Attacks.—Acclimatisation.—Inter-epidemic Conditions.—Difficulty of Measuring Influence of External Conditions.—Summary.

AMONG the influences which promote or check the growth of an epidemic are those which bring about accumulation or lessening of the susceptible units in the population. This accumulation varies in meaning. As regards malarial fevers, it simply implies that a number of persons susceptible to

malaria of a given degree of intensity are placed within range of the miasma. Proximity of person to person has no apparent importance in itself. In the next group, including diphtheria and erysipelas, concentration of susceptible persons becomes significant, as well as their individual exposure to infection. Not only may they become infected one from another, as well as from non-living media in which the contagium is able to exist, but if their proximity be sufficiently close, in school or in hospital for example, it seems that the poison may become intensified, increasing in virulence as well as in quantity. In diseases of more stable type, such as small-pox and measles, the effect of accumulation is again simple. It is a matter of greater or less facility of transmitting infection from A to B. But at every point other controlling conditions are in operation. The sufficiency of accumulation is dependent upon the constantly changing seasonal or "accidental" conditions of weather, upon school influences and other social factors, and upon intentional or unintentional precautions in the way of isolation of the sick. Moreover, the power of the contagium to overcome obstructions to its diffusion may be variable in its different phases of intensity. And lastly susceptibility is a relative term, not constant in itself as regards either individuals or populations, and dependent further upon the potency of the contagium. Susceptibility to a severe epidemic type does not necessarily imply any susceptibility to a milder phase of the same disease, nor is it constant in a given person under different conditions or at different ages. In small-pox, for instance, there are all degrees of susceptibility, from complete absence of natural or acquired immunity, down to a vanishing point among those who have recently been vaccinated, or who have recently recovered from small-pox. The different classes are exposed to the same infection, and it is found that as the protection (measured in terms of more or less vaccination more or less recent) diminishes, so does the liability to attack increase, and with the liability to attack the average severity of attack. Notwithstanding the assumed constancy of type, we find mild and fatal attacks side by side and infected one from the other. The mild case is mild, not because of any attenuation of the virus, but because the resistance is great, and, so far as small-pox is concerned, it seems to make little difference in the character of attack, whether the infection be derived from a slight or severe previous case. The epidemic type is masked, but not altered, by the resistance of the individual. This can scarcely be affirmed as regards diseases of mobile type, such as diphtheria, and it is doubtful whether it is so in scarlet fever.

It is not always a simple matter to determine the relative susceptibility of different classes of persons, for example, the two sexes. Mortality returns show that while most zymotic diseases kill more males than females, the balance is reversed in diphtheria and whooping-cough. The conclusions naturally suggested by these data are somewhat modified by the observation that the attack rate by no means necessarily corresponds to the death-rate if calculated for the two sexes separately:

Metropolitan Asylums Board Hospitals, 1871-91.

		Cases.	Deaths.	Case Mortality.
Scarlet Fever	Males	19,887	2,051	10.3
"	Females	22,224	1,982	8.9
Enteric Fever	Males	4,041	676	16.7
"	Females	3,674	662	17.3
Typhus	Males	964	216	22.4
"	Females	1,175	217	18.5
Diphtheria	Males	1,360	478	35.2
(1888-91) "	Females	1,715	555	32.4

Scarlet fever, diphtheria, and typhus attack more females than males, but the case mortality is higher among the latter; and, conversely, enteric fever shows a heavier incidence upon males, coupled with a lower case mortality. In each instance the greater incidence is associated with the lesser fatality. This raises a suspicion of unequal facilities for infection, of "superadded waves," and more detailed information is needed before the true relation of sex to these diseases can be finally established. To take another example. In scarlet fever the greatest incidence of attack is in the fifth year of life, but the greatest case mortality is in the second year. Possibly the difference may prove to be due to some unequal exposure to infection, which, up to 5 years of age,

⁵ *Zeit physiol. Chem.*, xvi, 243.

brings about a greater and greater liability to attack, notwithstanding a lessening susceptibility. After the fifth year it may be supposed the increasing exposure is no longer able to counteract the still increasing immunity, and the incidence of attack grows less year by year.

