ANAPHYLAXIS AND STATUS LYMPHATICUS: THEIR RELATION TO INTENSIFIED TYPES OF DISEASE IN INFANCY AND CHILDHOOD.

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I.

In two preceding papers published in this Journal (1, 2) a description was given of abnormal types of two very common bacterial infections—pneumonia and tuberculosis. In each case the illnesses occurred in childhood, and in a few in infancy. In all the deviation from the standard type was in the same direction—in that of greater sharpness and intensity of the clinical reactions. The phrase hypersensitiveness was used to describe these examples of intensified pneumonia and intensified tuberculosis. In both these diseases, the one acute and the other chronic, post-mortem examination was made in a number of cases, and in addition to pneumonia and tuberculosis, showed clear evidence of the abnormal condition of body termed "status lymphaticus."

In the present paper I propose to discuss these two groups of illness further, and especially in connection with the following propositions:

Firstly, that these abnormal types of illness, which in the meantime may be labelled "fulminant," are clinical illustrations of the pathological condition, anaphylaxis.

Secondly, that the morbid condition of body, status lymphaticus, which was present, is more than detached coincidence, but is essentially connected with the distorted and intensified type of illness.

Thirdly, that other fulminant types of illness in young people may be anaphylactic, and also explained by abnormal constitution.

ANAPHYLAXIS.

It will perhaps make the subsequent argument clearer if, at the outset, a brief statement is made of our present knowledge of anaphylaxis. Anaphylaxis may be described broadly as that condition of body in which abnormal reactions follow the repeated injection (hypodermic, intra-peritoneal, or intravenous) of a substance which, at the first injection, produced no apparent disturbance of health, the amounts used both at the first and at the repeated injections being often, in each case, very small. The
list of substances used in this way that may produce anaphylaxis is large, but is confined to the proteins. While partially-digested protein, in the form of peptone, will produce this reaction, the end-products or amino acids are said not to do so.

General Anaphylaxis.—As to the reactions produced, they appear suddenly, are violent, and may produce death in a few minutes (anaphylactic shock). If the animals recover, they do so quickly and completely. The symptoms and disturbances vary in different animals, but may be generally stated as spasmodic contraction of non-striped muscle (stomach, bowels, bronchi, uterus, pilomotor muscles), sudden and profound fall of blood-pressure, with vascular dilatation, capillary hemorrhages, evidence of intense irritability followed by depression of the central nervous system seen in convulsions, paralysis, loss of consciousness.

It is not necessary for the purpose of our argument to go into the very difficult problem of the mechanism of anaphylaxis; it is usually discussed in the terms of immunity, and in relation to it. It must differ considerably in different animals; for example, in the dog and in the guinea-pig. And though the general character of the changes is the same for animals of one species, there is considerable range in the degree of those changes in different individuals of the same species.

Though the term anaphylaxis was introduced by Richet using congestin, a poison prepared from the tentacles of certain actiniae, most of our knowledge of the condition has been based on the use of horse serum in guinea-pigs, rabbits, and dogs. Among laboratory animals it has not been possible to induce anaphylaxis in the rat. The word anaphylaxis would seem to be unfortunate. It expresses something "opposed to immunity"; and yet there is much evidence that the reactions in anaphylaxis are due to excessive activity of the processes of immunity. The term hypersensitiveness is more accurate and cautious; it implies no theory, but merely describes the objective phenomena. And, indeed, in the literature of anaphylaxis, the word hypersensitiveness is often used synonymously with it.

The experimental phenomena of horse-serum anaphylaxis are specially important, because they throw light on the clinical phenomena produced by the hypodermic injection of horse serum in man in the various antitoxic sera.

Local Anaphylaxis.—In the above cases anaphylaxis reveals itself in certain general body-reactions, e.g., fever, general effects on vascular and muscular tissues, etc. But occasionally the changes are more localised. We have what may be called a local, as well as a general, anaphylaxis. Arthus described in rabbits a local sloughing of tissues at the site of repeated hypodermic injections of horse serum. This is known as the Arthus phenomenon, and is to be contrasted with
the general anaphylactic reaction seen in its extreme form in the guinea-pig, and known as the Theobald Smith phenomenon. But we have an even earlier example of local experimental anaphylaxis in the work of Koch in 1890. He showed that a single injection of living tubercle bacilli under the skin of a guinea-pig produced an ulcer, then an infected gland, and finally a generalised tuberculosis; but that a repeated injection produced a much more violent local reaction ending in necrosis, with an absence of the generalised infection.

