VOLUME I.

# ANAPHYLAXIS and SENSITISATION,

## with special reference to the skin and its diseases.

THESIS

submitted by

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# ANAPHYLAXIS AND SENSITISATION WITH SPECIAL REFERENCE TO THE SKIN AND ITS DISEASES.

## INTRODUCTION. SCOPE OF THESIS.

The object of this Thesis is to describe and discuss the phenomena of anaphylaxis and sensitisation in so far as they affect the skin. Before taking up each section separately, it will be well to give a short general description of our present knowledge of these phenomena and an explanation of the numerous terms which will be used throughout this work.

Anaphylaxis was the term introduced by RICHET 1902. to describe the series of phenomena which occur on reinjection into animals, after an interval of several days, of certain substances which were harmless on first injection. As the animal had been rendered more susceptible to the substance injected, RICHET thought the condition was the opposite of Prophylaxis or Immunity, and gave it the name Anaphylaxis.

THE/

## THE PHENOMENA OF ANAPHYLAXIS.

As animals such as the guinea-pig give much more intense reactions than human beings it is best to study the phenomena of anaphylaxis in them. Horse serum can be injected in fairly large doses into guinea-pigs without producing any symptoms. When, however, a small dose of horse serum is injected subcutaneously, intraperitoneally or intravenously into a guinea-pig, and ten days later a second injection is given, the animal develops symptoms of distress and usually dies within an hour or so. A few minutes after the second injection the animal becomes restless shows symptoms of difficulty in breathing, and urine and faeces are usually discharged. This stage of excitement is rapidly followed by one of paresis, the animal falling on its side and the limbs jerking. The convulsions continue with increasing paralysis, and the animal dies from asphyxia. If the animal be not very susceptible the symptoms may be delayed in their appearance and in these cases the animal may recover. These are the symptoms of anaphylactic shock. If the animal recovers, for some days afterwards (at least 10-12 days) it is found to be in a state of Anergy, i.e. the opposite of Allergy or sensitisation. During this stage of Anergy, large doses/

doses of the sensitising agent can be injected with impunity, and in this way the animal can be permanently immunised.

## INCUBATION PERIOD AND DURATION OF SENSITISATION.

For 8-10 days after the sensitising injection, subsequent injection of the sensitising substance produces no signs of anaphylaxis. If a second injection is given during the incubation period, the animal will probably become immune rather than hypersensitive. ROSENAU and ANDERSON[203] found that the degree of hypersensitiveness increases from the 10th to the 21st day after which it gradually diminishes somewhat. They showed[205] that the animal may still be sensitive 1096 days later and that the sensitiveness probably lasts all the life of the animal. This corresponds with what is known to occur in man in bacterial sensitisation. Persons who have once had a tuberculous infection will always give a positive skin Pirquet reaction for the rest of their lives.

The amount of serum necessary to sensitise a guinea-pig is astonishingly small. ROSENAU and ANDERSON found that 0·000,001 cc. might be sufficient to /

to cause sensitisation but the initial dose given is usually 0·001 cc. Larger doses of serum will also sensitise but the incubation period is longer. To obtain a fatal result the second or toxogenic dose must be considerably larger than the minimum sensitising dose.

PFEIFFER[181.] has shown that during anaphylactic shock the temperature falls. BIEDL and KRAUS, FRIEDBERGER[91.] and ARTHUS[14.] also showed that there is a diminished coagualability of the blood. Leucopenia and diminution of complement are also found. Post-mortem the most striking change is a permanent distension of the lungs resembling emphysema. This was described by GAY and SOUTHARD and later by AUER and LEWIS[18.] and confirmed by ANDERSON and SCHULTZ[7.]. The alveoli of the lung are distended and rupture of the walls sometimes occurs. The bronchioles are contracted and death results from asphyxiation, the heart continuing to beat after respiration has ceased. The lung changes are extraordinarily like those seen in human beings in Asthma.

Rabbits can be sehsitised similarly to guinea-pigs but not so easily. The symptoms differ in some respects from those in guinea-pigs. Dogs may also be sensitised but the reaction is not so violent and/

and death not so frequent. Many other animals such as cats, horses, sheep etc. have been used and although the symptoms vary somewhat according to the species, on the whole, the reactions are similar.

## ANAPHYLAXIS IN MAN.

Some have expressed doubt as to whether the reactions seen in man after second injections of a foreign serum are truly anaphylactic, but taking into consideration the differences which exist between the anaphylactic reactions in different species of animals it is not to be wondered at that the reactions in human beings differ considerably from those seen in the guinea-pig, rabbit etc. The reactions in man will be discussed later under Serum Disease.

As it is now known that Anaphylaxis and Immunity are very closely linked, many consider the term a bad one and prefer to use that of Supersensitiveness, Hypersensitiveness or Sensitisation. PIRQUET also introduced the term Allergy which means an altered reactivity. The substance which causes anaphylaxis is called an anaphylactogen, sensitiser or allergen according to PIRQUET.

So far as we know at present only proteins are capable of acting as Anaphylactogens. These proteins may be derived from animal tissues, such as blood/

blood serum, milk etc, vegetable and plant tissues and bacterial substances. Several workers have claimed to have produced anaphylaxis with non-protein substances such as lipoids, but RITCHIE and MILLER, WHITE[192.] and others have shown that, when the lipoids are pure, anaphylaxis cannot be produced.[266.] It is however possible that non-protein substances may combine with protein in the tissues and so cause anaphylaxis. In this way certain reactions, such as those produced by drugs like Salvarsan may be explained.

The purer a protein the more readily it acts as a sensitiser. There seems to be still some doubt as to whether the whole protein molecule or only a part of it is required to produce sensitisation. All proteins produce anaphylaxis most readily when in solution because they are then more easily absorbed into the body-cells.

METHODS/

## METHODS OF SENSITISATION.

The anaphylactogen may be introduced into man by injection as in treatment with sera. Absorption through the skin by rubbing may also cause sensitisation. It will be shown later that rubbing the juice of the Primula plant into the skin can cause sensitisation. Absorption may also occur through the intestine. Guinea-pigs have been sensitised by feeding them on serum and meat. This was proved by ROSENAU and ANDERSON.[196] In this way human beings often become semsitised to such foods as eggs, shell fish, pork etc. Further reference to this intestinal absorption of proteins will be made later, when discussing eczema and urticaria in children.

ROSENAU succeeded by keeping guinea-pigs in stables with horses, in sensitising them to horse serum. This explains the method by which asthmatic persons may become sensitive to horse serum without previously being actually injected with it. The emanations from the horse may be absorbed by inhalation, but there is also always the possibility of their getting into the mouth and being swallowed. This may occur by inhalation through the mouth or contamination of food with the hands or clothes which have been in contact with horses. ROSENAU and AMOS[194] showed that the exhaled/

exhaled breath of men when condensed and injected into guinea pigs could sensitise them to injections of human serum.

CHRONIC/

## CHRONIC ANAPHYLAXIS.

It has been shown by BOUGHTON [43,44] that if repeated anaphylactic shock is induced in guinea-pigs by injections of egg-white and beef serum, these animals show lesions of the smaller arteries of the kidneys, liver, spleen and heart, characterised by degeneration and regeneration of the endothelium, oedema and fissuring of the intima and media and sometimes splitting of the internal elastic lamina. These lesions are not found in the larger arteries, capillaries and veins. Perivascular infiltration is also present in many cases. The changes in the arterioles lead to corresponding degenerations in the kidney tissue. These changes are similar to the chronic degenerative changes seen in man in the so-called toxaemias and autointoxications.

PREVENTION/

## PREVENTION OF ANAPHYLACTIC SHOCK.

### 1. DESENSITIZATION, ANTIANAPHYLAXIS or ANERGY.

As already stated, if an animal recovers from anaphylactic shock it is found to be in a state of desensitisation, antianaphylaxis or anergy, and further doses of the sensitising agent can be injected with impunity. This refractory period lasts at least 10-12 days, but may continue for several weeks. After the refractory period is past the animal again becomes hypersensitive, but usually not to the same degree as before. OTTO,[177.] ROSENAU and ANDERSON, and BESREDKA and STEINHARDT[34.] showed that sensitised animals can be rendered refractory or antianaphylactic by the administration of small doses of the protein used to sensitise. The doses must be too small to cause any symptoms. It is possible by repeated small doses so to desensitise an animal that it will withstand doses many times larger than the one necessary to cause fatal anaphylaxis in a sensitive animal which has not been so treated. Intravenous injection causes desensitisation in a few minutes; intraperitoneal in a few hours and subcutaneous injection may take 24 hours to produce an effect. This method of desensitisation has/

has been used to prevent anaphylactic shock in human beings, who are being treated with serum injections. BESREDKA[28] recommends that the quantity to be given be split up into fractional doses which are injected every 10-20 minutes, gradually increasing the amounts, till the full dose has been given. A prophylactic injection of the serum can also be given per rectum and the real therapeutic dose later on.

LEWIS[137] also found that desensitisation could be accomplished in animals by the slow intravenous injection of the sensitising substance. By means of the Woodyat[302] pump minute measured doses of the serum may be injected very slowly at measured intervals of time. COCA[54] also found this method of desensitisation to be effective. MARBE and RACHEWSKI[155] also used a modification of the above method. They gave a preliminary cutaneous inoculation of the serum, which in about 1½ - 2 hours protected the animal, so that a full dose could be given with safety. They found that this cutaneous inoculation only protected the animal for 48 hours, and after that time the animal was even more hypersensitive than it was previously. For the condition of protection induced by this preliminary cutaneous inoculation they propose the name "l'etat phylactique", and for the subsequent heightened hypersensitiveness /

hypersensitiveness "l'état ana-anaphylactique".

Desensitisation may also be accomplished by feeding a sensitive individual on increasing quantities of the substance which produces the symptoms. PARK [178.] quotes such a case of an infant which was breast-fed. This child was given a little cow's milk at the age of six weeks and 3-4 hours later vomited, became collapsed and suffered from diarrhoea. No such symptoms occurred after drinking goat's milk. This child was desensitised by feeding on increasing quantities of cow's milk beginning with 0·0001 cc. well diluted. At first very slight symptoms were produced, but these gradually disappeared. The dose was gradually increased according to the symptoms till the child could take large quantities of cow's milk daily with impunity. This method of desensitisation by feeding will be again referred to under food sensitisations.

WELLS and OSBORNE [260.] found that by feeding animals for a long time with oats they became anti-anaphylactic so that no satisfactory anaphylactic reaction could be obtained by two properly spaced injections. Therefore feeding animals for a short time on foreign proteins, especially animal proteins, will sensitise them to these proteins, whereas feeding them for longer periods will desensitise them.

It/

It is to be noted that the state of anti-anaphylaxis or desensitisation is not the same as immunity. It is not premanent as the animal later goes back to the sensitive condition again.

## 2. OTHER MEANS OF PREVENTING ANAPHYLAXIS.

BRODIN, RICHET and ST. GIRONS[46] found by experiments on dogs that the intravenous injection of Sodium chloride counteracts anaphylaxis when given in doses of not less than 0·8 grm. per kilo weight.

FRIEDBERGER and HARTOCH[93] also obtained the same results in guinea-pigs by injection of hypertonic salt solution. DALE[68], who also worked at this subject, thinks that the salt acts by diminishing the irritability of the smooth muscles of the body, which by their contraction are responsible for many of the symptoms of anaphylactic shock.

FRIEDBERGER and HARTOCH'S results were later confirmed by ZINNSER, LIEB and DWYER.[275]

Similarly SICARD and PARAF[221] found that 10-15 grm. of Sod. Bicarb. by the mouth 15 minutes beforehand or 0·5-2 grm. Sod. carbonate intravenously will ward off anaphylactic shock.

BESREDKA /

BESREDKA[28] also showed that Calcium Chloride when injected the day before the intoxicating dose prevents anaphylactic shock. This is interesting because Calcium Chloride has long been given for the treatment of Urticaria.

Sodium hyposulphite was also found by LUMIÈRE and CHEVROTIN[139] to prevent anaphylaxis if added in small amount to the serum before injection. Adrenalin too has a remarkable effect in preventing or relieving anaphylactic shock. PELZ and JACKSON found that it prevented anaphylactic shock in dogs. It has also been used with success in Asthma, serum sickness and Urticaria.

Atropin was found by AUER and LEWIS[17] to prevent shock in guinea-pigs. Belladonna is used extensively in the treatment of Asthma.

Chloral Hydrate was found by RICHET, BANZHOF and STEINHARDT[22] and BANZHOF and FAMULENER[21] to prevent shock in animals. The animal must be deeply under the hypnotic. JOHN THOMSON[238] also found chloral hydrate useful in treating infants suffering from a certain type of convulsions which he considers of anaphylactic origin.

Anaesthetising a sensitised animal can prevent symptoms of shock. Chloroform, ether, and similar drugs have been used. Whether this is simply due/

due to the paralysis of the nervous system and consequent prevention of symptoms or not is doubtful. BRONFENBRENNER and SCHLESINGER[48] found that certain anaesthetics increase the antitryptic action of the blood and therefore they argue that that is sufficient to stop the activity of the proteolytic enzyme, which they consider necessary for the production of the shock. BESREDKA[28] found that preparations of opium and morphine had no effect in preventing anaphylactic shock.

Quite recently DUPREZ[85] showed that it is possible to prevent anaphylactic shock in the guinea-pig by the previous injection of a lipoidal emulsion. The mechanism of this result has not yet been worked out.

PASSIVE/

## PASSIVE ANAPHYLAXIS.

It has been shown by GAY and SOUTHARD,[98] RICHET,[190] OTTO[177] and others, that the serum of a hypersensitive animal, when injected into a normal animal will render the latter hypersensitive; therefore passive anaphylaxis can be produced. Passive anaphylaxis can be produced by transference of serum to an animal of the same species (homologous) or to an animal of another species (heterologous). Passive anaphylaxis takes some time to develop. By intravenous injection of the serum, it takes about four hours till the animal is anaphylactic; by intraperitoneal injection about 24 hours and by subcutaneous injection 24-48 hours are necessary. Passive anaphylaxis lasts for some days or weeks but is never so permanent as active anaphylaxis. In addition to serum from a hypersensitive animal, the serum of an animal in the incubation stage before sensitisation can be demonstrated, can also produce passive anaphylaxis. Likewise injection of serum from an anti-anaphylactic animal and immune serum are able to produce it.

ANDERSON,[4] SCHENK[209] and others have shown that the young of sensitised female guinea-pigs are sensitive. This is an example of homologous passive anaphylaxis. SCHENK also claims that it can be transmitted through the sperm of sensitised males.

SPECIFICITY/

## SPECIFICITY OF ANAPHYLAXIS.

The anaphylactic reaction is to a high degree specific. Group reactions, however, occur. An animal sensitive to sheep serum will react, but less violently, to goat serum. Similarly animals sensitised to human serum will react to the sera of the higher apes.

ROSENAU and ANDERSON[201.] found that guinea-pigs sensitised to human milk or dog's milk, did not react to cow's milk but that animals sensitised to sheep's milk might give a definite reaction to cow's milk. This indicates that when the milk is from an animal of a closely allied species heterologous reactions are apt to occur.

WELLS and OSBORNE[260.] have also shown the same group reactions in anaphylaxis due to vegetable proteins. Pure "Hordein" from barley will produce an anaphylactic reaction in a guinea-pig sensitised to pure "Gliadin" of wheat. There seems to be some chemical reactive group common to both these substances. Anaphylaxis therefore shows a species specificity. An animal cannot be sensitised to its own tissues. The only exception to this seems to be the crystalline lens of the eye. UHLENHUTH and HAENDEL[241.] showed that animals can be sensitised to their own lens/

lens protein. WELLS[258.] showed that, although there is a species specificity, there is also a specificity by which it is possible to distinguish proteins in the same substance. WELLS was able by the anaphylactic reactions to distinguish four proteins in the white of the hen's egg, viz. ovomucoid, crystallised egg albumin, globulin and ovovitellin. This is an example of a chemical specificity which is independent of the species specificity.

As with animal and vegetable proteins, so with bacterial proteins group reactions may occur. HOLOBUT[108.] found that specific reactions could be obtained with B. typhosus and B. Coli. But interaction between the two organisms could also occur. Other observers, however, maintain that bacterial anaphylaxis is absolutely specific for each organism.

THEORIES/

## THEORIES AS TO THE MECHANISM OF ANAPHYLAXIS.

Many theories have been put forward to explain the mechanism of Anaphylaxis. None, however, give an absolutely satisfactory explanation of all the phenomena. As true anaphylaxis is due to a protein, this protein, when injected, acts as an antigen i.e. a substance which leads to the formation of antibodies. There are produced also under certain conditions precipitins, agglutinins, lysins and complement fixing bodies. These are intimately connected with the changes in anaphylaxis.

One of the chief points of controversy is, as to whether or not a poisonous substance is produced in the reaction. If some poison is produced, it has to be decided whether this poison is produced in the cells of the body (cellular theory) or in the circulating fluids (humoral theory). If no poison is produced then, the symptoms may be due to some disturbance of the balance of the colloids or enzymes in the circulating fluids (physical theory).

As many workers have used different terms for substances concerned in the reactions, I think it will conduce to clearness if a short summary is given of the views of those who have done most work on the subject/

subject and if, after that, the cellular, humoral and physical theories are discussed.

RICHET suggested that when the sensitiser or anaphylactogen is first injected, it causes the production of a substance which he called "Toxogenin". This toxogenin on the second injection of the protein combines with the protein to produce a poison called Apotoxin, which through its action on the nervous system causes the symptoms of anaphylaxis. It will be seen later that RICHET'S apotoxin is practically FRIEDBERGER'S Anaphylatoxin under another name. In the latter's theory Toxogenin corresponds to antibody and complement.

GAY and SOUTHARD[98] think that every antigen consists of two elements, one toxic (anaphylactin) and the other non-toxic or sensitising. On the first injection the toxic anaphylactin is eliminated from the body and the non-toxic sensitising element is retained in the body cells. When a second injection is given the toxic anaphylactin in the reinjected protein is rapidly absorbed by the sensitised cells and anaphylactic shock results.

BESREDKA[29] also assumes that there are two distinct elements in the antigen, viz. sensibilisogen and antisensibilisin. On the first injection the sensibilisogen/

sensibilisogen causes the development of an antibody which he calls Sensibilisin and the antisensibilisin is excreted or destroyed by the animal. On the second injection the antisensibilisin element in the antigen combines with the Sensibilisin and produces a toxic substance which causes the symptoms of anaphylaxis.

NICOLLE[167] thinks that anaphylaxis is due to two substances, viz. Albuminolysin and Albuminocoagulin. Sensitisation produces a large amount of the former and a smaller amount of the latter in the tissues. The second dose of antigen is rapidly lysed by the albuminolysin with the formation of toxic substances.

FRIEDBERGER[89, 90.] explains Anaphylaxis on the basis of EHRLICH'S side-chain theory of immunity. The foreign protein calls forth the production of side-chains which unite with and neutralise the antigen. FRIEDBERGER assumes that these side-chains or receptors remain sessile in the cells. When antigen is re-injected for the second time it combines in the presence of antibody with complement to produce a toxic substance called "Anaphylatoxin", which produces the symptoms. This theory explains the absence of complement in anaphylactic shock. After sensitisation the cells of the body contain sessile receptors which have a great affinity for the antigen.

VAUGHAN/

VAUGHAN and WHEELER think that when a protein antigen is injected, the tissues produce a specific ferment which digests it and splits up the protein. By boiling proteins with an alcoholic solution of Sodium hydrate they split up the protein into a non-toxic alcohol-soluble part and a toxic alcohol-insoluble part. The toxic part when injected into normal guinea-pigs caused death with all the symptoms of anaphylactic shock. This toxic part of the protein can be obtained from all proteins and seems to be identical in all, hence the uniformity of symptoms in anaphylactic shock in the same animal whatever the protein used to produce the shock. The specificity of the reaction is due to the non-toxic part of the protein which varies in each case. VAUGHAN and WHEELER[243.] think "that protein susceptibility and immunity are different manifestations of the same process. Both depend on the development of a specific proteolytic ferment." When the specific ferment splits up a living foreign proteid (such as a bacterium) before it has time to multiply we say that the animal is immune. When the cleavage action is less prompt, but sufficiently so to split up the living proteid before it elaborates a fatal amount of the poison, the animal sickens but recovers. When the action of the ferment is still less prompt and the living proteid/

proteid constructs enough poison to kill, then its liberation causes death. This specific proteolytic ferment is stored up in the cells of the animal as a result of the first injection and remains as a zymogen until activated by the second injection of the same proteid. We regard the production of the specific zymogen not as the formation of a new body but as resulting from an alteration in the atomic arrangement within the proteid molecule and a consequent change in its chemism".

There is some doubt as to where the protein which produces the poison is derived from. JOBLING and PETERSEN[115], BRONFENBRENNER[47] and others hold that it comes from the animals own serum. DOERR thinks it is derived from the serum by the absorption of the inhibitory antibodies. VAUGHAN[242], FRIEDBERGER[90] and others think that it comes from the injected protein.

In support of the cleavage of protein is the further evidence of the reactions which can be produced with substances such as peptone, agar etc. BIEDL and KRAUS[39] showed that the injection of peptone produces symptoms in the dog similar to anaphylaxis. This was confirmed by KARSNER[122] in the guinea-pig. The symptoms and post-morten findings are the same as those produced by anaphylatoxin. BORDET[41] and BESREDKA and STROBEL/

STRÖBEL[35] found that agar treated with serum produces similar anaphylactoid phenomena. Similarly KEYSSER and WASSERMANN[125] found that Barium Sulphate and Kaolin, when mixed with complement, produced a substance with similar action to ananphylatoxin. NOVY and DE KRUIF[169] also obtained like results with serum peptone and serum agar. KOPACZEWSKI[129] found that anaphylactic shock could be produced by the contact of serum with Pectin which is a non-nitrogenous colloid substance. BORDET showed the same to hold good for pararobin, FRIEDBERGER and TSUNEOKI[96] for Kaolin, SCHMIDT and NATHAN[165] for Starch, and KRITCHEWSKY[134] for the sap of a Cotyledon plant. Histamin, which is an Amin produced by splitting off carbon dioxide from Histidin by chemical agencies, can also when injected, produce symptoms like anaphylactic shock.

All these reactions with substances, which contain no nitrogen, help to support the view that anaphylactic shock is due to the cleavage of protein by specific ferments with the production of a toxic substance.

The work of DOERR, JOBLING and PETERSEN and others tends to show that neither specific antigen nor complement are necessary for the production of the anaphylactic reaction. Similarly the presence of antibody/

antibody is not essential as the anaphylactic poison can be produced in vitro. An animal in a state of Antianaphylaxis to a given antigen is not protected from the effect of anaphylatoxin.

It must, however, be pointed out that although many hold that the symptoms produced by these non-nitrogenous substances are almost identical with those of true Anaphylaxis, there are others who think that the reaction should be called anaphylactoid and separated from true anaphylaxis. But all will admit that the reactions are similar and related in some way.

CELLULAR/

## CELLULAR AND HUMORAL THEORIES OF ANAPHYLAXIS.

A great deal has been written on the question of whether the anaphylactic reaction occurs in the blood stream, i.e. between antibodies or other substances in the serum and the antigen, or in the cells between the sessile antibodies and the antigen. The fact that passive anaphylaxis can be produced shows that the blood of the sensitised animal contains some substance which can be transferred from one animal to another. As already seen various names have been given to it. RICHET speaks of Toxogenin, BESREDKA of Sensibilisin, NICOLLE of Albuminolysin, and PIRQUET of Allergin. Many object to the use of the term antibody for this substance. If used in the sense that it is protective, antibody is not a good name. However, it is a convenient term to use for want of a better.

Precipitins and agglutinins occur in the anaphylactic condition but most workers are agreed that they play a secondary role in the process. The supporters of the humoral theory assume that the Toxogenin, Sensibilisin, Albuminolysin or Allergin is a specific lytic amboceptor which by union with complement forms a ferment capable of splitting the protein/

protein molecule so as to produce a toxic substance capable of producing the symptoms of anaphylaxis.

FRIEDBERGER'S theory that sessile receptors in the cells with a great affinity for antigen assumes that the cells play the chief part in the reaction. VAUGHAN and WHEELER'S split-protein theory also assumes the storing up of the specific proteolytic ferment by the cells.