Whether from high resistance as in small-pox, or from low infectiveness as in diseases of inconstant type, attacks occur which are so slight as to be scarcely recognisable. Such, for example, are the slight forms of small-pox, with, perhaps, only one or two doubtful papules; and the slight forms of diphtheria which are indistinguishable from simple sore throat, and which are only diagnosed on giving rise to diphtheria in others, or on being followed by paralytic sequelæ. Such, too, are the slight cases of typhus which pass for "febricula" or "simple continued fever;" and the slight cases of scarlet fever in which there is only a little sore throat, perhaps only a faint rash, perhaps only slight desquamation without any rash having been observed. It is open to doubt whether the limits of possibility in the way of modification have ever then been reached. Since there are gradations of severity of attack down to those which are recognised with difficulty and by indirect evidence, it becomes a question whether there may not be a continuance of the gradation below the clinical horizon altogether. A hint to this effect is given by the excessive fatality of bronchitis and pneumonia at times when measles, whooping-cough, or influenza have been epidemic; of kidney diseases after scarlet fever epidemics, and the like. Many of the deaths so recorded doubtless follow upon well-marked attacks of the antecedent zymotic, but this can scarcely be the case with all.

The "shadow wave" usually accompanies or follows closely upon the zymotic wave. The death certificates in the majority of instances would not omit a reference to a known attack, say of measles, occurring within a few weeks of the fatal issue of a case of bronchitis, especially as (by hypothesis) the complication which causes death is the direct outcome of the zymotic disease. If both measles and bronchitis were mentioned on the certificate the death would be credited to the former and not the latter, preference being given to the zymotic in accordance with general rule. It would seem, therefore, that if the increased mortality attributed to respiratory disease, which accompanies and follows epidemics of measles, be really due to measles, the antecedent attacks of measles must not only escape mention in the certificate, but must as a rule have escaped notice altogether. The number of deaths attributed to kidney diseases at ages under ten years rise and fall with the scarlet fever death-rate year by year, and must therefore follow closely upon the antecedent scarlet fever, since the latter reaches its seasonal maximum in late autumn. Had the secondary curve attained its maximum in the following year, it might have been supposed that the absence of mention of scarlet fever in the certificates was due to lapse of time.

During an epidemic of influenza the general death-rate increases greatly, and particularly the mortality from phthisis, respiratory diseases, and heart disease. Indeed, the Registrar-General infers that in January, 1890, the deaths directly attributed to influenza were only about a sixth of those actually caused by it.

Unperceived attacks may also contribute to the explanation of the immunity from certain diseases conferred by residence in localities where they are endemic. Acclimatisation seems to be almost limited to diseases of the mobile class, which are only slightly protective; long and continuous residence in a malarious region confers some immunity, which is lessened or lost in case of temporary removal to a non-malarious country. This seems to imply a necessity for constant renewal, and to negative the alternative view that the immunity is simply the expression of a natural insusceptibility, demonstrated rather than caused by the previous exposure to malaria. Something of the nature of a constantly repeated slight infection suggests itself as a possible explanation of the temporary immunity; and also of the fact that changes in the internal organs may be found in persons who have escaped any known attack. It has been observed, too, that in districts where enteric fever is endemic, its incidence is disproportionately great upon newcomers, older residents escaping more easily. Young troops newly quartered in certain Indian stations have been found to suffer much more

heavily from enteric fever than their seniors, while natives are affected least of all. As regards influenza, there is room for suspicion of acclimatisation in another sense, although the uncertainty as to the identity of the affections so named precludes any very definite conclusions. The well known instances of St. Kilda and Whaurekauei¹ lend themselves to such an explanation. These are small insular communities, far removed from ordinary traffic, and it is recorded that the arrival of strangers is almost always followed by the rapid diffusion of a catarrhal illness among the inhabitants, no matter whether the newcomers are or are not suffering from any catarrhal or other symptoms.

Assuming the malady to be the same time after time, it would seem not to be lastingly protective, since the outbreak is repeated upon each new arrival; nor is it capable of establishing itself upon a permanent footing. It seems clear, too, that the islanders are more susceptible than the visitors. If it be granted that among the many kinds of cold, catarrh, and febricula which are prevalent in all large communities there are some which are infectious and slightly protective, and readily capable, moreover, of attenuation and intensification, the exaggerated susceptibility of secluded islanders is not difficult to explain. The strangers are "acclimatised" to the disease they bring, but the islanders are not.