In both these forms of anaphylaxis, general and local, the leading characteristic may be described as a violent intense reaction to repeated injection of horse serum, in so small a dose that the first injection produced no apparent reaction at all.

The object of this paper is to show that both the general and the local anaphylactic reactions are pure experimental types of biological phenomena which have their analogues in clinical medicine; and that striking examples of these analogues are to be found respectively in the cases of fulminant pneumonia and in the special forms of tuberculosis known as scrofula, described in previous papers (c. 2). Both in the experimental and in the clinical types hypersensitiveness characterises the reaction; but in the course of this paper I hope to show that there are other and more essential resemblances.

Clinical Examples of General Anaphylaxis.—A number of clinical types of anaphylaxis have been established; and they also will be found to fall into the same broad divisions of general and local forms.

Serum Disease.—Of the general forms, the serum reactions following the hypodermic injection of antitoxic horse sera in diphtheria, tetanus, etc., may be taken first. They seem exactly to reproduce the conditions of the animal experiments with the same substance. The investigations of von Pirquet and Schick and of E. W. Goodall have collected a large and accurate body of data on this subject of "serum disease." The reactions include fever, various types of rash, oedema, arthritis, etc., and appear after a latent or incubation period of one or two weeks. They occur much more frequently, and as a rule much more severely, in second attacks of diphtheria, where a second injection of serum has thus been given. This latter group is specially important, because in them the human experiment seems an exact replica of the animal experiments. In this group the reactions are not uniform, either in their severity or in the duration of their incubation periods. The variations are divided into three classes—the ordinary or normal reaction, appearing in from 8 to 16 days; the accelerated
reaction, appearing (and usually in exacerbated form) in from 1 to 6 days; and the immediate reaction, with intense phenomena, developing in a few hours or even in a few minutes, and in a few cases terminating in death. In some of these fatal cases of "immediate anaphylactic reaction" the post-mortem appearances of status lymphaticus have been found. It is not known what determines the wide variation in the severity of reaction in these cases of repeated injections of antitoxic horse serum, but it is very important to remember the fact that great variation in the degree of reaction occurs. This fact has been a little neglected in discussions of the anaphylaxis of "serum disease," but it is clear that there are many degrees of intensity, from the ordinary anaphylactic reaction to the intense "immediate" reaction. If the one is called hypersensitiveness, it would be strictly accurate to call the other super-hypersensitiveness.

*Food Anaphylaxis.*—The violent urticarias and cedemas following the use of certain kinds of food by certain individuals form another established group of cases of food anaphylaxis. The unique feature of the cases of this group is that the protein substance causing anaphylaxis is swallowed in the ordinary way. The previous examples of anaphylaxis have all been produced by the parenteral introduction of protein. Food anaphylaxis is apparently produced by the passage of undigested protein through the alimentary mucous membranes. These cases are further interesting in that there is no apparent evidence of previous sensitisation in many of them.

*Pollen Asthma.*—Attacks of hay-fever and of asthma, produced by the pollen of certain plants and grasses and by various animal emanations, form another well-defined group of clinical examples of anaphylaxis.