A great deal of experimental work has been done by WEIL, COCA[56], SCHUTZ[216], DALE[65] and others by isolating the various organs of sensitised animals and perfusing them or applying to them the specific antigen in order to see whether these organs react to the poison or whether the poison can be extracted from them. WEIL was particularly emphatic that cellular antibody alone was responsible for the reaction of acute anaphylactic shock. The humoral theory is committed to the belief that the circulating antibody may exercise a protective (immunity) or an injurious (anaphylaxis) function depending on various accidental circumstances. WEIL thought that the cellular theory explained the relation of anaphylaxis and immunity better than any other, the circulating antibody being essentially protective as in immunity and the cellular antibody always the agent of anaphylactic symptoms.

WEIL/

WEIL showed that in dogs it is the liver cell which is sensitised and all the features of anaphylactic shock in that animal appear to be due to the effect of the antigen on the sensitised liver.

The symptoms of anaphylaxis are due to the contraction of the smooth muscles of the body, e.g. the emptying of the bladder and bowel and the difficulty in breathing and death from spasm of the bronchioles. SCHULTZ isolated the smooth muscle of sensitised guinea-pig's intestine, uterus, bladder, aorta and vena cava, freed them from blood and suspended them in RINGER'S Solution. He applied various sera to them. They contracted when normal serum was applied but to a very much more marked degree when the horse serum to which the animal had been sensitised was applied. Objection has been made to the above type of experiment on the ground that the reaction is not purely cellular as some blood is always left in the tissues. LARSON and BELL[136] showed that it is impossible to wash all the blood out of an organ by perfusion methods. The efferent fluid becomes free from blood and albumin in a short time, but these substances reappear if the perfusion is suspended for a few minutes. By perfusing organs with LOCKE'S fluid containing Indian ink the course taken by the fluid through the organ has been mapped out and it

has/

has been found that a surprisingly small part of the capillary system is really washed out by the perfusing fluid. Therefore they conclude that this type of experiment does not remove circulating antibodies completely and therefore does not establish the presence of cellular antibodies. COCA[56] on the contrary, holds that perfusion experiments are valid. He experimented with living sensitised guinea-pigs. He removed the blood but only so much as to leave less than a single minimal sensitising quantity and then introduced Indian ink in Saline Solution into the circulation. The animal was killed two minutes later, and the liver, lungs etc. showed an even distribution of ink particles all through the organs. Therefore he quotes perfusion experiments as uncontrovertible evidence of the cellular site of anaphylaxis.

PEARSE and EISENBRAY[179] replaced the blood of a normal dog with that of a sensitised animal and also conversely replaced the blood of a sensitised dog by that of a normal dog. Each dog was then given an intoxicating dose of the sensitising antigen and symptoms were produced in the sensitised dog with normal blood but no symptoms occurred in the normal dog with sensitised blood. Therefore they hold that the reaction was a cellular and not a blood reaction. COCA confirmed these experiments with the guinea-pig.

MANWARING/

MANWARING, KUSAMA and CROWE[150, 151.] did a large number of experiments by perfusing the liver and lungs of sensitised and normal animals and they showed that the perfusion of sensitised lungs with antigenic serum causes them to respond with bronchiole constriction such as occurs in anaphylactic shock. From these and other experiments by SIMONDS[222.] and others, there is evidence to show that in anaphylaxis the toxic substances are produced in the liver and act on the lung.

DALE also did perfusion experiments with isolated uterine muscle on guinea-pigs and claims to have proved "beyond reasonable doubt the intrinsic hypersensitiveness of that tissue to the specific antigen".

Experiments on passive anaphylaxis also support the cellular theory. A certain interval of time is necessary after the transference of blood before the animal becomes sensitised. WEIL has also shown that the simultaneous injection of antigen and the blood of a sensitised animal fails to produce anaphylaxis. During the interval of time the cells anchor or produce the sensitising substance and only after that has occurred is the animal passively sensitised. On the humoral theory the incubation period necessary for passive anaphylaxis cannot be explained.

From/

From the foregoing discussion therefore we must conclude that the bulk of the evidence goes to support the cellular theory of anaphylaxis. But as BORDET said in a recent lecture on the subject in Edinburgh, probably both the cells and circulating fluid play a part. The blood certainly is required to convey the antigens and antibodies to or from the cells and therefore the two elements must be intimately concerned in the reactions.

PHYSICAL/

## PHYSICAL THEORIES OF ANAPHYLAXIS.

DOERR[75] commits himself to an exclusively physical theory. He thinks that the blood contains preformed toxic substances such as are produced when the blood clots. These toxic substances are held in abeyance by "hindering bodies" in the complement. When the hindering bodies are removed or adsorbed on the second injection, the colloid equilibrium of the serum is disturbed and the toxic substances in the complement are liberated to produce anaphylactic symptoms. DOERR considers that this theory explains the reactions due to certain colloids such as Pectin etc.

JOBLING and PETERSEN[115] also hold that anaphylaxis is due to an alteration in colloids. They think that the serum proteins are normally protected from digestion intravitally by the presence of protective lipoids (unsaturated fatty acids) i.e. antiferments or antitrypsin. Partial removal of these antiferments by adsorbents like agar, bacteria etc. allows the proteolytic ferments in the serum to split the proteins and proteoses into toxic products (so-called anaphylatoxins).

DOLD[77] and BRONFENBRENNER also agree with the above views that anaphylaxis is due to the removal of the/

the antitrypsin from the serum so that a poison is produced by autodigestion of the serum. DALE also thinks that anaphylaxis is due to a change in the dispersion of the protoplasmic colloids.

The reactions produced by KOPACZEWSKI with Pectin, BORDET with agar and such like non-nitrogenous substances tend to support the physical theory of colloid dispersion.

As already mentioned however, there is still some doubt as to whether the reactions produced by these substances are truly anaphylactic. NOVY and DE KRUIF however strongly maintain that these reactions to peptone, agar etc. are examples of true anaphylaxis. Others prefer to separate them and refer to the reactions as peptone shock, colloid shock and anaphylactoid shock.

THE/

## THE NERVOUS SYSTEM AND ANAPHYLAXIS.

That the nervous system is concerned in the production of anaphylactic symptoms is probable. The fact that anaesthetics prevent anaphylactic shock taking place supports the view, but as already mentioned BRONFENBRENNER and SCHLESINGER[48.] found that certain anaesthetics increase the antitryptic action of the blood and they consider that it is for that reason that anaphylaxis does not occur. Application of antigen to isolated organs of a sensitised animal to produce contraction of the unstriped muscle of the organ gives no assistance as the nerve endings are still present.

ARNOLD and LESCHKE[12.] think that the effects of anaphylaxis are produced through the nervous system because, although the anaphylactic poison causes contraction of the muscles of the bronchi, bowel, uterus etc, it also causes dilatation of the muscular coats of the vessels. They therefore think the symptoms of anaphylaxis can be explained by the exciting effect of the anaphylactic poison on the endings of the parasympathetic system in the smooth muscles.

The antagonistic effect of atropin (which paralyses the vagus endings) in retarding anaphylaxis supports this contention. SHEURER and STRASMAN have shown/

shown that section of both vagi does not prevent the spasm of the bronchial muscles in anaphylaxis, so that if the reaction occurs through the nerves it must do so in the nerve endings in the muscle. POTTENGER[185.] came to the conclusion that in toxaemias, the disturbances of visceral function are produced through irritation of the vegetative nervous system while the anaphylactic syndrome is due to a general stimulation of the vagus. In support of this, EPPINGER and HESS[86.] showed that vagotonic persons react very readily and strongly after sensitisation to foreign protein. Intracutaneous reinjection of serum produced in such persons not only a local reaction but also a general urticaria.

CZERNY also in grouping children under different diatheses referred to what he called the exudative diathesis and showed that children of that diathesis have a mild type of thymus activity with parasympathetic irritation. This expresses itself as eczema, urticaria, and asthma. These children have a "hair-trigger" sympathetic nervous system in which the vagus is so irritable that explosive symptoms are readily produced by foreign proteins. As the vegetative nervous system is closely linked with the endocrine glands, CZERNY also thinks that in all children of/

of the lymphatic diathesis there is an underlying want of balance of the secretions of the ductless glands. As will be shown later certain persons can be much more readily sensitised than others and heredity plays an important part in Asthma, Eczema etc. Probably the essential factor for successful sensitisation is the possession of such a diathesis as CZERMY described.

Further investigation, however, is necessary before any definite conclusions can be drawn as to the part played by the nervous system.

THE/

## THE DUCTLESS GLANDS IN ANAPHYLAXIS.

The ductless glands such as the thyroid and suprarenals may play a part in the reactions of anaphylaxis but it is doubtful whether they are affected by the reaction products or through the action of these products on the nervous system. As already stated the administration of Adrenalin can prevent Anaphylactic shock in animals. It is also known to be of great use in the treatment of asthma, serum sickness and urticaria. In surgical shock with lowered blood pressure, BEDFORD[25] found that the epinephrine content of the suprarenal blood was greatly increased and this, he thinks, is a reaction to prevent dilatation of the vessels and lowering of the blood pressure. SMITH and RAVITZ[226] examined the epinephrine content of the suprarenals in sensitised and shocked animals and found it to be the same as in normal control animals.

There is therefore no definite evidence of any change in the suprarenal secretion in anaphylaxis.

Thyroid has been used with benefit in Asthma. It may act by stimulating the suprarenal secretion and GRAHAM BROWN ascribes the beneficial effect of iodides in Asthma to the same cause.

By/

By examining the blood sugar in thyroid diseases JANNEY and ISAACSON[114] found that thyroid disease favours protein catabolism, thus linking the thyroid to anaphylaxis in which there is marked evidence of protein catabolism.

KEPINOW and METALNIKOW[124] published some recent work on the relation of the thyroid gland to Tuberculin sensitisation in infected animals. In one series of experiments they found that in guinea-pigs from which the thyroids had been removed and which were subsequently infected with Tubercle, an injection of Tuberculin produced practically no general reaction whereas in control animals with thyroids, a marked general reaction occurred. They also found that passive sensitisation to tubercle could be induced with the serum of tuberculous guinea-pigs, but not with the serum of tuberculous thyroidectomised animals. KEPINOW also found that in animals from which the thyroid had been removed the injection of the toxogenic dose after previous sensitisation failed to cause anaphylactic shock. APPELMANS,[9] on the contrary, obtained exactly opposite results. He found that anaphylactic shock occurred in guinea-pigs sensitised to serum, whether their thyroids had been removed or not.

Further work is necessary, however, before the part played by the ductless glands in anaphylaxis can be estimated.

CHANGES/

## CHANGES IN THE BLOOD IN ANAPHYLAXIS IN RELATION TO THE SKIN.

A discussion of the biochemical changes in the blood such as the formation of precipitins, agglutinins, complement fixing bodies, is outside the scope of this work. Reference has already been made to the diminution of the coagulability of the blood in anaphylactic shock as demonstrated by BIEDL and KRAUS, ARTHUS,[13] FRIEDBERGER, and WEISS and TSURU.[266] WITZINGER,[269] in studying the effect of foreign serum injections in man on the coagulability of the blood, found that the first sensitising injection was regularly followed by an acceleration of coagulation, which subsided in 24 hours. On the 7th - 10th days after injection a second acceleration of coagulation occurred. The reinjection of serum, however, (i.e. the intoxicating dose) was followed in 5 or 6 hours by a marked retardation of coagulation.

Extraordinarily little attention seems to have been paid to the coagulability of the blood in skin diseases, but in some cases of chronic urticaria, a disease which will be seen later to be anaphylactic in nature, a diminished coagulability of the blood has been noted. Leucopenia in anaphylaxis has also been/

been referred to. This change does not seem to be common in skin conditions, the reverse condition being more likely to occur. The fact that the skin is so exposed to secondary infections with pus-producing organisms of all kinds would vitiate any results which might be obtained by blood examination in most skin diseases.

Eosinophilia, however, is a blood change which has a close association with anaphylaxis and with many skin conditions. STCHASTNYI[231] and ANDRÉ and COURMONT[8.] demonstrated a considerable increase in the blood eosinophile cells after injection of haemolytic sera. HOWARD[109.] found that injection of egg albumin into animals caused a blood eosinophilia. SCHLECHT[211-214.], by repeated injections of foreign albumin into guinea-pigs, found that eosinophilia was produced both in the blood and locally in the peritoneum at the seat of injection. This eosinophilia begins after an incubation period of 4-8 days, which is associated with a hypo-eosinophilia. Negative results were obtained by injecting normal saline, RINGER'S solution, nuclein and vitellin. Positive results followed injection of serum albumin, and globulin, egg white and peptone. SCHLECHT thinks that the eosinophile cells may have a special function of absorbing albumin and that their presence is a protective/

protective reaction on the part of the body. SCHLECHT and SCHWENKER[215.] also found that the bronchi and lungs of guinea-pigs in anaphylactic shock show a marked local eosinophilia and SCHLECHT also showed in the local reaction produced at the seat of reinjection in a sensitised animal (ARTHUS phenomenon) that a marked collection of eosinophile cells occurred in the epithelium and corium of the skin. Adrenalin, which controls certain cases of Asthma and Urticaria, was also found to cause a diminution or complete disappearance of eosinophile cells from the circulation.

It was also shown by STCHASTNYI[231.] that injection of alien red cells caused both a local and general eosinophilia.

WEINBERG and SEGUIN[265.] likewise found that the toxogenic dose of antigen produced an eosinophilia which appeared 1-3 days later, They think this is due to a direct irritation of the haemopoietic system by the antigen.

HERRICK[104.] did a number of experiments on guinea-pigs by giving intraperitoneal injections of an aqueous extract of Ascaris lumbricoides. This caused a marked eosinophilia of the blood. HERRICK concludes that sensitisation of the animal is necessary before an eosinophilia can occur because it is impossible to produce/

produce such eosinophilia when the animals are immune to the extract. He also states that the substance in the extract of the round worms which causes the sensitisation is a protein and that previous sensitisation is necessary for the development of the eosinophilia.

The question is, what exact relation a blood eosinophilia bears to sensitisation, and whether all diseases in which eosinophilia occurs are anaphylactic. COWIE and COLHOUN[63.] go so far as to state that unless there is an eosinophilia, any given condition cannot be anaphylactic. I do not think, however, that there is sufficient evidence to support that view in every case. Eosinophilia is known to occur in Asthma, and hay fever, which are admittedly anaphylactic conditions. But it may also occur in Spleno-medullary leucaemia, Rheumatic fever, Scarlet fever, Typhoid fever, Septiaoemia, infection with intestinal parasites, some bone diseases, and malignant infections. It also occurs after malaria and pneumonia. Enough is not known about all these conditions from which to draw conclusions, but it is possible that all cause sensitisation to some protein, either bacterial or otherwise, and so lead to an eosinophilia.

Of the diseases of the skin the Pemphigus group (including dermatitis herpetiformis) is always associated/

associated with a marked eosinophilia up to 40% or 50%. Unfortunately not much is known as to the cause of these conditions, but they are generally considered as intestinal toxaemias. This question will be discussed later under these diseases. In Urticaria which is undoubtedly a sensitisation condition, eosinophilia often occurs. It has also been recorded in eczema, (especially if widespread), psoriasis, scleroderma scabies, Lepra, Lupus (if extensive), Pellagra, erythema multiforme and Impetigo contagiosa.

STRAUBLI[228-230.] thinks that eosinophilia in skin diseases occurs as a result of disturbances of the intestinal tract in consequence of autointoxication as well as by absorption from the outside. That absorption of chemical substances may cause eosinophilia is shown by the fact that LEREDDE found an eosinophilia after ingestion of Antipyrin, BEZANCON and LABBE[137.] after administration of Potassium Iodide. EWING[87] and DA COSTA[60.] state that eosinophilia occurs after injection of Tuberculin. BERGER[26.] found that it occurred in infants after ingestion of foreign protein because he found that infants previously fed exclusively on the breast, almost regularly developed eosinophilia in 7-10 days following the administration of cow's milk.

MOSCHOWITZ/

163.
MOSCHOWITZ is a strong upholder of the connection between anaphylaxis and eosinophilia. He thinks "that the invasion of eosinophiles in increased numbers into the organism is the expression of an active agent or the agent itself in the production of anaphylaxis". He suggests that the relief of anaphylactic diseases might consist in the administration of agents known to cause a negative chemotaxis for eosinophiles and states that injection of dead bacteria are known to act in this manner.

It is therefore evident that eosinophilia occurs in the blood in many conditions, especially of the skin, which are admittedly associated with sensitisation; but at present there is not sufficient evidence to show what the exact nature of the reaction is.

ANAPHYLAXIS/

# ANAPHYLAXIS IN MAN.

## SERUM SICKNESS.

Serum sickness is now generally acknowledged to be a true anaphylactic phenomenon. It is the name applied first by PIRQUET and SCHICK to the clinical symptoms which follow the injection of horse serum. The serum of other animals, e.g. the ox or rabbit may also produce the same symptoms. Although most often due to the use of antitoxic sera for diphtheria or tetanus, the symptoms are caused by the horse serum and not by the antitoxine. The larger the dose of serum the more likely are symptoms to occur. KER[285.] says "we may expect to chiefly meet with them in mild and moderate cases (of diphtheria) which have received very liberal dosage".

The chief features of serum sickness are skin rashes, pyrexia and joint pains, but oedema especially of eyelids and adenitis may occur. Vomiting may also occur but is not very common. The most important symptom is the skin rash which may assume various forms. Urticarial rashes are the most common. Typical urticarial wheals of large size and irregular shape appear usually near the site of injection first, but/

but spread to other parts of the body and limbs. Itching may be intense. The rash may continue to come out for two or three days. The urticarial rash usually appears from the eighth to the eleventh day after injection.

The rash may however be in the form of a multiform erythema with large bluish-red blotches or patches with circinate outline. Occasionally haemorrhages and morbilliform and scarlatiniform rashes occur.

KOLMER[127] states that in 1000 consecutive cases of diphtheria treated in the Philadelphia Hospital for Contagious Disease a rash developed in 43% . Rashes may occur after a primary or after several injections. They are due to the foreign serum, when injected, calling forth the production of an antibody or ferment, which acts on the serum still in the circulation. This causes its cleavage and liberates a poison which causes the symptoms. It takes several days till this antibody is formed and that is why the rash does not usually appear till the 8th - 11th day. It has been shown by WEIL[300.] that a foreign serum on injection remains in the circulation for many days. As soon as the antibody is formed in the circulation in sufficient amount, i.e. after 8-11 days, the symptoms appear. If the dose of serum is small, although the antibody is formed, there may not be any serum left in/

in the circulation to cause symptoms. That is the reason why trouble is more likely to occur after large doses of serum than after small doses. If, on the other hand, a person has had an injection of serum some weeks or months previously, the reinjection is likely to be followed by an "immediate" reaction within 24-48 hours. The antibody is already there and immediately reacts with the antigen. If the reinjection is made a year or more after the first injection, the symptoms usually appear in 4-7 days, i.e. an "accelerated" reaction. The explanation of this reaction is that although no antibody is present at the time of reinjection, the body cells having been previously stimulated to produce antibody, can do so more quickly, hence the accelerated reaction. But if a small amount of antibody is still present at the time of reinjection, one gets an "immediate" local reaction within 24-48 hours at the site of injection followed in 4-7 days by a general "accelerated" reaction.

The immediate reaction described above therefore corresponds very closely to the milder forms of anaphylaxis as seen on laboratory animals. A sensitised animal such as the rabbit, if it is subjected to an anaphylactic shock and recovers, frequently shows within the following days a very marked general urticarial rash with wheals and great itching, which leads/

leads to such vigorous scratching that the animal almost denudes itself of fur.

In human beings severe forms of serum disease characterised by sudden onset within a few minutes after the injection, have been recorded. These cases show extreme prostration and dyspnoea and may end fatally as in anaphylactic shock in animals. These fatal cases are very rare considering the number of injections given. Asthmatics, who are sensitive to the horse, are particularly liable to this risk. SUMNER[298.] reports such a case this year in a girl aged 8 who died within 5 minutes after a prophylactic injection of antidiphtheritic serum. DEAN[292.] also recorded in 1922 a case in a soldier who died with cyanosis, vomiting and collapse 70 minutes after the fourth injection of antitetanus serum. In this case a post-mortem was performed and it was found that the liver had a deep purplish colour and seemed to contain an excess of blood. Microscopically the liver showed extreme congestion with swelling of the liver cells and in some cells a disappearance of the nucleus. The lungs showed an irregular dilatation of the capillaries with the alveoli dilated in some places and compressed in others. DEAN points out the similarity between this anaphylactic shock in man and in the dog, and thinks that the chief and essential change is in the/

the liver and that the dilatation of the capillaries of that organ cause the fall in blood pressure. Somewhat similar cases have also been reported recently by PEHU and BERTOYE[292], MARTIN[291] and others. To show how small a dose can produce fatal results, a case of BOUGHTON'S[277] may be quoted. A man, aged 29 who had suffered for 10-12 years from horse asthma was given a dose of 1 minim of horse serum and died within 45 minutes. In this case all the gross and microscopical appearances at the post-mortem were like those of experimental anaphylaxis in animals.

JOUSSET[284] and others, who have given large numbers of serum injections without producing any signs of anaphylaxis, hold that the risk of a fatal termination is nil, but in the face of the cases referred to above there is no doubt that the risk does exist. Probably not more than 50 fatal cases have been recorded but although that is a small percentage in the total number of cases treated, one must admit the possibility of grave danger.

THE/

## THE PREVENTION OF SERUM DISEASE: DESENSITISATION.

Before giving horse serum, especially in individuals in whom there is any suspicion that they may be sensitive either from previous inoculation or from attacks of asthma, urticaria etc. it is advisable to test the patient. The injection of a small dose to produce a general reaction is inadvisable in view of BOUGHTON'S fatal case after a dose of one minim, but by the application of the cutaneous test valuable information without risk may be obtained. The serum is applied to a small scarified area of skin and within 15 minutes a wheal surrounded by an area of erythema appears. The intracutaneous test may also be used. These cutaneous tests will be referred to fully when the cutaneous reactions come to be discussed.

If the person to be inoculated is sensitive to horse serum then, if possible, ox serum should be used for the treatment and it is a good plan to use ox antidiphtheritic serum for all prophylactic injections so that if the person develops diphtheria at any time later, the horse antidiphtheritic serum can be used.

Even in cases where one has no reason to suspect/

suspect a previous sensitisation, and the case is not urgent it is advisable to give a preliminary injection of .5 cc. of serum, followed in 3 or 4 hours by the therapeutic dose. Preliminary rectal injection of the serum, as recommended by BESREDKA, may also be used. MACKENZIE[290] recommends that in sensitive persons, the first desensitising dose should be given subcutaneously, beginning with not more than 0·025 cc. This dose should be doubled every half hour till 1 cc. is given. Then 0·1 cc. is given intravenously the dose being doubled every twenty minutes till 25 cc. has been given. Four hours later 50 cc. may be given and after 8 hours larger doses still. Various modifications of the above method have been recommended by others.

LEWIS[288] has shown that acute anaphylactic shock can be prevented in sensitised animals by giving otherwise fatal doses of diluted antigen intravenously at very slow rates. This method can be used for human beings who require intravenous injection of serum. WOODYATT[302] has devised a pump operated by an electric motor and attached to the syringe. By this means as small a volume as 0·1 cc. per minute of diluted serum can be injected into the vein. LEWIS[289] also investigated the route of absorption of serum /

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serum on subcutaneous injection. He found that the serum was absorbed by the lymphatics. This method of absorption is too slow to account for the sudden fatal cases. He thinks that these cases are probably due to an accidental intravenous injection of the serum.

## CONCLUSIONS.

1. Serum sickness with its associated skin rashes is a true anaphylactic phenomenon and corresponds to the anaphylactic reactions in animals allowance being made for the difference in reaction in different species.
2. Fatalities after serum injections are deaths from true anaphylactic shock resembling most closely anaphylactic shock in the dog.
3. Desensitisation or antianaphylaxis can be successfully achieved by suitable methods.

## NATURAL HYPERSENSITIVENESS.

In serum disease the hypersensitive state is produced artificially by injection of the serum, but there is a large group of cases where individuals are found to be extraordinarily susceptible to certain foods, animal emanations or plants. These used to be called Idiosyncrasies. The study of anaphylaxis, however, has done much to explain many of these phenomena, and it will probably be found that, as more is discovered, they ~~will~~ are all ~~be found to be~~ sensitisation phenomena of varying character. It has long been known that certain persons, on eating certain foods, such as egg albumin, pork, oysters, lobsters, crab, strawberries etc. suffer from urticarial rashes, indigestion, diarrhoea and vomiting, etc. Hay fever and horse asthma are examples of the same phenomenon where the reaction takes place by the inhalation of the substance to which the individual is sensitive. Also it has been suggested that drug eruptions come into the same category. The fact that the symptoms are produced by minute quantities of the offending protein, that such cases give a positive cutaneous reaction to it and that they may be desensitised by ingestion or inoculation with the protein all point to the phenomena being anaphylactic.