Among diseases of fixed type the interval between epidemics may be bridged over by sporadic cases, or the disease may disappear altogether and await reintroduction. There are other possibilities as regards the opposite group. Some of them may lurk in outside media for periods to which it is difficult to assign any limit; or the continuity may be eked out by attacks in lower animals. Further than this, the disease may assume and retain a mild type, so mild it may be as to escape recognition. The modified attacks which are easily identified when they occur in association with severer forms during an epidemic are less so when they occur alone. Diphtheria, erysipelas, influenza, and pneumonia have already been referred to in this connection. Murchison says of typhus: "It is probable that many cases of so-called febricula, where the fever only lasts for two or three days and is not attended by rash, occasionally result from a small dose of the typhus poison; at all events cases answering to this description sometimes occur in the same family, and at the same time as true typhus." Occasionally in crowded manufacturing towns and villages we meet with typhus outbreaks which at the present day we cannot suppose to have arisen *de novo*, but which seem to have had their beginnings in cases of illness, which, apart from subsequent history of typhus, would have received no name more definite than febricula or simple continued fever.

Mr. Spear directed attention to the occurrence of a mild form of typhus among children in connection with such outbreaks; and Dr. Theodore Thomson has suggested as probable "the more or less universal existence of a specific organism, which under ordinary conditions does not develop sufficiently to display its potential infectivity, but which under special conditions may so develop."² Among diseases of more constant type the modification never goes so far as to cause doubt of their identity, except in individual attacks, where the resistance is high.

The varying quality of epidemic diseases has to be taken into account in all epidemiological inquiries. The relation of scarlet fever to rainfall may serve as an example. Dr. Longstaff has shown that, broadly speaking, scarlet fever is most fatal in years when the rainfall is low, and least fatal in years of high rainfall. The recognition of varying phases of virulence makes the relation still more close, for it enables us to account for the occasional occurrence of high mortality in wet years, and low mortality in dry years. Other things being equal, the greater prevalence in dry years will bring about higher mortality; but as the percentage of fatal attacks varies from 1 to 15, prevalence is not the only important consideration. There is, however, some reason to suspect that the cycle of severity as well as the varying prevalence may have a direct or indirect relation with rain. But at best annual totals of rainfall are very crude data. The necessity for much more measured detail is shown by the fact that the

¹ Dr. Parsons, *Report on the Influenza Epidemic of 1889-90*, p. 84.

² *Public Health*, May, 1890.

mean annual curve of rainfall attains its maximum (not minimum) at the same time as the scarlet fever curve.

Attempts are constantly made to measure the effects of preventive measures by comparison of periods before and after their adoption. For want of a better basis, death-rates are often used as a measure of prevalence, on the tacit assumption that the case mortality and type remain constant—an assumption which is far from being sound. And in taking the mean of a number of years as representing the average mortality from a given disease some regard must be paid to its cycles of increasing and lessening energy. It would be unsafe to draw conclusions as to the effect of preventive measures upon scarlet fever, for example, from the comparison of periods shorter than fifteen years, seeing that, until lately, the tendency was to a cycle five or six years in duration; and as each successive wave after 1870 was lower than its predecessor, and the rhythm has now ceased to be evident, other elements of uncertainty come in. For the real question at issue is, Has the course of the disease been different to that which it would have followed had the supposed preventive measures not been adopted? It is scarcely possible to answer this question by crude statistics of deaths, for quality as well as quantity have changed, and social as well as climatic influences are far from constant.

As regards small-pox and vaccination, we can measure results far more accurately, for although the intensity changes and climatic conditions are inconstant, the course of events under the old and new order of things can be observed concurrently, year by year and day by day; and it is this fact which makes the protective influence of vaccination perhaps the most clearly-established of all points in preventive medicine. In every epidemic the two classes—the unprotected and the artificially protected—can be observed side by side under like conditions. But even in regard to small-pox the change of type has led to fallacy. At Leicester it has been alleged that with speedy isolation of persons attacked, and quarantine of those exposed to infection, small-pox may be held in check, and that vaccination is unnecessary even if beneficial. The proof advanced is that small-pox has not succeeded until lately in spreading among the imperfectly-vaccinated population of Leicester.

Many fallacies in this line of reasoning have long ago been pointed out. It ignores the assistance rendered by vaccination, even in Leicester. It presupposes early knowledge of all cases, however slight; compulsory isolation and quarantine; and the observance of a like thorough policy in all other localities, rural as well as urban. And further, if Leicester escaped because it had and used means of isolation and quarantine, how are we to account for the temporary escape of Keighley?