*Acute Infectious Diseases.*—With regard to the incubation period and the symptoms of invasion of the acute infectious diseases, there is a division of opinion. There seems to be present something similar to the conditions of an anaphylactic experiment. There is the primary inoculation of foreign bacterial protein; there is a latent period during which the amount of foreign protein is increasing; there is, finally, the sudden appearances of disturbances, fever, vomiting, exanthems, etc. Von Pirquet and Schick, Vaughan,6 and others regard the symptoms of onset of the acute fevers as anaphylactic. Goodall refuses to admit this. For the main propositions of this communication, given at the outset of the paper, the determination of this question is a crucial one. If
these propositions are true, they can be harmonised with the views of von Pirquet. The cases of fulminant pneumonia in infants and older children, described in a previous paper,\(^1\) can be interpreted in the light of anaphylactic phenomena. If the symptoms of onset of an ordinary case of pneumonia represent normal anaphylaxis, those of fulminant and acutely fatal pneumonia may represent intense exaggerated anaphylaxis. And an exact analogy seems to be found in the contrast (and the resemblances) between the normal reaction of "serum disease" in one patient and the immediate reaction in another. *Both in the ordinary and in the fulminant pneumonia the symptoms of onset are anaphylactic; they differ in intensity, but they agree in their essential biological character.*

**Clinical Examples of Local Anaphylaxis.**—The best known are the cutaneous and conjunctival tuberculin reactions. There are also the mallein and luetin cutaneous reactions in glanders and syphilis, and Twort’s reaction in Johnes’ disease of cattle, an enteritis produced by acid-fast bacilli somewhat resembling tubercle bacilli in their form. Of these various examples, the one that is relevant to this discussion is the cutaneous tuberculin reaction. This reaction differs in intensity in different individuals, and its intensity may be increased to an extreme point in certain forms of tuberculous infection. It was shown in a previous paper\(^2\) that scrofulous types of tuberculosis showed this intensified tuberculin reaction. I would submit that in the local reactions in scrofula we have an exaggerated form of local anaphylaxis, just as in fulminant pneumonia we have an exaggerated general anaphylactic reaction.

**Pathological Resemblances.**—I think it can be shown that these alleged instances of clinical anaphylaxis, namely, fulminant pneumonia and intensified local tuberculosis (or scrofula), show pathological character similar to those in accepted instances of anaphylaxis. The leading pathological features of anaphylaxis may be given as vasomotor paresis (vascular congestion); constriction of certain types of non-striped muscle; oedema of the loose connective tissues, both subcutaneous and internal; destruction of the more delicate body epithelia; the production of these changes by very small doses of virus.

**Vasomotor Paresis.**—Vascular congestion of many tissues and organs is emphasised in all histological investigations on anaphylaxis. It was so prominent in Richet’s experiments on dogs that he called the substance by which it was produced *congestin.*\(^7\) It is beautifully demonstrated in Scott’s\(^8\) plates and photographs.
Fig. 1.—Section of lung of T. H., at 12 years. Fulminant institutional pneumonia. Shows extreme dilatation of smaller blood-vessels.

Fig. 2.—Section of medulla of kidney from J. W., at 11 years. Institutional pneumonia. Duration of illness 3 hours. The part is infiltrated with blood corpuscles, partly in dilated blood-vessels, but chiefly in the collecting renal tubules.

Fig. 3.—Lung, L. P. Infant, at 9 weeks. Found dead. Fulminant broncho-pneumonia. Note in upper left quadrant dilated infundibulum and strongly contracted proximal portion of bronchiole, and to right of this cross-section of bronchiole with convoluted epithelium, suggesting constriction of bronchial muscle.

Fig. 4.—Section of lung from F. B., at 12 years. Fulminant institutional pneumonia. Note the empty, and in some cases dilated, alveoli, widely separated by edematous and cellular exudate.
It is shown also in the general cyanosis of cases of "immediate" reaction in serum disease.

This vascular congestion was marked in the cases of fulminant pneumonia described in the previous paper and alluded to in this. It was demonstrable both in life and after death—in the cyanosis of the skin noted in the cases of institutional pneumonia, both in the fatal and non-fatal cases; and in the various organs and tissues after death, both in the infantile cases of fulminant pneumonia, and in the group of institutional pneumonias. This congestion was naturally most marked in the lungs, but it was an outstanding feature in sections of the kidney, thymus, liver. It is illustrated in Figs. 1 and 2, which show the great dilatation of the smaller blood-vessels of the lung and of the vessels of the renal medulla.