The/

The fact that it is not definitely known in every case how such individuals become sensitive is not against the anaphylactic theory. It will be shown later that proteins can be absorbed unchanged through the bowel and that sensitisation can be produced by rubbing the juice of plants into the skin. Inhalation into the lung or absorption through the mucous membranes of the nose or throat are also possible. As already mentioned it has been shown that guinea pigs can be sensitised to animal and vegetable proteins by feeding the animals on them. Heredity has been shown to play a part. COOKE and VAN DER VEER[307] showed that liability to asthma, hay fever, urticaria etc. runs in families but the actual sensitiveness of the individual is probably acquired. Members of certain families appear to be much more easily sensitised than other individuals and it is probably this faculty of "sensitisability" that is inherited. Evidence of this will be brought forward later under plant sensitisations. In support of this also is the fact that these sensitisable individuals are often sensitive to several proteins and may become desensitised to one protein and later become sensitive to another.

THE/

# THE RELATION OF ANAPHYLAXIS TO ACUTE AND CHRONIC DISEASES.

As we have already seen in Serum disease the incubation period before symptoms occur and the other phenomena can be explained on the anaphylactic theory. So in infectious diseases PIRQUET[317] pointed out the similarity between their course and a case of serum sickness. During the incubation period antibody formation is going on and when that is sufficiently developed an antigen-antibody reaction takes place as in serum sickness with the liberation of the toxic substance which causes the symptoms. The incubation period of most infectious diseases (8-12 days) such as small-pox, measles, chickenpox, etc. corresponds closely to the incubation period of serum sickness. PIRQUET[319] applied the same principle to the study of vaccinia. As the result of a primary vaccination the virus grows on the skin. About the third or fourth day an elevated papule occurs surrounded by an erythamatous area and by the 7th or 8th day a vesicle is formed. These changes are due to the virus growing and multiplying in the skin, but by the 8th day or so antibody is beginning to be formed, a reaction occurs with marked local pain and swelling and often general symptoms. In this process the virus is destroyed and the/

the vaccination heals. At this time, usually about the tenth day, a general vaccinal exanthem may occur. This rash is bright red, slightly raised, "measly" eruption and appears simultaneously on all parts of the skin especially on the back, the extensor aspects of the limbs and on the forehead, cheeks and ears. It is usually very itchy and may go on to vesiculation. As it fades it becomes browner and develops lichen-like papules. That the body is not in the same position as it was before vaccination is shown on revaccination of the same individual. The virus introduced again into the skin a month later is at once attacked by the antigen-antibody reaction before it has had time to multiply and in a few hours a slight reaction with only papule formation develops, which begins to involute in 24 hours. This corresponds to the immediate reaction described under serum sickness. If the revaccination takes place some years after primary vaccination, the reaction takes 3-4 days to begin as the antibody is in slight amount or absent, but owing to previous vaccination can be more rapidly called forth producing what corresponds to the "accelerated" reaction of serum sickness.

PIRQUET suggested the term Allergy for the altered reaction capacity seen in serum sickness, revaccination etc. He thinks it is not identical with anaphylaxis/

anaphylaxis but is included under the complex of "Immunity Reactions". It is interesting to note that as far back as 1798 JENNER noticed during his experimental work in small-pox, that if a person had once passed through an attack of small-pox or cow-pox, he may respond to the cutaneous application of the virus if made years afterwards, by an "early local cuticular inflammation". This is the first known observation of an anaphylactic phenomenon and describes accurately the accelerated reaction.

Of course all the symptoms of acute diseases cannot be explained on the anaphylactic theory. The question of how many of the symptoms are due to toxines also comes in. In diseases like diphtheria the toxine produces effects quite apart from the protein of the bacteria. But taking everything into consideration the course which acute infectious fevers run can be explained fairly satisfactorily on the assumption that they are due to bacterial anaphylaxis.

The relation of anaphylaxis to chronic diseases such as asthma, etc. has already been mentioned, but there is still the large group of chronic infections such as tubercle, syphilis etc. which will be more fully discussed separately. All the evidence goes to show that these are examples of sensitisation to bacterial proteins.

## RELATION OF ANAPHYLAXIS TO IMMUNITY.

There is still difference of opinion as to the relation of anaphylaxis and immunity. VAUGHAN 326. and his supporters go so far as to say that the mechanism in both cases is identical. They hold that in immunity the antibody is circulating in excess in the blood and by combining with the antigen protects the body cells and prevents the antigen reaching the antibody in the cells and so symptoms do not occur. The question is too complicated to discuss fully here but the toxin-antitoxine reaction also comes in in questions of immunity. That the hypersensitive reactions play a part in the protection of the body against infection is undoubted. Local hypersensitive reactions lead to hemming in and destruction of organisms. DANYSZ and others hold that in infectious disease the individual passes through a period of hypersensitiveness before the stage of immunity is reached. That sensitisation persists after the disease dies out is an important fact. For example it will be seen later that cases of Kerion Ringworm may give a positive skin reaction on the application of the ringworm fungus many years after healing. This hypersensitive state of the skin cells leads to a local/

local reaction on reapplication of the infecting agent and this reaction leads to the destruction of that agent. Therefore the hypersensitive state of the individual protects him against further infection and causes, for practical purposes, an immunity. The same is seen in diseases such as syphilis. There is no absolute immunity to it and so long as an individual has syphilis he cannot be reinfected. Whilst he has syphilis he is sensitised to it and as will be seen later an attempt to reinoculate him leads to the production of a hypersensitive reaction which at most produces a local reaction and prevents a general spread.

Desensitisation by bacterial vaccines in infections and by protein substances in conditions such as asthma can be accomplished. This leads to at least a temporary cessation of symptoms, but does not seem to be quite the same as immunity. The effects are not lasting. All the evidence therefore goes to show that sensitisation plays a part in protecting the body against disease, but that other factors, e.g. toxines, play a part.

URTICARIA/

## URTICARIA INCLUDING ANGIONEUROTIC OEDEMA.

As we have already seen the most frequent rash in serum sickness is an urticaria clinically indistinguishable from an ordinary nettle-rash. We have also seen that all the evidence points to serum sickness being anaphylactic. It is not a very far step to take, therefore, to suggest that Urticaria also is anaphylactic in origin. This was first done by WOLFF-EISNER[399] in 1907 and since then many others have supported this view. WOLFF-EISNER included all forms of Urticaria both from external and internal causes; but it will be well to treat each group separately.

### URTICARIAS OF EXTERNAL ORIGIN.

The causes may be roughly divided into three groups.

(1) Vegetable irritants such as nettles.

(2) Animal irritants such as bites from pediculi, bugs, gnats, fleas, mosquitoes etc. and stings from bees, wasps, etc, and

(3) Physical irritants such as scratching (dermographism) rubbing or stroking the skin etc.

(1)/

## (1) VEGETABLE IRRITANTS.

All of us have experienced the effects of handling the ordinary nettle. The wheal, which results, is typically urticarial. WOLFF-EISNER included the nettle sting when he suggested that urticaria was a sensitisation phenomenon. With this view I cannot agree. In order to gain information on this point I experimented on myself. I stung the inner aspect of my left forearm with the leaf of the common wild nettle (Urtica dioica) every day for a month on the same area of skin. On the first occasion redness appeared in 30 seconds and in two minutes definite minute wheals were visible. These wheals gradually increased in size for about 40 minutes and then slowly disappeared after about 4 hours. Immediately the nettle was applied the usual stinging sensation was felt, which persisted at intervals till some time after the wheals had disappeared. There was never any real itching; it was more a tingling sensation. Next day, where the wheals had been, minute punctiform haemorrhages were distinctly visible not unlike minute flea bites. On repeating the application of the nettle daily to the same area I always experienced the same stinging sensation as at first and the wheals/

wheals always appeared in about two minutes or so, but they did not last nearly so long. Whereas at first they persisted for about 4 hours, at the end of a month the wheals all disappeared in about an hour and a half. Therefore no alteration had occurred in the reaction except that the skin seemed to show a certain degree of tolerance, but no increased sensitiveness nor immunity was produced.

I then stung both forearms simultaneously to see if there was any difference between the skin of the arm which had been repeatedly stung and that of the other arm. I found that the reaction was practically identical on both sides, but the stinging sensation was distinctly more marked and lasted longer on the arm which had not been stung repeatedly. I next crushed up the nettle leaf and rubbed it well into the skin of the arm. It produced wheals in a few minutes and these wheals were always situated at the mouths of the hair follicles, where the juice had penetrated. No dermatitis occurred such as occurs on application of plants like the primula to sensitised individuals. This showed that my skin was not in any way sensitised to the nettle.

If a nettle sting is a sensitisation phenomenon the first application of the nettle, like the sensitising/

sensitising dose, in anaphylaxis, should produce no symptoms. Like practically all individuals in this country, I had been repeatedly stung by nettles before I did these experiments. Therefore I could not hope to get any information on this point from adults. I therefore tested the skin of the legs of three infants at the Royal Maternity Hospital with the kind permission of the late Dr. J.W. Ballantyne. These infants were normal children of one, ten and thirteen days of age respectively. All three reacted within two minutes with the typical nettle sting with wheal formation. I also touched the skin of one of our clinical assistants, an Australian, who, as far as he knew had never been stung previously by a nettle and he also reacted immediately.

From these results I conclude that the nettle sting is not a sensitisation phenomenon, but a mechanical irritation from the puncture of the skin by the fine hairs on the leaf and the injection of an irritating fluid.

## (2) ANIMAL IRRITANTS.

Bites from insects cause reactions which vary with the insect and the individual bitten. It is well known that in some persons a mosquito bite may/

may lead to a very great local reaction whilst in others little or no inconvenience is experienced. BOYCOTT[333.] in 1912 performed some very interesting experiments with fleas on laboratory attendants. He found that the wild rats (Mus decumanus seu Norregicus) in the Pathology Department of Guy's Hospital, London, were infected with two kinds of fleas, viz. Ceratophyllus fasciatus (common English rat flea) and Xenopsylla cheopris (Tropical rat flea). Both species bite man freely when given the opportunity. BOYCOTT found that ordinary persons show no reaction after being bitten experimentally by either species for the first time, but he assumed that people living under ordinary good conditions in this country are not exposed to the attack of rat fleas. Two individuals were taken, A. who was known to give a prompt and extensive reaction to the bite of the human flea (Pulex irritans) and B. to the bite of the cat flea (Pulex felis). To A. was fed cheopis and to B. fasciatus. No effect was produced at first but after 5 feedings in six weeks each gave an extensive local reaction at the site of the bite. BOYCOTT therefore concludes that by repeated bites these individuals had become sensitised. Control persons who had not previously been bitten gave no reaction. To test the specificity of/

of the reaction the fleas were reversed, fasciatus being fed to A. and cheopis to B. In both cases a violent reaction was produced at the first bite. BOYCOTT suggests that the absence of specificity might be due to the individual being sensitised to "ratness" rather than to "fleaness", because it is possible that the flea, when biting, injects along with its own protein, material from its immediately preceding host. But man becomes reactive to the human flea, and that would involve the possibility of man becoming sensitised to "manness". BOYCOTT thinks that it is much more likely that there is a biological similarity between cheopis and fasciatus. This would bring it into line with the findings in anaphylaxis which are quantitatively but not qualitatively specific as regards tissues of the same group.

Eleven months later the sensitiveness of A and B. was tested again. A who had originally been sensitised to cheopis still reacted well to it but failed to react to fasciatus and B. who had originally been sensitised to fasciatus still reacted to it and also to cheopis.

385.
STOKES in 1914 made some interesting experiments with the Black fly (Simulium Venustum) a kind of gnat of the same family as SAMBON described as causing the spread of Pellagra. These insects produce papulo/

papulo-vesicular lesions which later develop into nodules. These nodules remain for days and itch periodically. WILLIAMS[397] also refers to this periodicity of itching after bites from Norwegian midges and East Anglian gnats. I can also corroborate the periodicity of itching from my own experience. Some years ago, whilst in Vienna, I was bitten repeatedly, as most people there are, by the ordinary bug (Cimex Lectularius). The bites produced very little effect for 24 hours, but after that they swelled up into large nodules which itched intensely once or twice in the 24 hours for several days. In summer I also experience periodic itchy lesions from the sting of some insect in this country, which I am unable to track. BRAMWELL[334] suggests that the periodicity of the itching may be due to the acid and alkaline wave, which passes over the blood during digestion. He noticed in his own case that gnat bites were always most irritable after getting out of bed in the mornings and the irritation did not cease till he had broken his fast. The irritation returned as soon as the stomach was empty and was relieved by the next meal. This does not agree with my own experience, which was the same as that of BEDDARD[332] who found that the itching recurred every 24 hours or so.

STOKES[385] found that the bites from the Simulium flies showed microscopically, in addition to other/

other cells, marked collections of eosinophile leucocytes. He also states that the natives in areas where these flies abound are practically immune to the insect whereas strangers always react in different degrees to the bites.

Some years ago when on holiday in Norway I was badly bitten by mosquitoes. In me the bites caused very little reaction but, in a Scottish lady, who was also bitten, each bite swelled up to such an extent that the whole face was swollen and the eyes closed and the arms were swollen to nearly double their natural size. On enquiry it was found that this lady had been badly bitten by mosquitoes in Canada on the previous year. On that occasion, however, they caused very little trouble. Evidently since her visit to Canada she had become semsitised and when bitten later in Norway gave a very marked reaction.

STEINER[384] found that immunity to the local manifestations of the Simulium fly gradually develops in the course of three years residence in an infected area. When one is bitten by a blood sucking insect, it injects a fluid to prevent coagulation of the blood and to this one probably becomes sensitised. Persons who go out to countries where flies and mosquitoes are numerous often have trouble for some time with/

with enormous oedematous reactions from bites but after repeated bites they apparently become desensitised and no longer react. This also explains the extraordinary absence of irritation among the poorer class of hospital patient from the bites of fleas and pediculi. They have been bitten so often that they are immune or at least desensitised and as these individuals are always being rebitten the desensitisation is kept up.

FREEMAN[349.] quotes CLEWES who had a case of a lady who, lived near Lake Erie and in whom a bite from a gnat caused such swelling that she had to go to bed for several days. CLEWES collected gnats, bruised them in a mortar and made a vaccine from the extract. After several inoculations the lady could lie out near the lake and "be bitten with pleasure".

Both STOKES and STEINER refer to cases where man and animals bitten by various species of Simulia in addition to showing marked local swellings developed a high temperature and collapsed. That insects can produce illness by introducing toxines when they bite was shown by MOORE[372.]. He bred the Pediculus corporis experimentally in large numbers and the insects were fed by being allowed to bite laboratory assistants. Persons bitten frequently began to complain of/

of general tiredness, severe headache and later chills and rise of temperature. MOORE himself who was bitten by 700-800 pediculi twice daily experienced a tired feeling in the calves of the legs, along the shin bones and soles of the feet, so intense as to prevent sleep. He had a general feeling of irritability and pessimism. Later he developed a rash like measles and the temperature rose. The symptoms and the rash disappeared when he stopped feeding the lice and reappeared each time when he began again. MOORE suggests that some of the symptoms seen in Trench fever may not be due to an organismal infection but to the bites of pediculi which introduce a toxic substance when they bite.

Stings from bees, wasps etc. are in rather a different category. These insects inject a very irritating fluid when they sting and everyone experiences pain and reaction on the first sting. They are analogous to the nettle sting on a large scale. The cases of death from multiple bee stings are not to be wondered at because the amount of shock to the nervous system and the amount of poison injected must be considerable. But it is a question whether collapse or even death following one sting from a bee is not due to anaphylaxis. It is well known that/

that those who work with bees and have been repeatedly stung become much more tolerant to stings than other people.

## CONCLUSIONS.

Therefore from the fact that fleas do not cause a skin reaction after the first bite, that a reaction develops later after repeated bites, that bites from insects show an eosinophilia and that repeated bites can lead to an immunity, I think we are safe to assume that unlike the nettle sting, such reactions are sensitisation phenomena. Whether reactions from stinging insects are associated with sensitisation is not so clear. They may be usually due to irritant poisons, but occasionally to sensitisation.

## (3) FACTITIOUS URTICARIA OR DERMOGRAPHISM.

This is the condition where wheals are produced by rubbing, or scratching the skin. In some cases of urticaria wheals can be produced in this way, and it is useful as an aid to diagnosis when no spontaneous eruption is present. In other cases it is present always in certain individuals who may never have had ordinary urticaria. Of course, if a blunt/

blunt instrument is drawn across the skin, in the normal individual, a faint red line appears in about a minute and the cases of dermographism are apparently very exaggerated forms of the same reaction. TRACEY[391] found that mechanical irritation of the skin by stroking with a wooden instrument leads to vaso-dilatation, brief in duration, followed by vaso-constriction which is long-lasting. He holds that it is caused by a double nerve mechanism, one of vaso-dilatation (autonomic) and the other of vaso-constriction (sympathetic) These nerve mechanisms are activated by two hormones, the hormone X of EPPINGER and HESS (Autonomym) which activates the vaso-dilatation mechanism and the hormone epinephrin which incites the sympathetic nerve endings and activates the vaso-constriction mechanism. WEIDENFELD[395] also found that in cases of dermographism the skin did not react over an area anaesthetised with cocaine and that epinephrin influenced the skin in such a way that it did not react to mechanical irritation. The extraordinarily rapid effect that subcutaneous injection of adrenalin has in causing the disappearance of the rash in certain cases of urticaria is also interesting in this respect. The cases of urticaria following shocks, emotional disturbances also may be produced in the same way although some of them may act by producing gastro-intestinal disturbances/

disturbances which lead to urticaria.

GILCHRIST[351-354.] examined microscopically, artificially produced wheals in cases of dermographism. Pieces of skin were removed 2, 5, 8, 15, 25, 40 and 60 minutes after the lesions were produced. He found an extraordinary degree of inflammatory change present. There was marked oedema of the connective tissue and fixed cells, profuse emigration of polymorphonuclear leucocytes and lymphocytes; pronounced fragmentation of the polymorphoneuclear leucocytes and connective tissue cells; apparent increase in mast cells and the presence of eosinophile cells; swelling of the cells of the sweat glands with fibrin scattered through the corium. In fact the typical picture of an acute inflammation was present and a fragmentation of nuclei as marked as that produced by diphtheria toxine. He thinks the only possible explanation is that some toxine is circulating in the blood in these cases, and when a wheal is produced some of the toxine is set free and produces death of cells, which is followed by acute inflammatory changes.

HODARA[360.] in 1913 confirmed GILCHRIST'S findings. He found the same changes in the normal skin of dermatographic patients but with less oedema of the cutis and epidermis than when wheals were present.

FISCHER/

345.
FISCHER produced an experimental urticaria on a gelatine plate by injecting formic acid into the gelatine with a hypodermic syringe and then immersing the plate in water. A typical urticarial wheal resulted wherever the acid had been injected. He holds that urticarial wheals are caused by oedema due to a localised increase of acid products in the skin as a result of the anaphylactic process. These acid products lead to the tissue colloids imbibing water.

Whatever the mechanism of the wheal formation, in dermographism in otherwise healthy individuals, there is no evidence to connect it with anaphylaxis.

URTICARIAS/

## URTICARIAS OF INTERNAL ORIGIN.

Under this heading are included the ordinary urticarial rashes with small or large wheals, the giant urticaria with large wheals (so-called angio-neurotic or QUINCKE'S oedema) and urticaria papulosa in children.

As already stated the type of the ordinary form of urticaria is the rash in Serum sickness which is anaphylactic in nature. It has long been known that in certain individuals certain foods cause urticaria. Shell-fish such as crab, lobster, mussels and oysters are very common causes, but meats such as pork etc. and eggs are also frequently found to have the same effect. Meats which are tinned or which have been kept too long, e.g. "high" game are also often to blame. Oatmeal, brown bread and foods of that kind cause urticaria especially in children, and fruits, especially oranges. It has been shown that many cases of urticaria give positive cutaneous food tests and that is a point in favour of their being cases of sensitisation. The food tests will be referred to fully later on.

These food urticarias are usually accompanied by no other symptoms but there are cases on record where severe symptoms like anaphylactic shock have followed/

followed the taking of some ordinary food. STOKES[386.] reports the case of his own son who, on the first occasion of his getting some raw egg-white, immediately became cyanosed, the face became greatly swollen with giant wheals and alarming collapse took place. The same thing happened when white of egg was applied to the head to keep his hair in position. The same boy could eat hard-boiled eggs with safety, but if he ate a soft-boiled egg he had a quick response with urticaria. Small quantities of foods to which such persons are sensitive will produce marked urticaria.

Intestinal parasites may also cause urticaria but whether the patient is sensitised to the worm or the worm alters the process of digestion and allows of sensitisation to some food or bacterial substance in the bowel is not quite clear.

It will be seen later under eczema that certain persons have the faculty of absorbing proteins by the bowel and throwing them, in an undigested state, into the circulation. This is probably the method by which sensitisation to foods occurs.

JOHN THOMSON[390.] also reported recently a case of an infant whose mother suffered during the 4 years preceding the child's birth from attacks of urticaria, local oedema and hay fever after eating acid fruits or bananas. During the first few months of life the baby who/

who was on the breast, had on several occasions a meal of cow's milk with no ill effect. When 7 months old she was given rice pudding and milk which was followed at once by urticaria and asthma. From that time onwards she had violent symptoms whenever she was given cow's or goat's milk or raw white of egg. Half a teaspoonful of milk was sufficient to bring on an attack in a few minutes. The breathing became difficult and there was sneezing and coughing and running at the eyes. An urticarial rash also appeared. The child was very ill and collapsed for two or three days. All infant foods made from milk caused the same symptoms. Peptonised milk did so, but to a less degree. Raw white of egg had the same effect, but the child could take boiled and fried eggs with impunity. The above is obviously a case of hypersensitiveness and it is interesting to note that as others have observed cooking the food so alters it that symptoms do not occur.

WHITFIELD[394.] described in 1921 some cases of what he calls auto-sensitisation. One was a young lady who received a severe blow from a cricket ball on the shin. A haematoma without any breach of surface was produced. Ten days later a generalised erythemato-urticarial eruption strongly resembling that seen after serum injections appeared. No other cause could/

could be found for it and WHITFIELD suggested that it might be connected with the absorption of broken-down tissue at the site of the bruise. The other case was in a lady who fell down stairs and damaged her left wrist producing a severe bruise. Again, on the tenth day, a general rash appeared as in the former case.

At the meeting of the British Association of Dermatology in Edinburgh in July 1922, BARBER[329] mentioned a similar case to WHITFIELD'S with an urticaria following an injury. BARBER, WILFRED FOX and SKINNER also mentioned that they had seen urticaria follow in 3-10 days after amputation of the breast. In all these cases there was no sepsis at the site of the operation.

Some weeks ago I saw a lady who suffered from urticaria every time she took exercise such as dancing. Are these cases of sensitisation to products of their own tissues? I hesitate to accept this view as the only organ, from its own body, to which it is known an animal can be sensitised is the lens of the eye. In my case the exercise might produce some substance in the muscles or there might be an increased absorption from the bowel which would account for the urticaria. It is also possible that increased circulation in the skin during exercise might excite an urticaria which would not otherwise have appeared.

Focal/

Focal infections such as tonsillitis, pyorrhoea, abscesses at the roots of teeth, infections of the bladder and bowel etc. have all been known to produce Urticaria. As an example of this, I saw recently a lady of 60 years of age who had suffered for 2 months from an extensive urticaria. She was dieted in various ways but with no improvement. Cutaneous food tests were done to all the common foods but all were negative. Her teeth were apparently all right, but 3 weeks or so after I first saw her she developed slight pain in one tooth. Her dentist extracted that tooth and found a small abscess at the root and within 48 hours the urticaria disappeared and has not returned after several months now. Therefore in searching for a cause all cases of chronic urticaria should have the teeth X-rayed for apical abscesses. Drugs such as quinine, iodides, salicylates formalin etc. may also cause an urticarial rash but these will be discussed under drug rashes.

RAVITCH[379.] reports four cases where removal of septic tonsils caused a rapid disappearance of urticaria. TURNBULL[392.] also describes two cases of giant urticaria in which the condition was entirely relieved after removal of the tonsils and a radical sinus operation where the sinuses contained pus.