A more probable explanation seems to be that the Leicester experiment with isolation and the Keighley experiment without it have only been tried during years of low intensity, when small-pox has scarcely been able to hold its ground in any part of England. Epidemic centres have been few, the chances of repeated importation comparatively small, and the power of diffusion slight. The real test has still to come, when the conditions are altered—as they seem likely to be within the next few years. It is not enough to introduce small-pox among a population imperfectly protected by vaccination. That the recently vaccinated will not take small-pox is certain, but it is not equally certain that the unprotected will at once be attacked. Something depends upon the quality of the small-pox itself, and it cannot safely be assumed that its power of epidemic spread is always the same even if equal facilities be afforded.

Underlying all that mere death-rates or even mere attack-rates can teach us there is a variable type of disease only imperfectly shown by such records.

SUMMARY.

1. Epidemic prevalence may be brought about either by increased potency of the disease itself or by increased mechanical facilities for diffusion.

2. Epidemics of the latter class, including water epidemics, milk epidemics, and, as a rule, seasonal prevalence, are attended with lowered case mortality, because the conditions under which they occur imply a lessened average susceptibility, and therefore a less severe average attack.

3. Underlying all great epidemics there is a change of epidemic type, a change in the quality of the disease itself.

4. There is evidence of a like change on a smaller scale in most if not all epidemic diseases, the intensity rising and falling at intervals which are not necessarily uniform for the same disease, and are very different in different diseases.

5. Whether on the larger or smaller scale, the intensification is marked by greater severity of attack, greater power of overcoming comparative insusceptibility, and greater power of epidemic diffusion.

6. While some diseases are capable of rapid or even abrupt changes in intensity, others are not; and this distinction serves to mark off broadly two principal groups: those which are mobile and those which are comparatively constant in type.

7. The first group—that of diseases which are capable of most rapid change in type—includes those which are most nearly allied to saprophytic life, most dependent upon filthy conditions; most able to infect soil, water, milk, and lower animals; most liable to relapses, and least protective.

8. Diseases of this class may be highly modified, and some of them may assume and maintain a form so slight that their true character is unrecognised.

9. Under favourable conditions, their intensity may slowly or suddenly increase, giving rise to epidemics of severer type.

10. Among diseases of this class, an epidemic normally begins and ends with the milder forms, the more severe attacks occurring at the time of greatest prevalence. The severity and prevalence rise and fall together.

11. In the second group, among diseases of more fixed character, extreme modification of epidemic type does not occur; but individual attacks may be extremely mild, owing to high resistance.

12. Among such diseases there is evidence of a rise and fall of intensity if the epidemic course be traced for a term of years, perhaps covering several minor epidemics.

13. In these brief outbursts of diseases of more constant type there is little, if any, change of intensity comparable to that of the mobile class; the prevalence being determined and controlled mainly by external conditions, but the type being that of the prevailing phase of a broad cycle.

MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, Etc.

ON THE TREATMENT OF DIABETES MELLITUS BY FEEDING ON RAW PANCREAS.

A. H., aged 39, a policeman. There was nothing of note in his family history. He had always enjoyed excellent health, until about three years ago, when he passed a large quantity of urine and lost flesh. He continued at his post till March, 1892, when he was admitted into St. Thomas's Hospital, where, according to his statement, he was carefully dieted, etc., and was discharged at the end of six weeks, incurable, and having lost weight during this treatment. He gradually got weaker and thinner, and suffered from shortness of breath. He came to the out-patient department of the North-West London Hospital on January 10th, 1893.

He then presented an extremely emaciated condition, appeared very feeble and prostrate, and complained of pains in his chest and a troublesome cough. His tongue was thickly coated with a dirty brown fur, and dryish, and was, as he expressed it, sticking to the roof of his mouth. There were some moist râles at the right apex, the abdomen was full, the liver dulness extended to nearly 2 inches below the costal arch, and there was a marked stomach splash to be elicited. The specific gravity of the urine was 1038; it had a marked trace of albumen, and was loaded with sugar.

On January 20th I recommended him to try the pancreas treatment, and gave him the following directions: To purchase daily a fresh sweetbread, to squeeze all the juice out through a sieve, to drink all this juice raw, and to very slightly cook the sweetbread and eat it.