**Constriction of Non-striped Muscle.**—This has been demonstrated in the heart muscle of the anaphylactic rabbit (Arthus), and also in the stomach and intestine, uterine and bronchial muscles of the guinea-pig (Auer, Dale, Schultze and Jordan). This constriction of the bronchial muscle in the guinea-pig is remarkable in that it is the actual cause of death by suffocation, owing to the loose and redundant character of the mucous lining. Contraction of plain muscle is absent from the anaphylactic reactions in the dog; but in man constriction of bronchial plain muscle is evident in the anaphylactic forms of asthma. It has even been suggested that the uterine contractions in menstruation and parturition are anaphylactic phenomena.

Fig. 3 shows a section of the lung from an infant of nine weeks, found dead in bed, the post-mortem examination showing bronchitis and commencing broncho-pneumonia, along with thymo-lymphatic hyperplasia (status lymphaticus). In the figure a bronchiole is shown in longitudinal section, its terminal infundibular portion dilated, while the proximal part is closely constricted. The convoluted character of the adjacent bronchiole in cross-section also suggests constriction of its bronchial muscle.

**Edema.**—Edema, especially subcutaneous and cutaneous, is one of the prominent features of anaphylaxis, both in laboratory animals and in man in serum disease. Scott has demonstrated this also in deeper structures, and especially in the interalveolar tissue of the lung in the anaphylactic guinea-pig.

Figs. 3 and 4 show this interalveolar pulmonary edema both in fulminant pneumonias of infants, usually described as cases of status lymphaticus, and in the group of institutional pneumonias in older boys. In the latter it was often extreme, the empty and
often distended alveoli being widely separated by very extensive interstitial œdema (see Fig. 4).

Epitheliolysis.—Auer and Lewis⁹ describe “extreme endotheliolysis and haemorrhage” in guinea-pigs dying 4 to 6 hours after the reacting dose (subcutaneous) of horse serum.

A similar rapid extensive destruction of epithelia is seen in the lungs of the cases of fulminant pneumonia. In Fig. 5, where the duration of illness was 6 hours, the bronchial lumen is filled with desquamated epithelium. In Fig. 3, the case of an infant found dead in bed, denudation of epithelium is already taking place in the bronchi. Fig. 6, showing a rapid ulcerative lesion produced at the site of the von Pirquet cutaneous reaction in a case of scrofulodermia, is another illustration of the same rapid intense necrosis of epithelial cells. Further, one of the clinical features of cases of scrofula is the tendency to widespread and obstinate catarrhs of mucous membranes and skin, evidenced in the seborrhœa and eczema, the chronic conjunctivitis and rhinitis, bronchitis, and diarrhœa of this constitutional condition.

Weakness of Virus.—One of the most astonishing things about experimental anaphylaxis is the violent and fatal effects produced by minute doses of an apparently innocent albumen. Guinea-pigs can be sensitised by a dose of 0·00001 c.c. of horse serum.

This same disproportion of cause and effect is seen in examples of human anaphylaxis. Severe general anaphylaxis is produced by the sting of an insect in one individual, while the same noxa in another will only cause a slight transient local irritation.

The local anaphylactic reaction produced by tuberculin on the skin of a sensitised (tuberculous) person is a very definite local lesion, but in an unsensitised (non-tuberculous) person the same amount of virus will produce no effect.

In the tertiary stage of syphilis “the gumma is a true anaphylactic phenomenon” (M’Intosh¹²). The same writer says with regard to parasypheils that “the very extensive lesions without the presence of spirochaeta pallida in any number must be due to the action of minute quantities of syphilis toxin on highly sensitised tissues.” (The italics are mine.)

Do these cases of acutely fatal pneumonia in infants and others, and do cases of scrofula show evidence of weakness of virus? Let us take first the cases of fulminant institutional pneumonia. At first sight it seems absurd to suggest that in illnesses so rapidly fatal the pneumococcal poison was weak in its quality or amount; it seems reasonable to suppose it was highly virulent. But yet the
Fig. 5.—Section of lung from F. B., aged 12 years. Fulminant institutional pneumonia. Shows a bronchus, cut in longitudinal section, its lumen filled with desquamated epithelium.