The/

The bursting of hydated cysts into the peritoneum is frequently followed by urticaria. CHAUFFARD BORDIN and LAROCHE[337] produced anaphylaxis in animals with injections of fluid from hydated cysts. As PONTARO[377] and others have shown, a high percentage of patients with hydated disease give a positive cutaneous reaction to cyst fluid. BARLING and WELSH[331] found that eosinophilia of the blood is present in 50% of cases of hydated disease in a marked degree, moderate in 25% and absent in 25%. DÉVÉ[343] in 1910 reported a case of death following operation for hydatids. This he attributed to anaphylaxis. In hydatid disease, therefore, the patient seems in most cases to be sensitised to the protein of the cyst fluid and any sudden absorption of that fluid may lead to urticaria or symptoms of shock.

Urticaria may be associated with other diseases such as malaria, rheumatism etc. but whether it is accidental or due to sensitisation to proteins from the infecting agent is not clear.

WARD[393] has recently noted the frequency of urticaria after specific fevers especially pneumonia and influenza. He estimates that it occurred in 20% of his cases of pneumonia. The eruption usually occurs within/

within a day or two after the temperature has come down to normal. Sometimes the temperature rises again slightly as the rash appears and occasionally there are joint pains. In such cases the rash is probably a sensitisation phenomenon due to the protein of the infecting organism. After pneumonia a cutaneous reaction is present indicating that sensitisation has taken place.

THE/

## THE DUCTLESS GLANDS IN URTICARIA.

Reference has already been made to these glands in Anaphylaxis. HOFFMAN[361.] found that dermographism, urticaria, asthma and hay fever (of which the latter two are acknowledged to be anaphylactic). are not uncommonly associated with exophthalmic goitre. LEVI and ROTHSCHILD[366.] also think that urticaria is an expression of hypothyroidism and cite cases where thyroid treatment caused rapid improvement and cure. They think that thyroid acts perhaps by its effect on the vaso-motor mechanism. RAVITSCH agrees with this view and states that in a good many cases of chronic urticaria thyroid extract is a specific. But he also states that in cases of hyperthyroidism with urticaria, X-rays to the gland will cure the urticaria. BARBER[328.] reports a case of chronic urticaria with enlarged thyroid whose eruption came out after the slightest exertion. Rest and removal of septic tonsils and administration of an autogenous vaccine from the tonsils brought about a great amelioration of the symptoms with a diminution in the size of the thyroid gland. That would suggest that the change in the thyroid was secondary to the toxic absorption from the tonsils and like the urticaria was a symptom of absorption/

absorption and not the cause of the urticaria.

HOLDEN[362.] also reports a case of angioneurotic oedema in a woman in whom the eruption disappeared during successive pregnancies, when the thyroid became more active and reappeared shortly after the birth of the child. Administration of thyroid extract cured this case. Therefore it is evident that changes in the thyroid, especially a diminished function, are commonly associated with urticaria.

BLOOD/

## BLOOD CHANGES IN URTICARIA.

WIDAL, ABRAMI, BRISSAUD and JOLTRAIN[396] showed proof of the anaphylactic origin of certain urticarias by an examination of the blood. In a case of giant urticaria, due to animal food, they found all the phenomena of anaphylaxis, viz. fall in blood pressure, diminished coagulability of the blood and leukopenia. WRIGHT and PARAMORE[400] reported in 1905 the delay in coagulation of the blood in urticaria, which they believed to be due to a deficiency of calcium content. On the other hand PEPPER and KRUMBHAAR could not find any deficiency in lime salts in urticaria.

PAGNIEZ and VALLERY-RADOT[374] also found in chronic urticaria that the blood changes corresponded very closely with those which occurred in anaphylactic shock.

SHATTOCK[383] found in cases of chronic urticaria a delayed coagulation time in 4 out of 5 cases. Therefore although the reports on the blood changes in urticaria are few, what there are, support the anaphylactic theory.

HEREDITY/

## HEREDITY IN URTICARIA.

COOKE and VAN DER VERR[307] showed that heredity plays an important part in Asthma, eczema and urticaris, and that certain families are much more liable than others to suffer from these diseases. CROWDER[341] reports a family in which numerous cases of angioneurotic oedema occurred in 5 generations. EDGERLEY and LUSH[344] also report angioneurotic oedema in 4 members of the same family. It is, I think, a general clinical experience that members of certain families are liable to urticaria. Heredity seems to play the same part in urticaria as it does in other sensitisation phenomenon, i.e. individuals of certain families can be more easily sensitised than members of other families.

DESENSITISATION/

## DESENSITISATION IN URTICARIA

If urticaria is a sensitisation phenomenon, then desensitisation should be possible. The fact that, in many cases, the eruption comes out in crops, with periods of quiescence in between, favours this view. PAGNIEZ and VALLERY-RADOT,[375] in a case of giant urticaria of the face with intense ordinary urticaria of the body, by giving the patient a small quantity of the albuminous substance, which caused the eruption, one hour before a meal containing this substance, succeeded in preventing the urticaria coming out. Later they found that the same result could be obtained by giving 0·5 grm. of peptone one hour before the meal. In asthma this method of desensitisation has also been successfully employed.

THE/

## THE NERVOUS SYSTEM AND URTICARIA.

Even in the urticarias due to local application of irritating substances, such as the nettle sting, the nervous system may play a part in the dilatation of blood vessels and the formation of the exudate. WEIDENFELD[395.] in 1910 made a great many experiments on the mechanical irritability of the skin in dermographism. He quotes the two theories as to the cause of the wheal.

(1) LUDWIG'S; that by contraction of the efferent vessels together with dilatation of the afferent vessels to the skin you get a raised blood pressure in the capillaries and the blood serum filters through, and

(2) HEIDENHEIM'S; that the capillaries secrete the oedema-fluid and that this secretory action is produced by chemical substances.

He found that if he injected adrenalin into the skin in dermographism and produced a pale area and then stroked that area, he did not get a wheal but a red area. Therefore a hyperaemia does not necessarily lead to an exudation even though the vessels are dilated. Injection of cocaine into the skin caused a contraction of the blood vessels and

no/

no hyperaemia resulted when the skin was stroked but a wheal formed. Therefore a wheal may form in spite of the part being anaesthetic. WEIDENFELD is inclined to support HEIDENHEIM'S theory and thinks that the occurrence of dermographism may be explained by irritation, from the central nervous system, of the secretory cells of the vessel walls producing the oedema. Redness or palor occur by dilatation or contraction of the vessel walls. He did experiments by applying adrenalin in cases of dermographism and showed that hyperaemia may be produced without exudation. This of course may just be a question of the chemical constitution of the toxine. In urticaria due to bee- and wasp-stings it is probably the chemical substance injected, which calls forth the exudate presumably by chemeotoxis; so also in nettle stings. If, in dermographism, the cells of the vessel wall secrete a chemical substance (ferment?) that substance would call forth a serous exudate and hence the wheal. But why should the vessels secrete this ferment in some people and not in others? KREIBICH[365] holds an almost similar view that wheals are due to irritation of cells of the sympathetic nervous system through sensory irritants. He thinks that the sympathetic ganglia are not diseased, but are hyperexcitable. HAZEN/

HAZEN[357] considers that it is impossible to study the phenomena of sensitisation without considering the vegetative nervous system. He thinks that all the cases of urticaria following frights, emotional disturbances and the case of HEBRA'S, which followed the passage of a uterine sound, were due to vagus irritation.

SAMBERGER[380] also regards urticaria as an endocrine disease in which the vagus dominates the sympathetic and therefore hyperaemia and exudation develop. He thinks that, in the wheal, there is a sympathetic ischaemia and this want of blood with its accompanying oxygen is registered in the form of a final hyperaemia and wheal formation. He quotes the beneficial effect of injecting atropin in urticaria in favour of his opinion.

TÖROK[388] holds the opposite view and thinks the nervous system has nothing to do with the formation of wheals. He found that a large variety of substances such as ptomaines, sera, bacterial toxines, and drugs produced urticarial lesions when introduced into the corium. He thinks they act by injuring the vessels and by repeated application bring about a hypersusceptibility of the vascular system. He cites GILCHRIST'S finding of inflammatory changes in the wheal in support of his view that the wheal is due to the presence of a circulating toxine.

UNNA'S/

UNNA'S theory that the wheal is due to a spasmodic contraction of the venules has no longer any great support. NEISSER thinks it is a vaso-motor neurosis with dilatation of the vessels. NEISSER[336] on the dog's tongue and BRUCK[336] on the frog's tongue produced an oedema by prolonged irritation of the glosso-pharyngeal nerve with a faradic current. BRUCK examined the tongues microscopically and found only oedema without inflammatory changes. KREIBICH also attributes the wheal to nerve influence. On the other hand there are many, including GILCHRIST, PHILIPPSON,[376] and TOROK, who hold that the wheal is a local inflammatory lesion due to a toxine without the influence of the nervous system. As all the reactions of inflammation are intimately bound up with the nerve mechanism of the vessels, probably both the nervous system and a local irritation play a part.

WHAT/

# WHAT EVIDENCE IS THERE TO SUPPORT THE ANAPHYLACTIC THEORY OF URTICARIA DUE TO INTERNAL CAUSES?

Before discussing this question some experiments performed by BRUCK[336.] must be referred to. BRUCK tried to produce anaphylaxis in animals with substances which are commonly the cause of urticaria in the human subject. He showed that both active and passive anaphylaxis could be produced with pig-serum and the fresh muscle of the river cray fish. He also quotes the case of a man who suffered from urticaria every time he ate swine-flesh. He withdrew blood from this man, separated the serum and injected it into three guinea-pigs in doses of 10 cc. As controls, other three guinea-pigs were injected with 10 cc. of normal human serum. Twenty four hours later two of the first set of animals were injected intraperitoneally with inactivated pig-serum and showed typical anaphylactic shock. The third animal of the first set was injected with sheep serum with no result. The second set of animals was injected with normal human serum similarly to the first set but no shock resulted. Therefore BRUCK concludes that, because the serum of a patient with urticaria due to swine flesh/

flesh, could induce passive anaphylaxis in normal animals, urticaria is a true anaphylactic phenomenon. BRUCK'S experiment seems to be an isolated one and has not been confirmed.

Another point in favour of urticaria being anaphylactic is the fact that in sensitive persons very small quantities of the offending food may cause the urticaria. So also a very small focus of absorption, such as a minute abscess at the root of a tooth, may cause a wide-spread urticaria. In both these cases the amount of actual food or poison absorbed is too small to account for the symptoms except on the sensitisation theory. The fact that urticaria from a given food may occur on the first occasion on which a child gets that food, is not against a previous sensitisation. I have seen a case of urticaria in an infant on the breast. The urticaria occurred every time that the mother took eggs, so that a child may become sensitised through the mother's milk. When the above child later was first given egg, had it developed urticaria, it would have been quoted as a case showing the rash on the first occasion which eggs were eaten. The periodic occurrence of crops of eruption is also in favour of sensitisation, the intervals representing periods of temporary desensitisation. The fact that the cutaneous food reactions

may/

may be positive one week and negative the next and then positive again later supports this contention. Urticaria is common in members of families which suffer from such sensitisation phenomena as asthma and hay fever. The blood changes in urticaria also closely approximate to those found in anaphylaxis . Desensitisation with peptone etc. has also been successfully accomplished.

THerefore the evidence on the whole, is in favour of urticaria and angioneurotic oedema of internal origin being a true anaphylaxis.

DRUG/

## DRUG ERUPTIONS (Exanthemata).

In this section are included only the rashes which occur after the administration of drugs whether given by the mouth, injected subcutaneously, intramuscularly or intravenously or through the skin as when a general rash appears after the local application of Belladonna plaster. The rashes produced locally by the external application of drugs to the skin will be considered separately under Dermatitis Venenata.

It is not necessary here to enumerate the drugs which commonly cause rashes nor to describe the kind of rash which each drug usually produces. The rashes may be urticarial, erythematous, papular, vesicular, bullous, squamous, pustular, purpuric, nodular or ulcerative. They are usually uniform in type in each case but may be multiform. They may appear soon after the drug is given or only after prolonged administration. Defective elimination in renal and cardiac disease undoubtedly predisposes but is not the true cause as rashes may occur in perfectly healthy individuals.

The fact that in certain individuals even small doses of a drug, given once or only for a short period in which a cumulative effect could not occur, may/

may cause a rash suggests that the rash may be a sensitisation phenomenon. A certain amount of experimental work has been done to try to elucidate this question.

BRUCK [1001.] describes the case of a doctor who took antipyrin for headaches. Whenever he took the drug he developed swelling of the lips and tongue with ulceration and an itchy dermatitis on genitals on one occasion. 16 years after this doctor had last taken antipyrin BRUCK used his serum to sensitise guinea-pigs passively. He first determined the dose of antipyrin which a guinea-pig could tolerate. He succeeded in producing what he considered passive anaphylaxis in the guinea-pig by first injecting the patient's serum and 24 hours later a dose of antipyrin. He therefore concludes that antipyrin idiosyncrasy is dependent on a true anaphylaxis. He did not succeed in producing passive anaphylaxis in guinea-pigs with the serum of patients with an idiosyncrasy to mercury. He also quotes LIEBKIND as getting a similar negative result. These cases, however must be looked upon with suspicion. Was BRUCK'S case really a case of an antipyrin exanthem? The fact that the swelling and ulceration took place on the tongue and lips where the drug was in contact, points/

points to its being a case where the mucous membrane was sensitive and the "dermatitis" on genitals might have been due to some of the antipyrin getting transferred there by handling. It looks more like a case of Dermatitis venenata due to antipyrin than a real exanthem. Therefore his conclusions apply to that condition and not to the true drug exanthem.

KLAUSNER[424] found that animals injected with serum from patients, who showed Iodide rashes after taking Potass. Iodide, and then later injected with 0·5 grm. kI always showed the same symptoms viz. collapse, dyspnoea and death within an hour; whereas the control animals injected first with normal serum showed no symptoms. Two of KLAUSNER'S patients developed a rash on the first occasion on which they took kI. So far as could be ascertained neither had had any kI before on any occasion. He suggests a congenital sensitiveness. It is possible that they might have got kI through their mothers whilst on the breast or as children been given kI in cough mixtures etc. Iodine is an unfortunate drug to experiment with, as it is contained in the thyroid secretion and so may be absorbed into the system from that gland.

COLE,[407] in criticising BRUCK'S and KLAUSNER'S results, thinks that their experiments were not sufficiently controlled and that the doses of kI used were too large and too strongly hypertonic and therefore/

therefore the results might have been toxic reactions. COLE himself repeated BRUCK'S and KLAUSNER'S experiments. He obtained serum from 3 cases. One was a man who showed an erythematous and pustular Iodide rash. Another was a man with a petechial iodide rash and the third was a non-susceptible man who had been taking kI in 2 grm. doses t.i.d. for six months. The serum of these three cases was injected into guinea-pigs and subsequently a non-lethal weakly hypertonic dose of kI given. Many animals were used and controls, using human serum, were made. Five of the twenty six guinea-pigs died in a sudden acute manner that is quite inexplicable. Some of them died with convulsions, others fell over, panted, became paralysed and died. Others just became apathetic, listless, then paralysed and died. On post-mortem examination nothing was found except a general congestion of the internal organs. There were no haemorrhages into the lungs or stomach, no oedema or distension of the lungs and no fatty change in the heart muscle. Therefore COLE does not think that they died of true anaphylaxis. He entirely agrees with BRUCK and KLAUSNER that Tuberculin exanthemata are due to anaphylaxis and that it can be transferred passively; but he does not think that the drug rash is the same as the Tuberculin rash. Tuberculin is a protein substance whereas kI has no protein. BRUCK suggested that the Iodine combines with/

with albumin and forms an iodo-albumin to which the patient is sensitised. FORD, 1024. on the other hand, has succeeded in immunising animals to a haemolytic glucoside derived from a poisonous mushroom. This glucoside contains no protein. COLE thinks that BRUCK'S, KLAUSNER'S and his own results with Iodides show that in some cases animals previously injected with serum from sensitive patients and then with kI may die with symptoms resembling anaphylactic shock, but does not think we are justified in calling it a true anaphylaxis. As already mentioned substances such as Kaolin, starch, agar, pectin and histamine can, when treated with serum, produce symptoms like anaphylaxis. Histamine which is an amin derived from Histidin obtained from the sap of a cotyledon plant, was used by KRITCHEWSKY, SMITH and others to produce symptoms like anaphylactic shock. But SMITH showed that the blood changes and temperature reaction in Histamine shock are not those of anaphylaxis and most workers are agreed that the shock produced by non-protein substances like Histamin is not true anaphylactic shock. In a man with a morbilliform copaiba rash, (see Cast 2 + Pl. 2) COLE had no success in the passive transferance of the susceptibility to guinea-pigs.

VOLK/

470.
VOLK also did a number of experiments in order to see whether Iodine-containing substances combined with albumin and so produced an Iodine protein, which might cause anaphylaxis., He injected guinea-pigs subcutaneously with iodoform and later injected iodised horse serum without producing any symptoms of anaphylaxis. He also made a series of experiments to produce active anaphylaxis in animals by repeated injections of antipyrin, quinine and arsenic but the results were negative. This corresponds with the results of KLAUSNER who found that guinea-pigs already anaphylactic to serum, show more severe symptoms on injection with antipyrin than do normal guinea-pigs. VOLK also attempted to produce passive anaphylaxis. The blood of a patient, recovering from an arsenical rash, was injected into a guinea-pig and 24 hours later a dose of sod. arsenate was injected with no result. So also the blood of a patient with a quinine rash was injected into four guinea-pigs and each was given later a dose of quinine. The result was nil. VOLK thinks that true anaphylaxis can only be produced by albumin bodies. Symptoms of paralysis or a kind of shock may be produced but he does not consider it a true anaphylaxis. VOLK quotes a case of syphilis who developed a dermatitis/

dermatitis of the skin from the application of mercurial ointment and also a general rash and symptoms of intoxication when the tonsils were painted with a solution of mercury and severe symptoms on taking kI. Yet this patient could tolerate injections of grey oil and corrosive sublimate quite well. He also had another similar case who developed a rash when he took mercury by the mouth but not when it was injected intravenously. Therefore he concludes that it is a cutaneous hypersensitiveness (not anaphylaxis) This will be referred to later under Dermatitis venena ta.

DORR [410.] tried to produce passive anaphylaxis to strychnine in animals but without success. He does not consider the symptoms sometimes produced by repeated injection of drugs as true anaphylaxis.

KYRLE [428.] did a number of experiments with animals injecting them first with the serum of patients who showed rashes on taking mercury, Codein or Bromide and then with the drug. Like other workers, his results show that such animals have more marked symptoms than normal animals and an immediate reaction followed sometimes by death. The symptoms were not exactly like anaphylactic shock. The experiments with Bromides and Iodides which are not such poisonous drugs/

drugs as mercury and Codein were all negative. It is significant that reactions and death only occurred with the use of large doses of the drugs and not with small doses as should occur if it were a true anaphylaxis.

482.
ZIELER also holds that BRUCK, KLAUSNER and the other workers have not proved their contention that the serum of patients with an idiosyncrasy to drugs can produce a passive anaphylaxis in animals. He injected animals with the serum of a case which showed a rash on administration of fibrolysin, of a case of iodide rash and of case of antipyrin rash, and then gave them a dose of the drug. In all cases he got a reaction which he attributed to poisoning. He admits that the previous injection of the serum intensified the symptoms but states that the clinical picture of poisoning from a drug such as antipyrin is somewhat like that of anaphylaxis.

415.
FRIEDBERGER and TETSUTA did experiments on the influence of Iodides on guinea-pigs by repeated administration. They injected Iodalbumin (prepared through iodisation of guinea-pig serum) into guinea-pigs. On reinjection with this iodalbumin no definite hypersensitiveness was shown. But on reinjecting the animals with Sod. Iodide signs of hypersensitiveness occurred; so also on reinjection with LUGOL'S Solution of/

of Iodine and with Iodoform. By injecting guinea-pigs first with LUGOL'S Solution, hypersensitiveness occurred on reinjection with Iodalbumin but not on reinjection of Sod. Iodide or LUGOL'S Solution. They also found that animals previously treated with Iodalbumin and reinjected with homologous Iodalbumin were anti-anaphylactic to a third injection of Iodalbumin. These experiments seem to support BRUCK'S view that in Iodide and Iodoform sensitiveness the reactions are due to the Iodine combining with albumin to form a compound to which sensitiveness may occur.

COOKE[408.] thinks that hypersensitiveness to drugs is allergic in nature and not to be confused with exaggerated normal reactions which he thinks should be considered as "idiosyncrasies". As proof of the allergic nature of drug reactions he quotes the influence of heredity. In 15 cases quoted, a positive antecedent history of hypersensitiveness existed in twelve and in the other three cases there was evidence of allergy such as asthma, hay fever or urticaria in the individual himself. The symptoms in drug allergy are separate from the normal or toxic action of the drug and are the same as occur with foods, pollens and animal emanations, viz. corzya, cough, bronchial spasm with urticaria or angioneurotic oedema in some cases and/

and frequently intestinal disturbances with vomiting and diarrhoea. In practically all there is an eosinophilia of from 10 to 15%.

WILE, WRIGHT and SMITH[478.] in 1922 investigated bromide and iodide eruptions. They found that the pustules are not sterile but consider that the bacteria present are probably secondary contaminations. Iodide and bromide could not be found in the purulent material from the lesions, although they could be demonstrated in the sweat and in the blood serum after ingestion of the drug. The percutaneous introduction of foreign protein in the presence of a circulating blood containing bromide resulted in one case in lesions simulating those produced spontaneously by bromides. They think this reaction parallel to the positive Luetin test (to be referred to later) obtained when iodides are being taken. Precipitins in the blood serum were not demonstrable in vitro by the addition in minute quantities of bromide and iodide salts, to the blood sera. These authors think that the local phenomena of iododermia and bromodermia do not find their explanation on simple bacterial or chemical grounds and the ultimate explanation probably lies in a complex bio-chemical reaction. They conclude that the classification of such cutaneous phenomena/

phenomena as sensitisation or allergy is as yet unjustifiable in the light of our present knowledge.

During the last few years a good deal of attention has been paid to the rashes which follow the administration of Salvarsan, Arsphenamin, Novarseno-billon and similar preparations. On repeated injection of these drugs the so called "nitritoid crisis" may occur. Death may even occur as in McDONELL'S[434.] case who received 2 intravenous injections of 0·6 Salvarsan at intervals of eight days. The first injection had no ill effect but 48 hours after the second injection, there was a marked rise of temperature, cerebral symptoms, with convulsions, difficulty in breathing and death on the fourth day from stoppage of the respiration. Several similar cases have been recorded by WECHSELMANN[472.] and others and symptoms seem to occur more frequently with one batch of material than with another. MARCHALKO and VESZPREMI[437.] who examined the brain in such cases found multiple haemorrhages which they attributed to the toxic effect of the drug. But, apart from these general symptoms, rashes have been frequently observed. These may be urticarial, erythematous and scarlatiniform. But the most striking is a general erythema with desquamation very closely approximating to the rash of/

of general exfoliative dermatitis. This eruption may persist for some weeks when it fades and the patient recovers completely. As will be seen later general exfoliative dermatitis is probably a sensitisation phenomenon and these rashes after Salvarsan etc. run a very similar, though shorter, course to that disease.

The cases of acute nitritoid crisis after injection of imperfectly alkalinised solutions of arsphenamin clinically resemble anaphylactic shock. SWIFT[467] has shown that guinea-pigs could be sensitised by the injection of a mixture of guinea-pig serum and Salvarsan and on reinjection, after a suitable interval, with the same mixture, show symptoms identical with anaphylactic shock. He thinks that in man a similar reaction occurs by the Salvarsan combining with his blood serum to form a mixture which acts as a foreign serum. SWIFT found that a guinea-pig never shows an anaphylactic reaction with untreated homologous serum. Injection of Salvarsan alone does not render a guinea-pig hypersensitive to a subsequent injection. Symptoms are only produced when the mixture of Salvarsan and serum is used. SWIFT states also that the hypersensitive condition induced in patients by repeated Salvarsan injections passes off after/

after a certain time and treatment may then be resumed but in some cases later injection may cause worse symptoms corresponding to the immediate or accelerated reactions seen in serum disease. If a small preliminary dose be given before the full dose a state of anti-anaphylaxis or desensitisation can be produced. EMERY and MORIN[413.] and others have adopted the method of giving small and progressively increasing doses at frequent intervals to prevent a reaction. The fact that a nitritoid crisis may occur after the first injection, seemingly ruled out anaphylaxis but as STOKES points out the newer physical conceptions of the mechanism of anaphylactic shock being due to a dispersion of the colloids of the blood serum may give the explanation. DANYSZ[409.] has shown that the arsphenamin solution is essentially colloid and that on its injection the arsphenamin base is precipitated out by the constituents of the blood plasma. If the solution is imperfectly alkalinised or if the serum of the patient is abnormal, rapid precipitation, followed by an acute reaction, ensues. STOKES therefore considers the reaction to arsphenamin as a form of anaphylactic shock. The nitritoid crisis as shown by MILIAN[439.] and others can be inhibited by previous injection of atropin as in anaphylactic shock.

The/

The production of antianaphylaxis as mentioned, further supports the anaphylactic theory. STOKES and CATHCART [465] found no clinical evidence to support the contention that rashes and symptoms after administration of arsphenamin were due to retention of the arsenic by injury to the kidney from the mercury which is often given. In many cases with rashes they found evidence that chronic focal or intercurrent infections may play a part in producing the eruption. They have seen serious and even fatal results with rapid extension and generalisation of a previously mild dermatitis following the stirring up of a focus of infection and removal of a septic focus has resulted in rapid disappearance of a severe dermatitis. They suggest that the post-arsphenamin dermatitis is based on an allergic instability produced either by colloidal changes secondary to arsphenamin injection or chronic or sudden absorption of bacterial sensitising protein from a focal or acute infection. In 33 cases of cutaneous eruptions after Arsphenamin 9 had severe eruptions of the general exfoliative type. Of these nine 80% had serious degrees of septic focal infection in gums or tonsils. In 12 cases of milder cutaneous rashes, either erythematous or urticarial only 17% had any degree of infection. In the 33 cases in only 6 could no focus of infection be demonstrated.

In/

In practice they find it better not to remove a focus of infection during the attack of dermatitis in case it causes an exacerbation of the rash. They are best removed before treatment with the drug or after the dermatitis has subsided. The cases of the sudden onset of an exfoliative rash following the application of external irritants such as Tinct. Iodi, or inunction of mercury, they explain as being due to the same cause or the dermatitis which AUER[983.] produced by applying xylol to the ears of sensitised rabbits. The external irritant causes a vaso-dilatation and brings a larger amount of antigen to the sensitised cells and so the dermatitis results. STOKES and CATHCART regard these reactions as not truly anaphylactic but prefer to call them cases of hypersensitiveness or allergic instability. HANZLIK and KARSNER[418.] suggest that they should be considered as "anaphylactoid". POMARET[455.], DANYSZ[409.] and others have suggested that the nitritoid crises following the injection of the arseno-benzol compounds are due to a precipitation in the blood. If a slightly acid solution of these drugs is added to an albuminous solution in vitro a precipitate consisting of a combination of the protein with the drug results. But SCHAMBERG, KOLMER and REIZISS[461.] showed by experiments that alkaline solutions of Arsphenamin do not cause precipitation in the presence/

presence of organic or inorganic constituents of the blood. The same workers also tested the haemolytic activity of Arsphenamin and found that it is haemolytic in practically all the concentrations in which it is employed whereas neo-arsphenamin is not haemolytic except in very dilute and very concentrated solutions. The injection of cloudy or turbid solutions of neo-arsphenamin will, almost invariably, give rise to severe nitritoid symptoms. But nitritoid crises may follow the injection of clear solutions. Whilst admitting that acid solutions of arsphenamin may cause intravascular precipitation the above authors do not think that nitritoid crises are due to a precipitation but to some undetected impurity in the drug. In no other way can the variation in the incidence of reactions with different lots of brands of the drug be explained.

In cases of marked intolerance to drugs of the arseno-benzol group TZANK[469.] tried to produce a passive anaphylaxis in the guinea-pig by the preliminary injection of the patient's serum followed the same or next day by arseno-benzol. At first all attempts failed but by altering the technique and giving the injection direct into the heart he succeeded in four cases in producing a definite typical anaphylactic shock/

shock in the animal. Controls carried out by the injection of serum alone and the arsenical salt alone failed to produce symptoms of shock. Also controls performed with the serum of three normal individuals gave rise to no anaphylactic reaction in the guinea-pig. Therefore he claims to have produced passive anaphylaxis in the guinea-pig.

## BLOOD CHANGES FOLLOWING THE INJECTION OF ARSENICAL COMPOUNDS.

MACKEE[436.] found that, although there was a fall in the number of red blood corpuscles after injections of Salvarsan in cases of reaction after injection, there was no haemolysis. He found no appreciable increase in the leucocytes but differential counts showed an increase of polymorphonuclear leucocytes and diminution of lymphocytes. MOORE and FOLEY[443.] in severe reactions to Salvarsan and the diarseno-benzol brands of arsphenamin found a leucopenia. Differential counts demonstrated an increase in the large lymphocytes and an increase in the eosinophile leucocytes.

CUTANEOUS/

## CUTANEOUS REACTIONS IN DRUG RASHES.

482.
ZIELER asks the question whether a cutaneous reaction, if present, cannot be used to test the sensitiveness of a patient to Salvarsan. Twenty-one cases ~~after~~ were tested by the intracutaneous injection of Salvarsan. Injection of 0·001 gave a positive reaction in almost all the cases and injection of 0·0001 a positive result in only four of the cases. Some of these cases had been previously treated with Salvarsan and others had not and in those patients who showed a marked cutaneous reaction subsequent injection of the drug caused no symptoms. Therefore he concludes that any skin reaction which can be obtained with Salvarsan is due to chemical irritation and is not a sensitisation phenomenon. Several other observers have reported local reactions at the seat of injection of arseno-benzol preparations.

401.
AZUA describes a case which had had 2 injections of Salvarsan the second 12 days previously, and in whom an injection of arsenic and strychnine caused the formation of an urticarial wheal at the seat of injection. He interpreted that as a local anaphylactic phenomenon.

408.
COOKE describes the production of violent bronchial/

bronchial asthma in nine cases by the administration of 10 grms. of acetyl-salicylic acid. In three of these cases urticaria was also present. Positive cutaneous reactions to acetyl-salicylic acid were only obtained in those cases where there was a clinical history of urticaria. In one case a general reaction followed the intradermal test with 0·1 grain of the same drug. COOKE does not think these reactions specific for the drug but dependent on a fraction of the chemical molecule as symptoms might occur with acetyl-salicylic acid and not with salicylic acid, methyl. salicylate etc. BOERNER [406.] experimented with himself. He was susceptible to quinine and suffered from a rash with intense itching of the skin, when he took the drug. He scarified a small area of his skin and rubbed in powdered Quin. Sulph. In 5 minutes the abrasion began to itch and in 10-15 minutes the area became oedematous in the centre with an area of erythema around it one inch in diameter. As six other individuals, who were not susceptible to quinine, gave no reaction to the same test, BOERNER concluded that the reaction was specific and not due to the irritation of the quinine. Solutions of Quin. Bisulph. in strengths of 1 in 10, 1 in 200, 1 in 500 and 1 in 1000 were also used and BOERNER found that he got the best reaction with a solution of 1 in 10. With that strength of solution the reaction was more marked than with powdered quinine. Guinea-pigs inoculated with/

with BOERNER'S serum and then 48 hours later with quinine failed to show any sign of anaphylaxis.

MOOK[442.] quotes the case of a medical student who developed an erythematous rash after taking quinine. This student gave a positive cutaneous and intracutaneous reaction to a solution ( $\frac{1}{5}$ gr. in 1 cc) of Quin. hydrochlor. in normal saline solution.

EDLAVITCH[441.] also confirms these observations in a person sensitive to quinine, With a 10% aqueous solution of Quin. Sulph. he obtained a marked cutaneous reaction with wheal formation and erythema. The reaction reached its maximun in about half an hour and disappeared within a few hours. The control area did not react. The test was repeated a fortnight later with the same result.

O'MALLEY and RICHEY[449.] in two cases with erythematous rashes following the administration of quinine found the skin test with a 10% solution of Quin. Sulph. a good index of hypersensitiveness. The intensity of the cutaneous reaction was found to be in inverse ratio to the degree of sensitiveness of the patient. These cases reacted to the various salts of quinine only, but failed to react to cinchonin, cinchonidin, salicylic acid, caffeine citrate, potass. iodide, atropin. sulphate and epinephrin. On desensitising these cases by giving a preliminary small/

small dose of quinine before each therapeutic dose the cutaneous reaction gradually diminished and disappeared on the tenth day.

The experiments of SMITH [463] have some bearing on the sensitiveness to quinine. He found that guinea-pigs and rabbits sensitised to ox or horse serum, if treated with moderate doses of quinine preceding the reinjection of the specific antigen, had their susceptibility increased from 3 to 10 times as compared with control sensitised animals.

WILE, WRIGHT and SMITH [478] found that percutaneous tests with solutions of iodides and bromides were uniformly negative in cases with rashes from these drugs. In one case of an extensive bromide rash (See Cast 3 and fig. 3. ) in an epileptic in which I did a PIRQUET test with a 10% solution of Pot. Brom. the result was negative. Both the control and the area treated with the bromide solution showed a wide erythema (fig. 4. ) but no wheal formation resulted.

Therefore except for the cases of Quinine rashes a positive cutaneous reaction does not seem to occur in cases of drug hypersensitiveness and the skin test is not reliable as a guide as to which drug is producing a rash; nor is the test of any value to determine whether a given drug may be given to a patient with safety.

DESENSITISATION/

## DESENSITISATION TO DRUGS.

In a case which developed an urticarial rash on the administration of Quinine, HERAN and ST GIRONS[421.] gave 0·5 milligrm. Quin. Sulph. an hour and a half before the ordinary dose and found that by that means no symptoms occurred. LAROCHE, RICHET and ST GIRONS[429.] also found that hypersensitiveness to quinine could be overcome by giving 1 mgm. Quinine A and 0·5 grm. Sod. Bicarb. one hour before the therapeutic dose. O'MALLEY and RICHEY[449.] in their two cases of Quinine rash found the above method quite efficacious in one case but in the other it only increased the tolerance but did not completely prevent symptoms.

WIDAL and VALLERY-RADOT[476.] report a case of sensitiveness to acetyl-salicylic acid. The drug was given first in a dose of 0·005 grm. and one hour later in a dose of 0·25 or 0·5 grm. This was repeated 13 times in 6 weeks, the preliminary dose being gradually increased from 0·005 to 0·03 grm. This sufficed to prevent all symptoms. They also record a case of a woman, aged 24, who took antipyrin for headaches every month. During nine years no bad effect was noticed and then suddenly every time she took the drug she suffered from intense itching of the chin and lips which became red and swollen. WIDAL and VALLERY-RADOT tried to find/

find how small a dose could be given without producing symptoms and found the dose to lie between 0·0001 and ·0002 grm. The administration of such small doses for two months completely desensitised the patient so that antipyrin could be taken in ordinary doses without discomfort. Desensitisation to drugs of the arseno-benzol group has already been referred to.

Therefore desensitisation either by preliminary small doses before each therapeutic dose or by repeated prolonged administration of minute doses can be successfully accomplished.

Adrenalin injected in a dose of 1 cc. (of 1 in 1000 solution) 15 minutes before each injection of Salvarsan was found by NÄGELI [447] to prevent the appearance of an erythematous rash and other toxic manifestations which otherwise had always previously appeared. As adrenalin is known to control some cases of recurrent urticaria especially the cases associated with Asthma, the above case is another point in favour of the anaphylactic origin of Salvarsan rashes.

GENERAL/

## GENERAL CONCLUSIONS ON DRUG RASHES.

1. The type of rash seen after the administration of drugs is usually of the urticarial and erythematous type such as is seen in serum sickness. Papular, pustular or nodular rashes may be due to the same reaction localised to the follicles, sweat or sebaceous glands through which the drug might be excreted. Similar rashes occur in the tuberculides and trichophytides which are definitely anaphylactic.

2. The fact that a patient may tolerate a drug for a long time and suddenly develop a rash, which occurs later, on, each administration, even although the drug has not been taken recently, excludes a cumulative effect and supports the sensitisation theory.

3. The latent period, after taking the drug, before the rash appears also corresponds to that seen in serum rashes.

4. The rashes are specific up to a point. All drugs of the same group give reactions such as copaiba, cubebs and turpentine, which are all allied balsamic substances.

5./

5. Experiments on animals to produce active anaphylaxis to drugs have been negative.

6. Experiments on animals to produce passive anaphylaxis to drugs were on the whole negative. A reaction was found which is probably not true anaphylaxis.

7. The "nitritoid crisis", following the administration of Arseno-benzol, compounds ~~correspond~~ is probably not a true anaphylaxis but may be a closely allied phenomenon.

8. Focal infections may have some bearing on the production of rashes after arseno-benzol.

9. Blood examinations are too few from which to draw conclusions.

10. The cutaneous test, except in the case of quinine rashes, has given disappointing results.

11. Desensitisation to drugs has been successfully employed.

12. Drug rashes have not been proved definitely to be phenomena of true anaphylaxis but the reaction caused by drugs is probably an allied phenomenon and in the present state of our knowledge probably best described as "anaphylactoid".

THE/

## THE ERYTHEMATA INCLUDING E. MULTIFORME, E. SCARLATINIFORME & E. NODOSUM.

GENERAL ERYTHEMATA resemble in many respects the exanthemata and are admittedly toxic in origin. They are closely allied to and often accompanied by urticarial lesions. The large group due to foods, drugs, bacterial toxines etc. is the same type of rash as is seen in serum sickness and probably is due to the same cause viz. a sensitisation to some protein. As these have been discussed under serum sickness, urticaria and drug rashes they require no further comment.

ERYTHEMA EXUDATIVUM MULTIFORME, however, is a distinct clinical entity and therefore requires further discussion. I think the cases following the taking of drugs, food toxines, bacterial infection etc. should be separated from the true E. multiforme. The former really fall better into the group of general erythemata of multiforme type. To this group belong cases like that of CORLETT'S.[489] His case was that of a boy who was shot behind the left ear and eight days later developed a general eruption with erythematous lesions with blebs arranged in a circinate manner. The/

The blebs contained a pure culture of the streptococcus which had evidently gained entrance at the gun-shot wound.

The typical erythema multiforms cases are those in which the eruption occurs chiefly on the hands, face and feet with erythematous, circinate, papular, vesicular, bullous or iris-like lesions. The eruption recurs at intervals and often for no apparent reason. In some cases however a typical E. multiforme may follow a definite lesion. NORMAN WALKER[509.] in 1901 described 4 cases following vaccination against small-pox. Other similar cases have been described by FOX[492.] and others. OSLER[505-508.] described cases of erythema multiforme associated with visceral lesions such as disorders of the gastro-intestinal tract, damage to the kidney, cerebral symptoms etc. He pointed out the similarity between these cases and serum sickness. CHRISTIAN[487.] also described a group of similar cases with erythematous, urticarial or purpuric lesions associated with visceral lesions. From analogy with serum sickness these cases are obviously anaphylactic. ANTHONY[484.] quotes a case of E. multiforme associated with infected teeth and enlarged glands; also cases with pus infections of the urinary tract with enlarged prostate. Pharyngitis/

Pharyngitis and other throat conditions may also be followed by E, multiforme. He also quotes a case of SABRAZES in a labourer who over-exerted himself for a long time in order to stimulate his companions to complete some work. This man developed E. multiforme possibly owing to absorption of muscular products. This type of case however is not likely to occur frequently today! ANTHONY explains the frequency of E. multiforme in Spring and Autumn as due to alterations in food and clothing at these periods and therefore alteration in elimination. Foods have been frequently reported as causing E. multiforme. ENGMAN[491] described the case of a girl who had an attack of E. multiforme every time she ate pork chops; GALLOWAY[494] a case due to eating blackberries and nuts and FORDYCE[495] a case of E. Iris after eating lobster.

Rheumatic symptoms are frequently associated with E. multiforme although not so frequently as with E. nodosum. But E. multiforme is not associated with true rheumatic fever and any rheumatic symptoms are possibly due to absorption from the throat or other septic focus.

Epidemics of E. multiforms have been described. These may be due to some special article of tainted food and HERXHEIMER[499] describes an epidemic of 14 cases among soldiers in barracks. Disinfection of the/

the rooms stopped the epidemic.

CUIFFINI[488] and LYONNET and MARTIN[502] tried to show a connection between E. multiforme and tuberculosis but the association of these two conditions was probably only a coincidence.

## CONCLUSIONS.

From the resemblance of the lesions in E. Multiforme to those in urticaria and serum sickness, the former disease is probably anaphylactic like the latter. In some cases the condition is due to sensitisation to a definite substance such as a food, or drug, but in others it is often difficult or impossible to trace the actual source of absorption. The teeth, throat, nose, accessory sinuses, gastro-intestinal or urinary tracts may be the seat of some infective process and the patient is sensitised to the protein of the infecting organism. The relapses alternating with periods of freedom from eruption also correspond to what occurs in urticaria. There is, however, no evidence to show why in one case a sensitisation leads to a true urticaria and in another to erythema multiforme. Further work is necessary to elucidate this point.

## ERYTHEMA SCARLATINIFORME.

Apart from generalised scarlatiniform rashes due to drugs such as quinine, enemata, ptomaine posioning etc. a recurrent scarlatiniform erythema very closely resembling scarlet fever, may occur. This rash is followed by desquamation. Nothing is known as to its cause but as it is not contagious it is probably not due to an infection like the fevers. From its resemblance to toxic rashes it is possibly a sensitisation phenomenon. In favour of this is the recurrence of the rash after intervals of freedom and the gradual diminution in the severity of the attacks till they cease altogether. Presumably each attack temporarily desensitises the patient and after several attacks a complete immunity results. It is possible that the condition is due to a sensitisation to some bacterial protein as foods and drugs seem to play no part in its etiology.

## ERYTHEMA NODOSUM. (see Cast N°4 + Pl. N°5.)

Whilst erythema nodosum is often classified as a form of E. Multiforme, the uniformity of the lesions and its clinical course point to its being a clinical entity. From its association with rheumatic symptoms/

symptoms E. NODOSUM was for long considered to be a rheumatic affection but more recent reports point to its possible association with other diseases such as tuberculosis, syphilis etc. It has been suggested that it is,

(1) an acute specific fever,

(2) an infection with the micrococcus rheumaticus,

(3) a manifestation of tuberculosis,

(4) a manifestation of syphilis,

(5) due to drugs,

(6) sensitisation to a fungus such as ringworm.

(1) E. NODOSUM as an ACUTE SPECIFIC INFECTION

552.
SYMES has recently discussed the question and strongly upholds this theory. In support of it he quotes the facts that the disease may be transferred from person to person and may occur in small localised outbreaks and in epidemic waves. It also has a definite seasonal and a fairly constant age incidence. The systematic distribution of the rash, the tendency to relapses and the conferment of immunity also support this view. ANDERSON and COOPER 511. and others have also reported more than one case occurring in the same family or household.

ROSENOW/

547.
ROSENOW in 1915 excised lesions from cases of E. nodosum, emulsified them and made cultures. From subcutaneous nodules he obtained a polymorphous sometimes clubbed, often curved, barred diplo-bacillus. This same organism was isolated in pure culture from each of six cases of E. nodosum. He also isolated the same organism from a cervical gland draining an infected tonsil in a case of E. nodosum and from the circulating blood in pure culture in two cases of E. nodosum. In smears from the original colonies all grades from bacilli to diplococci were found. On artificial culture it became a definite bacillus. ROSENOW thinks that it is one organism in different forms. Injected intravenously into dogs, rabbits and guinea-pigs it showed a striking affinity for the subcutaneous tissues producing local subcutaneous haemorrhagic inflammatory lesions with enlargement of the regional lymphatic glands. From these lesions the organism was repeatedly isolated. On artificial cultivation and on animal passage the affinity for the subcutaneous tissues disappears. By passage through animals its virulence increases and it assumes the form of a streptococcus and acquires an affinity for the joints, muscles, fasciae and endo-cardium producing haemorrhages in the muscles and heart valves. Soon after injection and later/

later a non-suppurative arthritis, myositis and endocarditis. ROSENOW considers it the cause of E. nodosum and thinks that it explains the relation of E. nodosum to rheumatism, measles, diphtheria, scarlet fever and Tuberculosis. These diseases afford it a focus from which it may gain entrance into the blood stream. ROSENOW'S findings however, have never been confirmed.

EMRYS - ROBERTS[520.] from a case of E. nodosum in a soldier isolated what he considered the Bacillus Influenza from the blood and NEAVE[539.] found a streptococcus in the blood of another case.

PERIGAL[542.], POLLOCK[544] and JOINT[533.] all report cases of E. nodosum within a few days after measles and CRAIG[519.] reports one case in a child peeling from scarlet fever. JOINT saw 9 cases of E. nodosum in 300 cases of measles and concluded that he was dealing with two diseases both occurring in epidemic form.

## (2) E. NODOSUM AND RHEUMATISM.

The association of joint pains and occasionally of endocarditis has lead many to support the rheumatic theory. Using the word rheumatism in the sense of an infection with the micrococcus rheumaticus there is no evidence to support the rheumatic theory/

theory except the clinical observations. The fact that salicylates help in the treatment is no proof of a rheumatic origin. It is quite possible that an organism such as ROSENOW described might produce endocarditis, pleurisy, arthritis etc. If E. nodosum were a true rheumatic condition one would expect it to occur frequently as a complication in rheumatic fever, and that is not the case.

## (3). E. NODOSUM AND TUBERCULOSIS.

Within recent years a great many writers have drawn attention to the frequent association of E. nodosum with Tuberculosis. Numerous cases like that reported by MEARA and GOODRIDGE[538] have been recorded. This case of E. nodosum developed tuberculous meningitis soon afterwards and the post-mortem examination showed tuberculosis of the meninges and lungs. Similar cases have been reported by OCHME[541] and others. The other type of case is where the patient with a recrudence of an old tuberculosis develops E. nodosum. Such cases have been reported by WARD[557] and others.

COURMANT, SAVY and CHARLET[518], PIC[543] and ALAMARTINE[510] did agglutination tests for tuberculosis in E. nodosum and always obtained positive results. POLLAK[544], CALDEROLA[515] and others found the Tuberculin Pirquet reaction to be positive in cases of E. nodosum but considering the frequency of positive reactions in all individuals/

individuals no great stress can be laid on these findings. TROISIER and MARFAN[537] gave intradermic injections of Tuberculin and obtained nodules resembling those of E. nodosum. MARFAN however considered that the nodules were less elevated, their limits less marked and their course shorter than in true E. nodosum. THIBIERGE and GASTINEL[554] also produced lesions like E. nodosum by injection of Tuberculin, but in the same patients they obtained identical lesions by injections of anti-diphtheritic and antitetanic serum and also by injections of salt water. ALAMARTINE[510] quotes the experiments of GOUGEROT and LAROCHE who by inoculation of Tubercle bacilli into animals produced cutaneous tuberculides which corresponded both macro and microscopically with lesions of E. nodosum. LANDOWZY[534], LAEDERICH and RICHET[534] report a case of typical E. nodosum with endocarditis and congestion of the apex of the right lung. In an excised nodule they found the tubercle bacillus and guinea-pigs inoculated from the nodule died of tuberculosis. GUTMANN also demonstrated the tubercle bacillus in the circulating blood and nodules in a case of E. nodosum. HOLLAND[531] on the other hand in 9 cases of erythema nodosum inoculated guinea-pigs with fresh nodes and on all obtained negative results.

From/

From all the above evidence therefore one must admit that there is a close connection between tuberculosis and E. nodosum. It may be in some cases a manifestation of actual tuberculosis in which the patient is sensitised to tubercle and on a recurrence of the disease develops an acute lumpy tuberculide indistinguishable from E. nodosum. On the other hand the two diseases may predispose to one another. Patients after an attack of E. nodosum may be specially susceptible to infection with E. nodosum. VETLESEN[556.] in a recent discussion of the subject "expresses no doubt as to the relationship of the two conditions and has learnt to regard E. nodosum as a danger signal".

As in tuberculosis so in leprosy, lesions like E. nodosum have been reported by HALLOPEAU and GRANDCHAMP.[526.] In these cases they found no leprosy bacilli in the lesions and think that the lesions were due to toxines and that they were dealing with leprides and not with a double infection with E. nodosum and leprosy.