Fig. 6.—Case of scrofuloderma. Mary Cain, aged 2½ years. Shows intense cutaneous reactions to human and bovine tuberculin, producing two ulcers with complete destruction of the whole skin.
following facts support the former hypothesis:—Pneumococci were, in many of the cases, cultivated only with difficulty from the lungs. Further, these fatal fulminant pneumonias were accompanied by non-fatal cases of illness. In this one school, and over a period of some ten years, 226 such cases were collected by M'Gowan and myself. Though the symptoms of onset in these were similar to those of the fatal group, yet in the 51 cases where pulmonary consolidation became a demonstrable clinical fact its area was in the great majority small, and, as described by the medical officers of the school, of an extent covered by the chest-piece of the stethoscope; and of these limited cases of pneumonia only one died.

There remained a large group of 175 cases, termed by us abortive pneumonia, because though the general signs and symptoms were those of the other two groups, the local physical signs of pneumonia were entirely absent. It is therefore not an unreasonable explanation that the fatal issue in the fulminant group was due, not to a gross or virulent poisoning by pneumococci, but to a hypersensitive (anaphylactic) condition of the body.

As to the cases of scrofula, the evidence seems to point in the same direction. The statement of Birch-Hirschfield, writing before the tubercle bacillus was discovered, is apposite in this connection. “The scrofulous constitution,” he says, “is characterised by a peculiar inflammatory reaction of the tissues against irritants of relatively even insignificant importance.” Further, cases of scrofula do not often die of general tuberculosis; indeed it is often said, and this by clinicians of great experience, that scrofulous children seldom become phthisical in adolescence. The tuberculous lesions of scrofula, severe as they are, present the picture of a tuberculosis, localised by the fiercely inflammatory reaction of the tissues. There is not seldom a failure to cultivate the bacillus from the caseous and purulent material of scrofulous lesions.

The severe local tuberculin reactions which characterise cases of scrofula, and which are illustrated in Fig. 6, can be explained in the same way. The ordinary or normal tuberculin reaction is accepted as an anaphylactic reaction; the intense reaction in scrofula, as in Fig. 6, is heightened anaphylaxis; and we have noted as one of the fundamental principles of anaphylaxis that the dose of the virus is small, while the reaction of the living tissue is disproportionately great.

In these various features, therefore—in the unusual congestion and oedema, in the suggestion of contracted bronchial muscle, in the rapid and intense destruction of epithelial structures, and in
the evidence, not of intensification of the virus, but of intensified reaction to the virus—the cases of fulminant pneumonia and of scrofula show a special stamp of pathological histology and physiology which is also the peculiar stamp of the phenomena of anaphylaxis, both experimental and clinical. And in both cases it is not the ordinary but an extreme anaphylactic reaction which is shown. In the cases of fulminant pneumonia the analogous type is to be found in the "immediate" reaction of a case of serum disease, in the cases of scrofula the experimental analogue is the Arthus phenomenon, that is, the local necrosis developing in the rabbit at the site of subcutaneous injection of horse serum where several injections of the same substance have been previously given.

(To be continued.)

RECURRENT LUXATION OF THE PATELLA.

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No medical practitioner can acquire much experience in his profession without there coming under his observation curious and troublesome cases of recurrent dislocation or subluxation of the patella. True traumatic dislocation of the patella is an uncommon event, and even surgeons of experience may only be able to recall one or two such cases, and in them the patellar displacement is often of minor importance to other coincident injuries. To cases of primary traumatic dislocation of the patella I do not propose further to refer in this communication. I desire only to consider a condition which is characterised by the outward displacement of one or both patella, and to offer suggestions as to how this condition may be brought about.

It is scarcely necessary to mention that the patella is a sesamoid bone developed within the tendon of the quadriceps extensor cruris. It articulates with the condyles of the femur over which it glides, and the shape of its articulation is modified to fit this trochlear surface. The prolongation upwards of the articular surface of the outer condyle, its comparative flatness in comparison with the corresponding articular surface of the internal condyle, and the fact that the outer border of the patella really projects beyond the edge of the articular surface, might be supposed to facilitate outward rather than inward dislocation. But more important