## (4). E. NODOSUM AND SYPHILIS.

In 1896 DE BEURMANN and CLAUDE[572.] reported cases of Syphilis with lesions absolutely identical clinically with E. nodosum. They thought the lesions were/

were due to the syphilis and were not a double infection. They pointed out that all intermediate forms occurred between E. nodosum and the typical gumma and recommended that these lesions should be called nodose syphilides. HOFFMANN[530] also later recorded similar cases in the secondary stage of syphilis and agreed with DE BEURMANN and CLAUDE that they were really nodose syphilides which were due to a syphilitic phlebitis of the subcutaneous veins. STÜMPKE[551] and CHAUFFARD and LE CONTE[516] however think that these cases are double infections with E. nodosum and syphilis as they differ from gummata in their evolution, benignity, and absence of ulceration. The spirochaeta pallida could not be demonstrated in the lesions and they may recover without antispecific treatment.

These cases, therefore, of E. nodosum occurring in the course of syphilis seem to be in the same position as the cases occurring in tuberculosis. Some of them may be true syphilitic lesions starting in the veins and others may be double infections, the syphilis, like tuberculosis, predisposing to the infection.

## (5). E. NODOSUM FROM DRUGS.

FORDYCE[522], SCHIDACHI[548], THIBIERGE[553], HALLOPEAU and TEISSEIRE[527] and others have recorded cases with nodose lesions/

lesions in the skin of patients taking Iodides. Although the lesions resembled E. nodosum, in most cases, they occurred on the front of the thighs and not over the shins. They were undoubtedly due to the drug and show how closely all nodose lesions, from whatever the cause, may resemble E. nodosum.

## (6) E. NODOSUM AND RINGWORM.

Acute nodular lesions indistinguishable from E. nodosum have been described in cases of Kerion ringworm. It will be shown later (page 289.) that these lesions are due to the blood infection with the ringworm fungus in a sensitised person.

Blood examinations were made by HOYER[532.] in 20 cases of E. nodosum. He found little change in the red blood cells apart from a slight reduction in their number in about two thirds of his cases. In most cases the total number of leucocytes was above normal at the time of the eruption and as this faded the number returned to normal. Early in the disease there was a neutrophilia, eosinophilia, monocytosis and lymphocytosis. As the eruption faded numerous neutrophiles with red shaped neuclei appeared and persisted for a considerable time. The author points out that these changes do not suggest a rheumatic condition

but/

but are more like those of anaphylaxis.

## CONCLUSIONS REGARDING E. NODOSUM.

1. The older conception of E. Nodosum as a rheumatic condition must be revised.

2. The cases described in the literature may be divided into two groups,
   (1) True E. Nodosum
   (2) False E. Nodosum.

3. True E. Nodosum is probably due to infection with a definite organism such as that described by ROSENOW. The distribution of the lesions and the clinical course are very constant. The disease seems to be infectious as it may occur in small epidemics. The skin lesions are to be looked upon as sensitisation phenomena due to the same mechanism as the skin rashes of the exanthemata. The deep nodose character of the eruption is due to its starting from a subcutaneous vein. Tubercle and syphilis, on the one hand, seem to predispose to infection with E. Nodosum and on the other hand E. Nodosum seems to predispose to infection with Tubercle.

4./

4. False E. Nodosum is the eruption which may occur in Tuberculosis, syphilis, leprosy and ringworm. The nodes are to be considered as sensitisation phenomena and would be better called acute nodose tuberculides, syphilides, leprides, trichophytides or microsporides. To the above group also belongs the nodose eruption which sometimes follows the administration of Iodides.

5. Both the true and the false E. Nodosum are sensitisation phenomena, a different antigen being responsible in each group of cases but the skin reaction is similar, if not identical in all. In both groups of cases the lesion centres round a subcutaneous vein, hence the similarity in the appearance of the nodes.

6. At present there seems to be no method by which the true and the false cases can be distinguished with certainty. If the causes which operate in false E. nodosum can be excluded, then one concludes that the eruption is one of true E. nodosum.

# PURPURA.

It is customary to divide the purpuras into two groups,

(a) PRIMARY or IDIOPATHIC, where the purpuric rash is the only or chief feature, and

(b) SECONDARY or SYMPTOMATIC where the eruption occurs in the course of some definite infection or poisoning.

The primary purpuras are usually divided into,

(1) Purpura simplex.

(2) Purpura Haemorrhagica (WERLHOFF's Disease).

(3) Purpura Rheumatica, Peliosis Rheumatica (SCHONLEIN'S disease).

(4) HENOCH'S Purpura.

The Secondary Purpuras may occur in association with,

(1) the exanthemata such as scarlet fever, smallpox, etc.

(2) Other general infections such as septicoemia, pyoemia, malaria, syphilis, general tuberculosis etc.

(3) Diseases of the blood such as Leucocythaemia, haemophilia, etc.

(4) Toxaemias such as malignant disease, disease of viscera specially the liver and kidneys etc.

(5) Drugs such as potass, iodide, quinine, chloral etc.

(6)/

(6) Serum disease.

The secondary purpuras need not be specially discussed. Their etiology is that of the condition which causes them plus some other factor. Some of them are anaphylactic such as those due to serum disease, others are generally admitted to be due to toxines which act by injuring the endothelium of the blood vessels.

The primary purpuras, however, require some discussion. They are closely allied to the erythemata and as in Peliosis rheumatica, may occur together with an erythematous eruption. It is known that in purpura there is a marked diminution in the number of blood platelets. HESS[565.] thinks this is due to a destruction of the platelets and that the platelet substance is in solution in the serum. He bases this opinion on the fact that, if normal blood is centrifugalised for two hours so as to remove the platelets, the coagulation time is greatly prolonged whereas in purpuric blood the coagulation time is but little affected by centrifugalisation.

In 1914 LEDINGHAM[566.] produced experimental purpura in animals. He found that an anti-guinea-pig-platelet serum was toxic for the guinea-pig and produced in it a condition which closely resembled purpura haemorrhagica in man. Later LEDINGHAM and BEDSON[567.] showed that anti-red-cell and anti-white-cell sera did/

did not produce purpura. It could only be produced by an anti-platelet serum. In the animals in which purpura was produced, a marked fall in the number of blood-platelets was found. These findings have been confirmed by MUHLISSER[569] and KRUMBHAAR, LEE and ROBERTSON,[568] GOTTLIEB[563] and WATABIKI.[571] BEDSON[560] in 1921 showed that antiplatelet serum contains a specific antibody for platelets and in 1922[561] he found that a reduction in the number of platelets alone is insufficient to bring about purpura. The intravenous injection of peptone or agar serum, both of which cause a diminution of blood platelets, fails to produce purpura. The other factor which he considers necessary is a degeneration of the blood vessel endothelium due to some toxine. In support of this is the fact that, if the endothelium of the vessels in a young rabbit be injured by the intravenous injection of anti-rabbit-red-cell serum and the platelets subsequently removed from the circulation by the introduction of agar serum, purpura is produced. From these experiments, therefore, it would seem that, in purpura, injury to the endothelium of the vessels together with diminution of the blood platelets are the essential factors.

As to whether purpura is anaphylactic in nature there is not much direct evidence on which to base/

base an opinion. If one assumes that in serum sickness the endothelal cell is sensitised, the circulation of the antigen would produce a reaction in and injury to the endothelial cell. If the blood platelets are not destroyed then the ordinary erythematous or urticarial rash would result, but if the blood platelets were destroyed then the rash would be purpuric in character. Similarly a purpuric rash might be produced by any toxic substance which destroys the blood platelets and injures the endothelium. This might account for haemorrhagic rashes from drugs, snake bites etc. The purpuras such as HENOCH'S purpura where visceral lesions occur are probably similar to the cases of E. multiforme with visceral lesions with the additional factor of toxic injury to the endothelium of the vessels.

DIXON[582.] recently reports very good results in the treatment of purpura haemorrhagica by injection of blood from one or other of the parents of the patients. WILSON[572.] also recently recorded a case of HENOCH'S purpura in a child who recovered rapidly after 3 injections of his father's blood serum. LINSER[1682.] also reports good results in two cases. This human serum treatment might cause benefit by the introduction of fresh blood platelets but NOBECOURT and TIXIER[570.] obtained good results in the treatment of

Purpura/

Purpura by injections of WITTE'S peptone. This last observation, although an isolated one, supports the sensitisation theory of the origin of Purpura.

DERMATITIS/

## DERMATITIS HERPETIFORMIS.

Dermatitis Herpetiformis is a disease which is allied in many ways to the urticarias, the erythemata and the Pemphigus group. The generally accepted view about D. Herpetiformis is that is is a toxaemia probably from a bowel absorption but as yet the exact nature of the toxine is undecided. The nature of the eruption however would suggest that it is a sensitisation phenomenon probably of intestinal bacterial origin. The periodicity of the attacks of eruption also suggest periods of sensitiveness alternating with periods of temporary desensitisation. The intense itching and the grouping of the eruption suggests a sensitisation of the nerve endings or peripheral nerves from which the reaction which causes the skin eruption arises and if one assumes this, it explains the difference between the eruption in urticaria and D. herpetiformis. In the former the endothelial cells of the skin vessels are sensitised and in the latter the nerve endings.

The almost constant and very marked eosinophilia in the blood is another point greatly in favour of the sensitisation theory. The good results obtained by autoserum therapy also point in the same direction. CORLETT[656], FORDYCE[1664], HOWARD FOX[1666], GOTTHEIL, HEIDINGSFELD/

HEIDINGSFELD[1670], LÖWENBERG[578] and HEUCK[1671], all report marked improvement in D. herpetiformis from autoserum treatment. LINSER[1678] also reports a very good result in a case of dermatitis herpetiformis in a pregnant woman (Herpes gestationis) from injections of serum from healthy pregnant women. LUX[1684] and ULLMANN[1704], however, found no benefit from autoserum therapy in D. herpetiformis.

The presence of Indicanuria in D. herpetiformis points to an intestinal absorption and CALVE[573] has shown that Indol and Skatol, which are produced by intestinal fermentation, if injected into rabbits, produce symptoms like those of anaphylactic shock and the blood shows a "crise hémoclastique" with a leucopenia and oedematous infiltrations of the internal organs occur. This change, he claims, is the same as that produced by protein shock. Therefore he considers D. herpetiformis to be a disease due to shock from absorption of Indol and Skatol.

So far as I can find, there are no records of cutaneous food tests having been done in D. Herpetiformis. I tested one case to several foods but with negative result.

The fact that arsenic so often acts beneficially in D. Herpetiformis suggests that the nervous system is implicated in this disease. Starvation treatment and drinking large quantities of water have also been/

been found to be very successful in bad cases. Presumably that is due to the dilution of toxines absorbed from the bowel. Intestinal antiseptics such as salol, calomel etc. probably also act by diminishing intestinal fermentation.

I think, therefore, that we may conclude that D. Herpetiformis is probably due to sensitisation of groups of cutaneous nerve endings to some bacterial protein from the bowel. Definite foods such as eggs have occasionally produced the eruption but that is the exception. Meat proteins, however, possibly produce a suitable intestinal pabulum on which bacteria flourish. The effect of dieting, intestinal treatment and the presence of indicanuria point to the intestine being the source of absorption. The blood eosinophilia and the success of autoserum therapy favour the sensitisation theory. The periodicity of the attacks with intervals of comparative freedom from eruption also point in the same direction and after months or years the patient passes from the sensitive condition on to complete immunity.

PEMPHIGUS/

## PEMPHIGUS.

The acute pemphigus of the new born and butcher's pemphigus are not included in this group. They are definite organismal infections. Pamphigus Vulgaris or Chronicus, P. foliaceus and P. Vegetans form a group which is very closely allied to D. Herpetiformis and much that applies to the latter disease, also applies to the former. There is the same eosinophilia and autoserum therapy also has given good results in some cases of Pemphigus. FISCHER,[1662.] LINSER,[1681.] WINFIELD,[1707.] PRAETORIUS[1689.] and HEUCK,[1671.] all report inprovement and in some cases cure, after autoserum treatment. GOTTHEIL and SATENSTEIN[1668.] in two cases obtained no result but these cases were probably too far advanced for any form of treatment to be effective.

TOMINASI[579.] in 1918 reports the result of the examination of 5 cases of P. vulgaris and 2 of P. vegetans. Blood cultures in all 7 cases were negative. From the vegetations in both cases of P. vegetans and from the internal organs of 2 cases of P. vulgaris which died, he isolated an organism identical with that first described by RADAELI in 1906. It is a motile bacillus with club-shaped swellings at each end. It is gram-negative and a facultative anaerobe. Complement fixation tests were made using this organism as antigen and/

and two, out of four cases, gave a slight positive result.

TOMINASI'S results agree very closely with those previously published by RADAELLI, PASINI and COPELLI. Out of 19 cases which have been examined post-mortem and cultures made, the same organism has been found in all. The organism is found in the heart spleen and liver, where it may be a mixed infection, but a pure culture has always been obtained from the bone marrow. Further work, however, is necessary before concluding that the above organism is the cause of Pemphigus.

The type of the eruption, the presence of a blood eosinophilia, the periodicity of attacks of eruption, the good effect of arsenic internally and of autoserum-therapy link the cases of Pemphigus to D. Herpetiformis and probably the same mechanism is responsible for both groups of diseases. Pemphigus is a much more serious disease than D. Herpetiformis, and it is possible that in the latter the infection is localised in the bowel and by absorption from the bowel the eruption etc. are produced; whereas in the former there may be an additional general infection of the blood and internal organs with the organism. That would account for the temperature which is so often present in pemphigus and for the fatal result.

Pemphigus/

Pemphigus foliaceus may begin as an ordinary P. chronicus or D. Herpetiformis and only develop the foliaceus eruption later. In all the cases I have seen 576. the Bac. pyocyaneus was obtained in pure culture from the skin. This would seem to indicate that P. foliaceus is due to the same cause as D. Herpetiformis or P. vulgaris together with a superadded infection with Bac. pyocyaneus.

Pemphigus vegetans also begins like P. vulgaris and later develops vegetating lesions. This would point to its being due to the same cause as P. vulgaris with a superadded infection, with an organism which produces the warty vegetating lesions.

SENSITISATION/

## SENSITISATION IN TUBERCULOSIS.

That a true sensitisation occurs in Tuberculosis is now generally admitted, so that it will be sufficient to mention the various hypersensitive reactions, which occur and discuss their significance.

## LOCAL, FOCAL AND GENERAL REACTIONS.

When a patient suffering from tuberculosis is given a suitable subcutaneous injection of Old Tuberculin within 24 hours a local reaction occurs at the seat of the inoculation. This is known as the local or "Stich" reaction, and indicates that the patient is sensitised to Tuberculin but gives no indication as to the seat of the lesion. The duration and the severity of the reaction depend on the degree of sensitiveness of the patient.

By absorption of the Tuberculin a general reaction may occur with a rise of temperature, headache, malaise etc. This is the general reaction and again does not indicate the seat of the lesion.

A focal reaction may also occur in all foci of tuberculosis in the body wherever they may be situated. If in the skin or subcutaneous tissues this reaction is shown by redness and swelling of the lesion for some days. (see Plates 6 and 7.) This reaction is of great value in diagnosis and for

practical/

practical purposes may be considered as diagnostic of tubercle. If the dose of Tuberculin be large and the reaction severe it may lead to a breaking-down of the lesion and a spread of the disease. This occurred frequently in the early days of the use of Tuberculin for treatment and did much to check the use of Tuberculin for that purpose. But with the smaller doses which are now generally employed the mild focal reaction is usually harmless if not in some cases beneficial. The newer preparations of Tuberculin, however in suitable doses do not give rise to marked reactions but a discussion of these is outside the scope of the work.

The phenomena of sensitisation occur in practically all forms of tuberculosis, but in the late cachectic stage of the disease, when the protective mechanism has broken down, they disappear. As would be expected a complement fixation reaction analagous to the WASSERMANN reaction in syphilis occurs in Tubercle. Many have worked at this subject. The most recent article is by NIMMO SMITH 596. who concludes that, where the WASSERMANN is negative, a positive tubercle complement fixation reaction is strong presumptive evidence of tuberculosis and that, in a clinically tuberculous patient, a positive reaction denotes activity of the lesion. The reaction disappears/

disappears in far-advanced cases. The specificity of the reaction is doubted by many. NIMMO SMITH states that non-specific fixations may occur notably when the serum gives a positive WASSERMANN reaction. Conversely several workers have recorded positive WASSERMANN reactions in Tuberculides etc. where there was absolutely no evidence of syphilis. This question of the specificity of the tubercle complement-fixation reaction is still in doubt, some like MILIAN[591.], holding that tubercle may give a positive WASSERMANN, whilst others, like TZANCK and PELBOIS[591.], that cases of tuberculosis giving positive Wassermann reactions are really cases of tubercle with latent syphilis. The sera of patients with tuberculosis have also been shown by ARLOING[580.] and others to give positive agglutination tests to the tubercle bacillus.

Passive sensitisation to tubercle has also been successfully achieved by BAUER[582.], HELMHOLZ[585.] and others by injecting the serum of tuberculous guinea-pigs and tuberculous patients into normal guinea-pigs.

Human beings and animals cannot be sensitised to tubercle by injections of Tuberculin. In order to obtain sensitisation with all the skin and other reactions, the individual must be actually infected with Tuberculosis.

CUTANEOUS/

## CUTANEOUS REACTIONS.

The most widely used test is the Von Pirquet reaction. The test is done by making a small scarification on the arm, short of drawing blood and rubbing a 25% solution of old Tuberculin gently into the area. In 24 hours an area of erythema surrounds the scarified area which is raised up into a papule in the centre (Cast 5. ) (Plate 8. ) A well-marked reaction lasts 4-5 days and then slowly fades. Severe reactions may lead to pustulation or necrosis in the centre. The reaction may also be delayed and only appear after 4 or 5 days.

## THE VALUE OF THE VON PIRQUET REACTION.

588, 589.

In 1909 I applied the Pirquet test to 75 cases of skin diseases in adults; 12 cases of Lupus vulgaris, one of tuberculous ulceration of the skin and 3 cases of tuberculides. All gave positive reactions. Cases of Lupus erythematosus, dermatitis, psoriasis, erythema multiforme, rodent ulcer, favus, D. herpetiformis, pityriasis rubra pilaris, acne, tertiary syphilis & prurigo gave positive reactions. In the 75 cases, which included 16 of tuberculosis, 40 (53%) gave positive reactions. Very similar results/

results have been obtained by many others, so that it is safe to say that a considerable percentage (over 50%) of apparently non-tuberculous individuals, and practically all cases of tuberculosis will give positive reactions. A positive reaction is therefore of no value in the diagnosis of a doubtful lesion. A negative reaction however, especially if repeated, is of great value as, for practical purposes, it may be considered to exclude tuberculosis. In young children the test is in rather a different position from what it is in adults. They have been more recently infected and a positive reaction is of more value. BONDY[60] in 1908 examined 350 new born children in the first four days of life and did not find a single positive reaction although 71% of their mothers reacted positively. He also quotes PIRQUET who tested 147 new born children, PROUFF, 54 and FEER, 70 new born children. Among these 271 children not one gave a positive reaction. LANGSTEIN[60] saw one positive reaction in 100 infants and BAUER 6 in 48 infants. Therefore it may be taken that new born children very seldom react positively. This may either be due to their not yet having been infected with tubercle or it may be due to a special non-sensitiveness of the skin of the new born. The following are some of the figures given by various authors for older children.

CATTERMOLE/

| | | | | | | |
|---|---|---|---|---|---|---|
| CATTERMOLE[606.] | 38% | positive | in | 66 | children | tested. |
| FISHBERG[613.] | 52% | " | " | 588 | " | " |
| KERFETZ[619.] | 53% | " | " | 276 | " | " |
| SALVETTI[636.] | 26% | " | " | 630 | " | " |
| VEEDER & JOHNSTON.[640.] | 44% | " | " | 1321 | " | " |

PIRQUET tested the value of the reaction in 100 cases which died later and were examined post-mortem and found that in only one case was the reaction positive where at the post-mortem examination no macroscopic tuberculosis could be demonstrated.

The severity of the reaction is not a very good index of the severity of the infection. In latent tubercle as a rule the reaction is not very marked, but if any extension of the disease occurs the reaction becomes stronger. It is well known that for some time after measles a PIRQUET reaction which was previously positive will become negative. This probably means that an attack of a disease such as measles temporarily destroys the antibodies to tubercle. It also explains the common clinical observation that multiple spots of Lupus vulgaris are very apt to occur after measles when the resistance to tubercle is absent. A similar disappearance of the skin reaction to Trichophytin in fevers will be referred to later on. Therefore it may be assumed that except after diseases such as measles a positive PIRQUET'S reaction may be taken/

taken as a sure sign of infection with Tuberculosis.

COLLIVER[608.] did experiments to see whether the skin of one part of the body was more susceptible than any other. He tested 50 children on the dorsum of the hand and foot, inside of the knee and on the shoulder, the neck, the back and on the ulnar side of the forearm and found no difference in the reactions. Therefore he concludes that there is no good reason for making the PIRQUET test elsewhere than on the arm which has the advantage of being convenient.

MONDOLFO and COSCERA[628.] performed the test on the arm and also near the seat of the tuberculous lesion and found in 82 cases that in the great majority of cases both reactions were positive or negative at the same time although the regional reaction was the more intense. It was rare for the regional reaction to be positive and reaction on the arm negative whilst the converse never occurred. MOLDOLFO and COSCERA also quote POLLITZER as obtaining similar results.

A great many observers have obtained negative PIRQUET tests in advanced tuberculosis or in acute general tuberculosis. This is generally attributed to the breaking down of the protective mechanism in the late stages of the disease, but McNEIL[625.] has shown recently that, by a more careful technique by scratching/

scratching the epithelium well off the surface of the skin and using undiluted Tuberculin, instead of a 25% or 50% solution, positive reactions may be obtained within a few days before death from miliary tuberculosis.

603. BOUVEYRON compared PIRQUET reactions from Tuberculin with those produced by the addition of certain drugs. He found that the addition of adrenalin to the Tuberculin increased the severity of the reaction, whereas the addition of quinine, antipyrin or pyramidon diminished the reaction. The administration of adrenalin to patients suffering from a tuberculous fever rendered the skin more sensitive to tuberculin, whereas the administration of quinine, antipyrin or pyramidon had the opposite effect.

## THE INTRACUTANEOUS TUBERCULIN TEST.

This method is not used so extensively as the cutaneous. It is rather more difficult to perform and the results are not so easy to interpret. BASS 598. and others report that it is more sensitive than the PIRQUET and like the Trichophytin tests, to be referred to later, is almost too sensitive. MONTI recommends it as an additional test in cases where the PIRQUET is negative.

KOLMER/

KOLMER, IMMERMANN, MATSUMANI and MONTGOMERY[802.] found that cutaneous and intracutaneous reactions to Tuberculin among persons reacting positively to both, were rendered more extensive by the administration of Pot. Iod. and Pot. Brom. This is similar to the effect of Iodides and Bromides on the Luetin test to be referred to later. SOLIS-COHEN[638.] found that the intracutaneous test can be done with T.R. just as well as with O.T. DEBRÉ and BONNET[609.] by experiments on guinea-pigs have shown that the reaction to Tuberculin introduced intradermically into guinea-pigs infected with living tubercle bacilli, varies more or less directly with the resistance of the animal. He found that in the heavier animals infected with tubercle, the health remains good till just shortly before death, whereas in the lighter ones there is a progressive loss of weight almost from the start. After death the heavier guinea-pigs are found to have a local lesion at the seat of inoculation, in process of cure, with infection of lymphatic glands, large tubercles in liver and spleen and tuberculous bronchopneumonia, and in the lighter animals there is very little local lesion at the seat of inoculation and a general tuberculosis throughout the body. If intradermal tests are done on infected guinea-pigs, they vary directly in intensity with the weight of the animal/

animal and the reaction is present for a much longer time the heavier the animal.

These results are similar to those found in human infants. In weakly poorly-nourished children tuberculosis is accompanied by a progressive loss of weight and early failure to respond to the tuberculin test whilst in better nourished infants the tuberculin reaction persists almost up to the time of death.

BRUSACCA[605], basing his work on the fact that it has been shown that tuberculous persons are hypersensitive to normal horse-serum, did a series of intracutaneous tests with horse-serum. In 119 cases of cutaneous tuberculosis he found that 80% reacted positively and three cases of pulmonary tuberculosis all gave positive reactions. The reaction was more marked in the early than in the advanced stages of the disease, in active than in torpid cases and in localised than in diffuse infections. He claims the superiority of the test over the PIRQUET test in that it is only positive when the disease is fully developed.

## THE "MORO" REACTION.

This reaction is obtained by rubbing into the skin an ointment consisting of equal parts of Old Tuberculin and anhydrous lanolin. The ointment is usually/

usually rubbed into the side of the chest or abdomen. About 1 grain of the ointment is used. In 24-48 hours several small red papules appear on an erythematous base and in more severe reactions the papules are larger, the erythema more marked and itching is present The lesions persist for 3-7 days and gradually fade leaving slight pigmentation. This test has very much the same significance as the PIRQUET test and has the additional advantage of giving fewer positive reactions in apparently healthy individuals, but according to EMMERICH it disappears earlier in progressing tuberculosis than the PIRQUET reaction.

In 1908 MORO[630.] did some interesting experiments with this ointment comparing it with the effect of pure lanolin. After rubbing one arm of a tuberculous patient with Tuberculin ointment and the corresponding spot on the other arm with pure lanolin, he obtained characteristic reactions on both arms. This he explains as a reflex nervous influence on the vaso-motor mechanism of the skin and describes it as a specific nervous "allergy".

For a number of years MORO'S ointment has been used in the Skin Department of the Royal Infirmary both for diagnosis and treatment. In doubtful skin lesions where tuberculosis is suggested the application of MORO'S ointment on lint freshly applied night and morning/

morning for 3 or 4 days, causes a severe local reaction with swelling of the lesion and an area of erythema around it. The lesion may also slough in places and ulcerate. In tertiary specific lesions either no reaction occurs or a very slight reaction due to a tuberculous focus elsewhere. A number of cases of Lupus vulgaris were also treated some years ago by applying the Tuberculin ointment for several days till a marked reaction was produced. The tubercle nodules ulcerated and sloughed out. The lesion was dressed with a simple zinc paste till it healed over. The results were rather disappointing but better results were obtained when pure carbolic acid was applied to each sloughed nodule when the reaction was at its height. One drawback to the method is the sickening smell produced in the ulcerated areas. This is very objectionable to the patient when lesions on the nose are treated by the above method.

Recently daily inunction of different areas of skin with Tuberculin ointment as suggested by Sir ROBERT PHILIP has been used with considerable success in the treatment of gland and other forms of tuberculosis.

The mechanism of these different Tuberculin skin reactions will be discussed later under cutaneous reactions.

A/

A modified skin test for Tuberculosis was introduced in 1909 by WILDBOTZ[627, 695] who made intracutaneous tests with the urine of cases of Tuberculosis. In 1900 MARAGLIANO[627] found precipitins in the urine in tuberculous cases and in 1913 HERTZ and BOYER and DEBRE and PARAF[627] found tubercle toxines in the urine in cases of kidney tuberculosis. WILDBOTZ[695] took urine from 200 cases of active tuberculosis, heated it to 50° -60° till it evaporated down to one tenth of its original volume. When injected intracutaneously he always obtained positive results in tuberculosis and negative results in other conditions. The reaction was only positive in staphylococcal infections, if numerous organisms were present in the urine. The most recent article on this test is by MAYR and HOFSTADT,[627] who tested 28 cases. They found that cases of Ringworm, Impetigo, furunculosis, secondary syphilis and eczema gave positive urine tests. They obtained a positive result in about one half of the cases where it was to be expected. In progressive cases, giving a positive Tuberculin test, the urine reaction was absent. MAYR and HOFSTADT think the reaction is untrustworthy although it is probably due to tuberculous antigen thrown out in the urine. They also quote BOEMINGHAUS, FARAGO and RANDT, KÖNIG, LANDGRAF, LEVI, ORLIANSKI, SCHÖNBORN, REINECKE, and SCHMIDT as obtaining positive or variable results/

results in healthy individuals. FARAGO and RANDT, GRASS, KUHN, LEVI and OFFENBACHER[627] obtained negative results in definitely tuberculous cases. BOSCH[602] found it always positive in tuberculous and negative in non-tuberculous cases and thinks that it is an improvement on the PIRQUET tests as it gives information as to the activity of the tuberculous process because it disappears quickly if the lesion heals. But on the whole the urine test does not seem to be as reliable as the ordinary Tuberculin skin tests.

IMHOF[618] also found the urine test constantly positive wherever an active tuberculous process existed. In addition to the auto-urine tests he also made autoserum tests simultaneously with intradermic tuberculin tests. He found that the auto-serum never gave so pronounced a reaction as the auto-urine. To avoid disturbing protein reactions with the blood serum he precipitated the albumin with alcohol and heated the serum for a few minutes. LEONI[620] also tested 80 cases of tuberculosis and 50 normal control subjects with auto-serum skin tests. He reports very satisfactory results and states that the results were always negative in the control cases even when syphilis was present.

## TUBERCULOSIS OF THE SKIN.

Tuberculous infections of the skin may be Lupus vulgaris, Tuberculosis cutis verrucosa or scrofuloderma. The lesions are all essentially the same and the different varieties depend on the method and situation of infection. In tubercle of the skin, as in all forms of tuberculosis, sensitisation occurs as is evidenced by a positive skin reaction. It is rather astonishing how little inflammatory reaction is often present round the nodules in Lupus vulgaris, as compared with the corresponding lesion, the gumma, in syphilis. Possibly this is due to the tubercle bacillus being so well hemmed in by giant, epithelioid and other cells and also to the absence of blood vessels in the nodules. As already mentioned multiple Lupus vulgaris lesions almost invariably occur after measles because the body loses its resisting power temporarily and the absence of the Tuberculin skin reaction prevents any reaction occurring between the skin and the Tubercle bacillus and therefore an infection with Tubercle, in which the bacillus survives, occurs, and not a tuberculide in which the bacillus is destroyed. Similarly in advanced cases of tubercle, disseminated miliary tubercle of the skin may occur, and here again the absence of a skin reaction allows the organism to grow in the skin and a tuberculosis and not a tuberculide results.

The/

The focal reactions in skin tuberculosis from injections of old Tuberculin and from the external application of tuberculin have already been referred to. They are signs of a true sensitisation to Tubercle. The improvement which sometimes occurs in Lupus from a course of Tuberculin injections shows that by this means the resistance can be raised to the infection but as this question is more closely related to immunity than sensitisation it is sufficient merely to mention the fact.

TUBERCULIDES/

## TUBERCULIDES.

Tuberculides are the skin eruptions which occur as the result of a blood-infection with the tubercle bacillus in a person who is sensitised to tuberculosis. They may be divided into three main groups,

(1) Lichen scrofulosorum (Cast Nº 6.) (Plate Nº 9.)

(2) Papulo-necrotic tuberculide (Cast Nº 7.) (Plate Nº 10.) and

(3) Erythema Induratum scrofulosorum (BAZIN'S disease) (Casts Nºs 8+9.) (Plates Nºs 11+12).

The first two are essentially similar and will be grouped together. Erythema Induratum is somewhat different and will be dealt with separately. As the etiology and pathology of these lesions are well-known it will be sufficient to state the views generally held now with regard to them, without quoting authorities.

### LICHEN SCROFULOSORUM & PAPULO-NECROTIC TUBERCULIDES.

These tuberculides occur in individuals who have a small focal lesion of tubercle and in whom the bacillus has gained access to the circulation. The tubercle bacilli are carried to the skin capillaries and a local reaction occurs in the skin where they lodge./

lodge. This reaction is essentially the same as the PIRQUET reaction but from the blood-side instead of from the exterior. The older view that they were due to tubercle toxines has now been disproved as the bacillus has been shown by numerous workers to be present and the earlier the lesion is examined the more likely is it to be found. The reaction which occurs between the tissues and the bacillus results in a destruction of the bacillus, so that the lesion heals with or without a scar and no infection of the skin remains. The reaction therefore is a protective one. Microscopically 670. the tuberculides show the same structure as all tubercle lesions with giant cells, epithelioid cells, plasma cells etc. After injections of old Tuberculin a general rash may occur all over the body. This rash is identical clinically and microscopically with Lichen. Scrof. and in many cases, 671. if not all, is a reawakening of a previous Lichen scrofulosorum which had disappeared.

The papulo-necrotic tuberculides are not usually so extensive as Lichen scrofulosorum and have been described under numerous names. The following are some of the names given to papulo-necrotic tuberculides occurring often in special situations such as on the face, viz. Acnitis (BARTHÉLEMY), Disseminated follicular lupus (FOX) Acne telangiectodes (KAPOSI) Acne agminata (CROCKER) Folliclis (BARTHÉLEMY) Dermatitis nodularis/

nodularis necrotica (HUTCHINSON, BOECK) Hydrosadenitis destruens suppurativa (POLLITZER, DUBREUILH) Toxituberculides (HALLOPEAU), Paratuberculoses, necrotic granuloma (JOHNSTON) Acne scrofulosorum and Acne cachecticorum (HEBRA). It is also a question whether some of the cases of Acne varioliformis are not cases of tuberculides.

Some workers have suggested that as the tubercle bacillus is present in tuberculides they should be called Tuberculosis lichenoides etc. but as they correspond to the syphilides, trichophytides etc. there seems no good reason why the name should be changed, so long as it is borne in mind that the lesions are due to the presence of the bacillus and not to toxines only. WISE thinks that the various forms and types of eruption depend on :-

(1) individual disposition of the patient

(2) the number of bacilli circulating, and

(3) the degree of immunity reaction residing in the affected individual.

652.

So far as I can find GOUGEROT and LAROCHE are the only workers who have succeeded in producing tuberculides experimentally in animals. Unlike other workers they did not scarify the skin but they pulled out the hair of the animal and rubbed in a culture of virulent Tubercle bacilli. As a result a papulo necrotic tuberculide was usually produced but sometimes Lichen. scrof. and erythema induratum lesions. Microscopically and bacteriologically these lesions corresponded/

corresponded to tuberculides in man. They found that the occurrence of tuberculides was hastened if the guinea-pig was previously sensitised by Tuberculin. They conclude from their experiments that a previous impregnation of the body with Tubercle toxine is necessary for the production of tuberculides and the severity of the reaction varies and so produces different types of tuberculide according as the bacillus is virulent, weakened or dead.

## ERYTHEMA INDURATUM SCROFULOSORUM (BAZIN'S DISEASE).

Erythema induratum is a much larger and more localised lesion than the other tuberculides. The lesion is a granuloma resembling tuberculous tissue commencing in association with the deep veins of the skin. CALCOTT FOX[650] and THIBIERGE and RAVAUT[641] produced tuberculosis in guinea pigs by inoculating them with material from E. Induratum lesions. I have seen a tubercle bacillus in pus from an ulcerated lesion. It is generally accepted now that the lesions are tuberculides where the patient is highly sensitised to the infection and the resulting reaction between the bacillus and the tissues causes the lesion. It begins deeply in the skin probably in a venule or arteriole and this gives it its characteristic/

characteristic clinical appearance. It is analagous to the gumma in late syphilis. WHITFIELD F 694 however doubts whether all cases are tuberculous. He considers that the form in young girls is undoubtedly tuberculous but in older persons one sees cases where the lesions microscopically do not have the tuberculous structure. In both cases the lesion originates in the deeper blood vessels. The question of acute erythema induratum lesions has already been discussed under erythema nodosum.

## OTHER SKIN LESIONS POSSIBLY RELATED TO TUBERCULOSIS.

For a number of years a controversy waged over Lupus Erythematosus and its association with Tuberculosis. There are still those who hold that it is a tuberculide but the recent work of BARBER and others has done much to clear matters up. Personally I do not think that Lupus erythematosus has any connection with Tubercle except that the individual liable to it is also the type of person who is liable to tuberculosis. This matter will be further discussed under Lupus erythematosus.

SARCOID/

## SARCOID TUMOURS.

These include the sarcoid of DARIER-ROUSSY, the multiple benign sarcoid of BOECK, Lupus pernio and lymphogranuloma benignum or STEINBERG'S Lymphogranulomatosis. In all these conditions there occur indolent bluish-red nodules which somewhat resemble clinically and microscopically Erythema Induratum although differing in their distribution from the latter disease. Opinions differ as to whether the above conditions are tuberculides or not. FRIEBOES, [651.] SWEITZER and MICHELSON, [690.] CIVATTE and VIGNE [647.] and others consider them to be true tuberculides, whilst BRUHNS and ALEXANDER, [644.] MARTENSTEIN and REJSEK, [673.] SCHAUMANN [683.] and others [684.] hold an opposite view. Injections of Tuberculin have been known to cause local reactions in Sarcoids. The whole question of the sarcoids is still in doubt. Possibly some of the cases described as sarcoids are tuberculides but it is by no means proved that all of them are of that nature.

## EXFOLIATIVE ERYTHRODERMIAS.

Acute lichen scrof. lesions or injections of Tuberculin may produce a scaly red rash but a generalised exfoliative erythrodermia has been described by some authors as due to tuberculosis.

BRUUSGAARD'S/

BRUUSGAARD'S case associated with universal tuberculosis of glands in which the bacillus was found seems to have been an example of this type of eruption but in the majority of cases no history of or association with tuberculosis is to be found. It is possible that in such cases the rash is a sensitisation phenomenon due to sensitisation to the protein of some organism which may be the tubercle bacillus in some cases and in others some other organism or toxins. At present we have not sufficient information on which to make a definite statement.

It has also been suggested that parapsoriasis is a tuberculide. The same suggestion has also been made with regard to pityriasis rubra pilaris but in both these conditions the evidence is inconclusive.

## LICHEN NITIDUS.

PINKUS[677] showed that in Lichen nitidus the structure of the nodules was that of a typical tubercle and ARNDT obtained a positive Pirquet reaction in one case and in another case sections stained by MUCH'S method showed one bacillus which looked like a tubercle bacillus. LEWANDOWSKY[666] had a case which showed no sign of tuberculosis clinically but when the patient died 2 years later an active tuberculosis was found post-mortem. Another case developed a tuberculous pleurisy and lichen scrofulosorum.

LEWANDOWSKY considers Lichen nitidus as a form of tuberculide. KYRLE and McDONAGH[664] obtained a general reaction to an injection of 1 mgrm. old Tuberculin, but inoculations of guinea-pigs with pieces of the lesions were negative; Nevertheless they are inclined to support LEWANDOWSKY'S opinion. The most recent article on this subject is by ZINGALE[697] who summarises all the previously recorded cases (46). Of the cases reported some showed no history of tuberculosis, others showed definitely its existence. He concludes that in all cases the cause is not the same and that one can neither admit or exclude tuberculosis as a determining factor.

## GRANULOMA ANNULARE.

This condition has been described under a great many names such as -

Erythema elevatum diutinum (CROCKER) 1894.

Ringed eruption (CALCOTT FOX) 1895.

Eruption circinée chronique de la main (DUBREUIHL) 1895.

Lichen Annularis (GALLOWAY) 1899.

Granuloma Annulare (CROCKER) 1902.

Tumores benigni sarcoidei cutis (RASCH and (GREGERSON) 1903 (GALSWSKY) 1908.

Erythemato-scleroses circinées du dos des mains (AUDRY) 1904.

Neoplasic/

Neoplasie nodulaire et circinées des extremités (BROCQ) 1904.

Sclerose circinée des doigts (AUDRY) 1905.

Acanthoma annulare (LESLIE ROBERTS) 1908.

Stereo-phlogose nodulaire et circinée (PELLIER) 1910.

Celluloma annulare (PERNET)

It has been suggested that the above condition is a tuberculide allied to Lichen nitidus and the sarcoids. GRAHAM LITTLE,[669] in 49 cases, in only 4 could find a tuberculous history and in only one was tuberculosis present. HUDELO,[658] CIVATTE and RABUT[658] in 1920 report the cure of a case by Tuberculin, but on the whole there is very little evidence to connect it with tuberculosis. Angio-Keratoma (See Cast 10. and Plate 13.) has also been classified, especially by French dermatologists as a tuberculide. It is a rare condition and occurs most commonly in tuberculous subjects. Apart from that there is nothing either in its clinical or histological appearance to connect it with tuberculosis. It is probably more closely associated with chilblains than any other condition and looks more like a congestion than an inflammatory phenomenon.

SUMMARY/

## SUMMARY.

1. That in tuberculosis a true bacterial sensitisation occurs is shown by the facts that:-

(a) Local, focal and general reactions occur on injection of Tuberculin.

(b) Complement-fixing and agglutinating substances occur in the serum in cases of tuberculosis.

(c) Passive sensitisation can be produced.

(d) Cutaneous reactions to Tuberculin - (Pirquet reaction, Moro reaction and intracutaneous reactions) are present.

(e) Tuberculides occur in various forms in man and have been produced experimentally in animals.

2. There is no definite proof that Sarcoid tumours, exfoliating erythrodermias, Lichen Nitidus, granuloma annulare or Angio-Keratoma are tuberculides.

SENSITISATION/

## SENSITISATION IN SYPHILIS.

Syphilis resembles, in many ways, the acute specific fevers. After an incubation period of about three weeks the primary lesion develops. This primary lesion is a local focus from which a spread takes place by the lymphatic vessels to the glands from which the spirochaetes enter the circulation. As in the specific fevers, the explanation of the rashes in syphilis is based on the principles of sensitisation. Early in the infection, before there is any sign of the secondary rash, antibodies are present in the blood. This is demonstrated by the presence of a positive Wassermann reaction in the blood serum. These antibodies are brought by the circulation to the skin where they sensitise the cells and the allergic reaction between the spirochaetes and the skin leads to the production of the various secondary rashes. The incubation period between the primary and secondary stages represents the time it takes to sensitise the individual completely. At the end of six weeks the individual's skin is allergic and the spirochaetes deposited in it through the circulation cause a reaction, which results in the roseolar rash. In this stage the individual is not very highly sensitised and therefore/

therefore the reaction is a comparatively slight one but evidently sufficient to cause a destruction of the spirochaetes in the skin. Later, if a further shower of spirochaetes is sent out into the circulation, the individual being now more highly allergic, a larger rash occurs - papular, papulo-squameous and later still nodular. Each of the secondary rashes becomes less and less extensive and the lesions larger and larger in size. Finally the tertiary stage is reached where the allergy of the skin reaches its maximum and the large nodular gumma in localised areas results. All the evidence available goes to support the idea that in syphilis one is dealing with a true bacterial sensitisation of the tissues analagous in every way in the secondary stage to the specific fevers and to the sensitisation which occurs in diseases like Tuberculosis. In the latter disease Lichen scrofulosorum and the papulo-necrotic tuberculides correspond to the secondary syphilitic rashes and lesions in erythema induratum to the tertiary gumma. In discussing the question of sensitisation in syphilis one cannot avoid the question of immunity to syphilis. The numerous experiments of METCHNIKOFF and ROUX and NEISSER 740. and his assistants showed that it is not possible to produce an active immunity to syphilis by subcutaneous or intraperitoneal injection of virus. It has long been recognised/

recognised that an individual is only immune to syphilis so long as he still suffers from the disease or only for a very short time after cure. The individual seems to be in the same condition, as will be referred to later under Ringworm, where only a relative immunity is present. This so-called relative immunity is really a hypersensitiveness. EHRMANN and FINGER and LANDSTEINER[111] showed that attempts to reinoculate syphilis results in the production of a lesion of the same character as that from which the individual suffers. If in the secondary stage a series of papules result and if in the tertiary stage a gummatous lesion develops; this raises the whole question of reinfection and superinfection. If superinfection occurs early enough, before the individual is fully sensitised, a smaller lesion resembling a primary but with a slightly accelerated incubation period is the result. As soon as the secondary or tertiary stage is reached any reinfection results in a lesion corresponding to the respective stages. Recently many cases have been reported in which within a few months after a definitely proved syphilitic infection an apparent reinfection with a lesion like a new hard chancre results.[761] VERESS and others think that these are not reinfections but early recurrences. They may occur on the site of the original chancre and cause the characteristic swelling of the glands so that they are indistinguishable/

indistinguishable from a real chancre but they may occur on any part of the skin or mucous membrane and imitate an extragenital chancre. TOMASCZEWSKI[758.] refers to cases of reinfections reported in syphilitics by DIDAY,[707.] MERKEL,[737.] KOBNER,[729.] GASCOYEN[716] and DUCREY[708.] and considers that in all except DUCREY'S case the lesions were probably pseudo-chancres, i.e. gummatous lesions. NEUMANN[746.] and UNNA[760] showed that in clinically healed lesions a perivascular cell infiltration can be demonstrated and they consider that the virus is still present and that gummatous lesions on the seat of old primary lesions are the result of a local regrowth of the virus. In the cases of pseudo-chancres either due to a local regrowth of the virus or to reinoculation, the pseudochancre is not followed by a secondary rash. Within recent years however since treatment with arsemo-benzol compounds came in, numerous cases have been recorded where a true reinfection probably occurred. In these cases the patient was cured of the disease and the second infection ran a course the same as the first. In 1921 BROWN and PEARCE[702.] did a number of experiments by inoculating rabbits with syphilis and then treating them with Salvarsan in doses insufficient to cure the infection. Such animals are highly susceptible to reinfection with syphilis. If this applies equally well to human beings it suggests that/

that treatment with drugs like Salvarsan may cause an infection to revert to the condition in which the patient was when first infected before sensitisation had occurred and thus a reinfection might occur whilst syphilitic lesions were still present from the first infection.

739.

NAKANO in 1913, by injecting into a case of congenital and one of tertiary syphilis an extract of syphilitic organs or extracts of cultures of spirochaeta pallida, produced swellings which broke down and ulcerated and left scars like gummata. From these results he concludes that in tertiary syphilis killed spirochaetes and their toxines can produce gummatous lesions.

740.

Experiments by NEISSER to produce passive immunity to syphilis were all unsuccessful.

Cases of malignant syphilis, where large ulcerating lesions occur early in the infection, are probably not due to any special virulence of the virus but to the patient being very early and highly sensitised so that excessive reactions occur wherever the spirochaetes lodge. The well known phenomenon of the rash in syphilis being made evident by administration of mercury is probably due to the mercury killing the spirochaetes in the skin and liberating substances which cause the reaction. It is analagous to the positive Wassermann reaction which can be

provoked/

provoked by a dose of Salvarsan.

It has been recognised for a long time that trauma has often a localising effect in the production of lesions in syphilis. In the secondary stage papules may appear at the seat of slight local irritation such as the pressure of the clothes and in the tertiary stage many cases of localised syphilitic lesions have been reported as the result of injuries, contusions, fractures, wounds etc. Some think that these are due to the injury wakening into activity spirochaetes which are already present. Spirochaetes have been found in the skin, glands, bones, and mucous membranes in cases of latent syphilis where no visible lesions were present and the injury might by lowering the resistance of the tissues cause these spirochaetes to start to grow. PASINI 748, 749. in a recent article thinks that the trauma produces a fresh cellular infiltration with a lowering or absence of local immunity. The effect of traumata does not seem to have any association with sensitisation.

## THE WASSERMANN REACTION.

It is not proposed to enter into a discussion on the Wassermann reaction. The volume of literature on the subject is enormous. Although now admitted not to be a specific antigen-antibody reaction, it/

it is sufficiently constant in the secondary and tertiary stages to be of use clinically. It is present in the largest percentage of cases in the secondary stage and to a less extent in the tertiary stage and in latent syphilis. The presence of complement-deviating substances in the blood in syphilis points to a sensitisation and brings syphilis into line with other bacterial sensitisations. NAKANO did a series of experiments to show that, from cultures of spirochaetes or material from syphilitic products, by digestion with guinea-pig complement, anaphylatoxin can be obtained.

## DESENSITISATION IN SYPHILIS.

Comparatively few attempts have been amde to desensitise patients with syphilis. As no true immunity is present it is doubtful whether desensitisation is advisable. If sensitisation results in a series of reactions which are protective in nature, then desensitisation, if it does not lead to immunity, would by removing the protective mechanism lead to a lowered resistance.

GROSGLUCK[719.] used an alcoholic extract of congenital syphilitic liver and found that, if injected, it acted in all stages of syphilis like mercury, Iodides/

Iodides and Salvarsan, but in rapidity and intensity of action it comes incomparable after these drugs. The best results were obtained in recurring secondary lesions. Less effect was seen in tertiary syphilis and still less in recent syphilis. The dose had no visible influence on the success of the treatment in secondary recurring syphilis. In tertiary syphilis as good results were obtained with small as with large doses. No information is given as to the permanency of the results. ERSETTIG[710] treated 14 syphilitics, all with positive Wassermann reactions, with injections of typhoid vaccine. He gave 3 injections, at weekly intervals, of typhoid vaccine. The first contained 500 million typhoid and 250 million paratyphoid bacilli; the second injection double and the third injection treble that dose; then two injections of Cholera vaccine containing 2000 and 4000 millions respectively. ERSETTIG found these vaccines capable of modifying the Wassermann reaction so as to change it from a strongly positive to a negative reaction. They also caused a modification of the syphilitic lesions ending in their complete disappearance even although no antisyphilitic treatment was given.

These results show that non-specific vaccines are capable of modifying the course of an infection like syphilis but whether, as already stated, the result is in the long run advantageous is very doubtful.

CUTANEOUS/

## CUTANEOUS TESTS IN SYPHILIS.

In 1906 JADASSOHN[791.] made a series of skin tests on syphilitics with an extract of congenital syphilitic liver. He only obtained one positive result and that in a case of malignant syphilis. He thought it was due to an "idiosyncrasy" in malignant syphilis.

In 1908 TEDESCHI[827.] tested syphilitics with a watery extract made from primary sores and obtained weak conjunctival but definite skin reactions. He found the reaction to be absent in healthy individuals and in syphilitics who had been treated with mercury.

In 1909 MEIROWSKY,[809.] using an extract of congenital syphilitic liver, obtained positive reactions in 96% of all syphilitics. In 116 controls, with normal liver extract, in one case only he obtained a distinct reaction and in two a slight reaction. He attributed, probably correctly, these control reactions to substances in the liver.

NICOLAS, FAVRE and GAUTHIER[814.] used a glycerin extract of congenital syphilitic liver which they called "Syphilin". They did cutaneous and intracutaneous tests and obtained much better results by the intracutaneous than by the cutaneous method. FONTANA[787.] used a similar "Syphilin" - a glycerine extract of mucous patches rich in Spirochaetes. In 51 syphilitics tested/

tested in all stages of the disease 53% reacted positively whilst 12·5% of non-syphilitic cases reacted. This high percentage of reactions in non-syphilitic cases can be explained in the same way as the agar skin reactions obtained by STOKES to be referred to later on. The material from the mucous patches might produce the reaction by acting as an adsorbent.

NAKANO[811.] using extract of congenital syphilitic liver ("Pallidin"); KLAUSNER using extract of congenital syphilitic lung also did similar tests to the previous workers and obtained high percentages of positive results especially in tertiary and congenital syphilis.

Up till 1911 the tests were all made with Spirochaete-containing material from syphilitic organs but by the cultivation of the spirochaete NOGUCHI[816.] was able to procure from the organism a pure extract which he called "Luetin". Luetin is made by grinding up in a sterile mortar ascitic-agar cultures of the spirochaete and mixing them with a culture of the spirochaete in ascitic fluid. It therefore contains agar diluted with ascitic fluid and the fragmented bodies of spirochaetes. As a control ascitic agar and fluid was used. NOGUCHI first used Luetin on infected rabbits and obtained positive results. Later he used it on human beings. The test is made intradermically. $\frac{1}{10}$ of a c.c. of the Luetin is injected into the skin

of/

of the left arm and an equal amount of the control into the skin of the right arm. The injections are given as superficially as possible, separate syringes and needles being used for the Luetin and the control. NOGUCHI found that in most cases the control left no lasting trace whilst the Luetin caused different kinds of reactions. In non-syphilitics as a rule an erythematous zone developed round the injection spot and in 24-48 hours a small papule developed, which began to disappear on the third day. Therefore only on the fourth day can the result of the injection be read. NOGUCHI obtained 3 types of reaction,

(1) papular

(2) pustular, and

(3) torpid.

The papular reaction (Cast N° 11.) (Plate N° 14), occurs especially in secondary syphilis and consists of a red-papule surrounded by a diffuse red zone. This reaction disappears in 14 days. The pustular form occurs especially in tertiary and congenital syphilis and in secondary syphilis treated with Salvarsan. The original papule develops in a few days into a pustule with a larger zone of redness around it than in the papular reaction. The torpid reaction is the least frequent. It occurs as a small pustule about the 14th day. NOGUCHI found one or other of these reactions to be present/

present in 100% of tertiary cases with symptoms, in 94% of latent tertiary cases, in 96% of congenital syphilitic cases. During the primary and secondary stages of syphilis the reaction is almost always negative except in cases where energetic treatment has been undertaken especially with Salvarsan. In Tabes and general paralysis of the insane, NOGUCHI found the reaction positive in about half the cases and in over 250 control cases he only obtained one positive reaction.

Since NOGUCHI first introduced Luetin it has been used by GRADWOHL[789], HOWARD FOX[788], KAMMERER[794], NOBL and FLUSS[815], ROBINSON[822], WOLFSON[829], KALISKI[793], DESNEUX[785], MARIE and BROUGHTON-ALCOCK[807], BÖRNSTEIN[776], NAST and NICKAU[776], TESCOLA[828], FAGINOLI and FISICHELLA[786], PERKEL[821], HANES[790], CALICO[779], KOLMER and GREENBAUM[801] and others. These workers used it in all stages and all forms of syphilis. It is not necessary to give details from all these observers, but on the whole the results were very much the same as those obtained by NOGUCHI, viz, positive results in the great majority of tertiary, latent, congenital and parasyphilitic lesions and in treated secondary cases and mostly negative results in primary and untreated secondary cases. The reaction is therefore a very valuable one because it gives most positive results in the stages of syphilis when the Wassermann is/

is not so frequently positive as it is in the secondary stages.

## THE SPECIFICITY OF THE LUETIN REACTION.

NEISSER[813] and BRUCK found that a reaction similar to that produced by syphilitic liver extract could be obtained also with a concentrated extract of normal liver. Therefore the reaction is not specific. NEISSER ascribes it to the condition of "Umstimmung" in the late stages of syphilis but as already stated non-specific agar reactions can be produced and the reaction is probably not an antigen-antibody reaction but an antiferment-adsorbent reaction. BOAS and DITLEVSON[773] obtained positive reactions in tertiary syphilis using gonococcal and colon bacillus suspensions. Working with Luetin they also obtained positive reactions in cases where there were no signs of syphilis. Also the control fluid frequently gave positive reactions probably from the agar which it contained. Therefore there is an altered sensitiveness of the skin in tertiary syphilis but what the exact explanation is has not yet been fully explained. BOAS and STURUP[774] also obtained positive reactions in late syphilis using extracts of enlarged glands in cases of soft sore. CHIEFFI[780] likewise found the Luetin reaction to/

to be positive in other conditions besides tertiary syphilis. Lupus, Leprosy, Trichophytosis, simple folliculites and ecthyma reacted positively. He also confirmed BOAS and DITLEVSON'S results with gonococcal vaccine instead of Luetin.

LAGANO[804] and BROUGHTON-ALCOCK, NOBL[815] and FLUSS, SCHMITTER[824], BURNIER[777,778] and KOLMER and GREENBAUM[801] also obtained non-specific reactions with Luetin. STOKES,[1510] as already mentioned, produced positive reactions by intradermal injection of solutions of agar in physiological serum. He found the reaction positive in 50-70% of the cases of tertiary syphilis. KOLMER and BROADWELL[799] found that there was no direct relationship between the presence of the Luetin reaction and the presence of agglutinins and complement-fixing bodies in the serum. Therefore they conclude that the test cannot be regarded as an index of the resistance to the spirochaete pallida. BORNSTEIN, NAST and NICKAU[776] also found that a non-specific lytic action is developed in the blood after Luetin injections.

In 1915 SHERRICK[825] found that a ·5% suspension of agar, if injected intradermically, gave rise to reactions indistinguishable from the Luetin reaction provided that the patient was taking Potassium Iodide. He also found that normal persons taking Potass. Iod. gave positive Luetin reactions and that the Luetin reaction/

reaction in syphilitics when involuting could be revived by the same drug. KOLMER, BROADWELL and MATSUNAMI[800.] confirmed SHERRICK'S work obtaining well-marked positive Luetin reactions in healthy persons taking Potass. Iod. BORBE[R 775.]G and COLE and PARYZEK[782.] also found the same reactions in persons taking Iodides. KOLMER, IMMERMAN, MATSUNAMI and MONTGOMERY[802.] found that in addition to Iodides, Bromide of potassium and sodium, when taken internally, caused similar but less marked reactions to Luetin. The chlorides of potassium and Ammonium only influenced the Luetin reaction to a very slight extent. The administration of protiodide of mercury also influenced the Luetin reaction to some extent. Ether and chloroform anaesthesia did not seem to influence skin reactions. Cutaneous tests were not as readily influenced by iodides as intracutaneous tests. These observers also found that the administration of Pot. Iod. and to a less extent of Pot. Brom. increased the phagocytic power of the blood serum for Bac. prodigiosus. They think that the increased severity of skin reactions in persons taking these drugs may be due to heightened leucocytic infiltration and phagocytosis at the seat of injection or to an increase of tryptic activity through the saturation of fatty-acid radicals according to the hypothesis of JOBLING and PETERSEN. STOKES in doing his agar reactions/

reactions in normal individuals found that Iodides, taken internally, appeared to favour a reaction just as they do in the Luetin test.

Therefore, before doing the Luetin test, the physician must always be careful to ascertain that the patient is not or has not recently been taking Iodides or bromides.

## SUMMARY.

1. The rashes in the secondary and tertiary stages of syphilis can be explained on the principles of sensitisation to the spirochaeta pallida.

2. An active immunity to syphilis has never been produced.

3. Experiments to produce passive immunity to syphilis were also unsuccessful.

4. There is no true immunity to syphilis. Persons with syphilis are protected from reinfection by the local hypersensitive reaction which occurs at the seat of reinoculation.

5. Malignant syphilis is probably due to a very high degree of sensitisation of the individual/

individual and not to an increased virulence of the spirochaete.

6. The Wassermann reaction, although not a specific antigen-antibody reaction, is sufficiently constant to be of use clinically especially in the secondary stage.

7. The intracutaneous reaction to Luetin, although not specific, is useful clinically especially in tertiary, latent and congenital syphilis. The administration of Iodides or bromides vitiates the test.

8. Desensitisation to syphilis with organ extracts and non-specific vaccines has been attended with partial success but further work is required before a definite opinion can be expressed as to its value.

# SENSITISATION and IMMUNITY to RINGWORM and FAVUS.

Ringworm and Favus have been looked upon, until comparatively recently, as purely local infections. The well known clinical appearances of the skin lesions were recognised and described by all the older writers. That they were due to the presence of a fungus in the skin was also known. Whilst the skin is the usual seat of the lesions in rare cases (such as those recorded by ROBERTSON and CUTLER and GILLETTI [875.]) Ringworm has been reported as affecting the mucous membranes of the mouth. There is also the well known case of Favus described by KAPOSI with lesions in the gastro-intestinal tract.

In all these cases the infection was considered as a purely local one affecting the skin and mucous membranes only. It was never suggested that these infections had any effect on the body generally. The one isolated fact which suggested some general effect, was that it has been known for some time that farm workers and others who have suffered from an attack of cattle Ringworm on the body and limbs, are immune to further attacks. In these cases the lesions were usually extensive, deep seated and accompanied by

a/

a good deal of suppuration.

A great deal of work was done especially by SABOURAUD [919] on the investigation into and cultivation of the different fungi which cause Ringworm and Favus in man and animals, but that work did not advance our knowledge as regards the changes which take place in the body during or after an infection with these diseases.

In 1887 COHEN [868] showed that the course of an infection with Aspergillus flavescens was influenced favourably by a previous infection with the same fungus but the first work bearing directly on this question was published in 1902 when NEISSER [907] reported the results of some experiments done by himself and PLATO on human beings suffering from Ringworm and Favus. These workers made an extract of the Ringworm fungus which they called "Trichophytin". The fungus was grown at room temperature in flasks containing 1% Witte's peptone, 3% maltose and ·5% Na.Cl. for three months. The mass of fungus was cut into pieces & bruised down so as to separate the elements as much as possible. The whole was then filtered through sterile filter paper, the filtrate tested for sterility and 0·25% carbolic acid added as a preservative. This "Trichophytin" therefore corresponded to the Old Tuberculin prepared from the Tubercle bacillus.

It/

It was found that, when this Trichophytin was injected into a patient suffering from a deep-seated Ringworm, it produced a general reaction with rise of temperature and symptoms of intoxication. It also caused a local reaction at the seat of injection which became hyperaemic and sometimes suppurated. In these experiments no therapeutic effect on the lesions was noticed.

The Trichophytin produced no local or general reaction in healthy men nor in those suffering from other diseases such as tuberculosis. As a control some of the culture medium was injected but had no effect on the Ringworm patients.

It was found that a reaction only occurred in patients suffering from deep-seated Ringworm, the reaction being entirely absent in superficial Tineas.

"Favin" an extract of Favus fungus, prepared similarly to the Trichophytin, gave no reaction in Favus cases and Favus cases gave no reaction to Trichophytin.

These experiments showed that in deep-seated Ringworm, but not in superficial cases, some change had taken place in the patient's tissues, which resulted in a general and local reaction. In other words the patient had become sensitized to the infecting agent.

As/

As a result of this work by NEISSER and PLATO many other workers started experimental investigations in Ringworm in man and animals.

BLOCH[841.] working alone and also with MASSINI[849.] did a great many experiments on man and animals. BLOCH was the first to prove experimentally that immunity resulted in animals after an infection with Ringworm. He found that certain kinds of Trichophyton fungi are pathogenic for guinea-pigs and rabbits. These animals, if properly inoculated, developed the disease with certainty every time. He found that Achorion Quinckeanum (the fungus of mouse Favus) and Trichophytin Gypseum were the fungi which most readily infected animals. When an animal is inoculated with either of these fungi a typical local lesion develops but spontaneous involution takes place beginning usually in 7-9 days after inoculation. All animals after a single infection (except when the primary spot is a very small one) are immune to further infection. This immunity was found to last in animals at least as long as a year and a half and coincident with the immune reaction it was found that the skin had become sensitized as was shown by the presence of a cuti-reaction, which will be referred to again later.

SPECIFICITY./

SPECIFICITY. Two interesting facts also emerged from these experiments. Firstly it was found that this sensitization and immunity were not strongly specific. The reaction is only specific for Trichophytosis in general. An animal, which had passed through an infection with Achorion Quinckeanum, and in which immunity had been produced, could no longer be reinfected with that fungus , but the same animal was also found to be immune to infection with Trichophyton Gypseum. This shows that the Achorions (Favuses) and the Trichophytons are very closely allied and BLOCH even goes so far as to claim that Achorion Quinckeanum is really a Trichophyton which forms scutula.

Secondly it was found that the only way to produce complete immunity was by skin inoculation, and that the lesion must be a deep one. Intra-peritoneal and subcutaneous inoculation did not produce the same results. BLOCH thinks that this is because the conditions necessary for the oxygenation of the fungus are so unfavourable inside the body that its growth and the production of immunising substances are interfered with.

849.

BLOCH and MASSINI also found that the size of the focus is of no importance for the occurrence of immunity. Likewise immunity is only obtained by inoculating with living cultures and producing an actual infection./

infection. Trichophytin and Favin, if injected previously, were found not to confer immunity and did not make the animal hypersensitive. This corresponds to what is known to occur in Tuberculosis, where injections of Tuberculin do not cause the skin to become allergic whereas an actual infection with Tuberculosis always leads to the production of a positive Tuberculin skin reaction. Similarly AXAMIT[837] in 1907 showed that injection of dead fungus from Blastomycetes is not capable of producing hypersensitiveness but living fungus can do so.

Following BLOCH many others did experiments on similar lines.

BRUHNS[853.] inoculated several varieties of Trichophyton cultures into animals and human beings. The stronger cultures such as BLOCH used (Trichophyton Gypseum and Achorion Quinckeanum) were found to cause an immunity. Cultures of other kinds did not do so. Those which caused the deep forms of Tinea left more immunity behind them than those causing the superficial forms, but individuals were found to vary. BRUHNS thinks that in most cases absolute immunity is not obtained. The immunity is only relative. An attempt to cure a case of tinea in men by repeated inoculation, was not successful.

BRUHNS and ALEXANDER[854.] did a great many experiments/

experiments by inoculating guinea-pig with Trichophytons, microsporons and Favus. When using the same fungus as BLOCH had used they obtained the same results as he did, thus confirming his work. On the whole they found that an infection with Ringworm in guinea-pigs and man produces only a relative but fairly marked immunity. They also confirmed, what has been long known with regard to deep seated Kerion Ringworm, that fungi which produce deep seated lesions have a greater immunising power than those which produce superficial ones. One may get a Tinea Barbae with deep lumpy lesions or superficial rings due to the same fungus. Therefore the difference is not due to the fungus itself. In the former case immunity results. In the latter it is absent. It all depends on whether the fungus comes into contact with the tissues of the body and produces a cellular reaction there.

866.
CITRON also repeated NEISSER and PLATO'S experiments by injecting Trichophytin, but did not succeed in getting any positive reaction even in deep seated Ringworm cases. This however may have been due to his cultures being old and having been repeatedly subcultured whereas PLATO worked with Cultures direct from man.

HANAWA/

HANAWA[880] did experiments by inoculating animals with Trichophytin Gypseum as BLOCH did and found that in guinea-pigs the lighter haired areas became more quickly immune than the darker haired areas. He also excised the skin lesions in normal and immune guinea-pigs to see what change takes place as immunity develops and the lesion heals. He found that, corresponding with the clinically rather sudden tendency to healing after 7-9 days, the relatively subacute inflammation which arises on first inoculation, passes on to a very acute necrobiotic inflammation.

The necrosis leads to sloughing of the surface layers and the formation of a crust in which well stained fungus elements are thrown off. The healing takes place in the first instance not by destruction of the fungus but by its elimination in the crust.

KUSONOKI,[889] also did a great many inoculation experiments on animals and found that in guinea-pigs an immunity can be produced by all kinds of fungi so that the animal can neither be reinfected locally nor in any other part of the body surface either with the same fungus or one of the same group. A very virulent fungus produces an immunity against slightly virulent fungi, but the immunity produced by a slightly virulent fungus is not strong enough to prevent infection with a/

a very virulent fungus. Like other workers KUSONOKI also found that the deeper the focus of disease, the more quickly and strongly the immunity developed. Not only the quantity but also the quality of the fungus endo-toxine is of great importance in producing immunity. It was found that it was more difficult to produce immunity in rabbits than in guinea-pigs, and that there is a certain relation between immunity and body weight. The immunity in animals can be inherited either in the case where the mother's immunity is acquired before conception or during the pregnancy. KUSONOKI found that the immunity produced is a relative one only and that in some cases on second inoculation an abortive infection took place. Numerous experimental observations in Ringworm were also made by PRYTEK.[920.] This observer like KUSONOKI and others, found that infection of guinea-pigs with ringworm of the skin always led to a state of sensitisation which showed itself by the fact that repeated inoculation either led to no result or to a modified form of the disease. This modified form of the disease came on quickly and ran a rapid course and is to be looked upon as a hypersensitive reaction rather than a true reinfection. PRYTEK'S experiments yielded varying results./

results. On the one hand complete immunity did not always result from infection with a fungus which produced deep foci, and on the other hand fungus from superficial lesions sometimes immunized completely. One experiment was done on man, and did not lead to an immunity. The person experimented upon was a doctor who allowed himself to be inoculated on the arm with Achorion Quinckeanum. A typical red scaly lesion was produced in which the fungus was found. The lesion suppurated and was cured by the application of Tr. Iodi. Nine months later the same arm was inoculated with Trichophyton Gypseum and a scaly ringed lesion with blisters at the edge developed and ran a course of some weeks. The same experiment done by BLOCH previously had produced a complete immunity to re-infection, but in this case no real immunity had been produced.

TRUFFI[951.] also did a great many experiments on men and animals. By subcutaneous injection of Trichophytin he obtained local and general reactions and usually focal reactions as well in deep Ringworms. In superficial cases of Ringworm he succeeded in producing a fairly good reaction by the application of Croton oil to the lesions thus causing a deep seated action of the fungus. Reactions occurred irrespective of whether/

whether the causal fungus of the Ringworm was the same as the one used to manufacture the Trichophytin. Reactions were also obtained with "Microsporin" but to a less degree than with Trichophytin. No reactions were obtained with Trichophytin in cases of Favus.

LOMBARDO[895, 896.] came to the conclusion from a series of experiments that inoculations with fungi are only able to bring the body into a state of allergy, which is shown by an altered and more rapid course of the disease. He did not succeed in producing a real immunity. But it would appear that although his results were correctly reported, his conclusions were wrong. He evidently did not realise that the skin reaction is not only a hypersensitive reaction, but an immunity, one as well, so that on reinoculation what was produced was not to be considered as a modified reinfection so much as an allergic reaction due to the presence of the fungus and its toxines.

LOMBARDO also quotes SKRINSKI, who used Achorion Quinckeanum, Microsporon Lanosum and Tr. Asteroides, as always obtaining an immunity after one attack of the disease.

LOMBARDO found that the allergy produced by an attack of the disease persisted as long as one year/

year and a half after the disease had healed. It is not strongly specific for the fungus which first caused it. He could not produce allergy either by injection of living or dead hyphomycetes under the skin or by intramuscular or intravenous injection of toxine or culture filtrates. As others found, it required an actual attack of the disease to cause sensitisation and immunity.

PRYTEK'S[920.] animal experiments were very thorough, as many as 359 inoculations being made, on 227 animals (guinea-pigs and rabbits). As stated, his results varied from an absolute immunity, to very little immunity at all, but he never saw a single case where the second infection ran the same course as the first. Therefore the first infection always had some sensitizing or immunizing effect. This sensitization or immunity is not a local one but a general one affecting the whole skin.

SAEVES[932, 933.] also repeated the experiments of BLOCH, KUSONOKI, BRUHNS and ALEXANDER and PRYTEK, by inoculating animals with Ac. Quinck. and Tr. Gypseum because the fungi have been shown to be very constant in their ability to produce Ringworm in animals. SAEVES found that during the clinical incubation time of guinea-pig Ringworm it was possible to demonstrate fungus, both culturally and microscopically/

microscopically more or less abundantly in the skin. The inflammatory signs are slight and remain so till the development of hypersensitiveness, when the typical clinical lesion appears. This agrees with PIRQUET'S work on Vaccinia and shows that in the dermatomycosis, the incubation period lasts till the moment when the specific hypersensitive reaction reaches its height and then the healing process begins, by an elimination of the fungus. SAEVES, too, like PRYTEK, found that on reinoculation of animals a modification of the course of the reaction always occurred. True complete immunity in the clinical sense, was only found exceptionally; complete immunity was developed especially after repeated inoculation. Most often the reaction appeared sooner and ran a shorter course than after the first injection, and it appeared sooner after a shorter incubation period, but on the whole the general characters of the modified lesion were very like the typical acute disease. Very often from the reinoculated areas abundant fungus was found microscopically, so that there was no doubt that it was multiplying in the skin. SAEVES also found that after the reinoculation has run its course, there occur peripheral nodules (containing fungus) arranged in a corymbiform manner similar to the Trichophytides in/

in human beings to be described later on.

SAEVES also investigated why some types of Ringworm such as Achor. Quinck. and Tr. Gypseum will produce a typical clinical lesion in animals on almost every attempt, whilst Epidermophyton Inguinale and Microspor. Audoini do not. He found that he could cultivate the latter fungi from the skins of inoculated animals 10-15 days after inoculation, showing that a rapid death of the fungus, when applied to the skin, is not the cause of their non-pathogenicity. This disposes of BLOCH'S view that the guinea-pig has an inborn natural resistance to Microspor. Audoini, and therefore the fungus dies rapidly on the skin. The most likely explanation is that Microsp. Audoini and similar fungi fail to bring the skin into a state of sensitization, and therefore into the possibility of reaction, and thus no clincial lesion results.

These experiments of SAEVES are important from a practical point of view. They show that fungus may lie and grow on the skin without producing a clinical lesion and if that occurs in animals it might also occur in human beings who might transmit the disease without themselves suffering from it. A mother might act as a carrier and carry infection from one child to another without herself showing any visible/

visible skin lesion.

SAEVES also by intracardial injection of guinea-pigs with a spore-suspension of Achor. Quinck. and Tr. gypseum succeeded in producing more or less widely distributed haematogenous Trichophytic skin lesions which corresponded in their clinical and histological picture with those produced by skin inoculation. Similar intracardial inoculation of Achor. Schonleinii and Epidermophyton Inguinale produced no lesions. If lesions are produced by the haematogenous route allergic signs are produced. In all experiments hitherto done by others in animals allergic to Ringworn, intracardial injection produced very varying results; either rapidly healing nodules containing fungus or more or less atypical Ringworm foci.

948.
THARDSHIMANJANZ likewise studied immunity reactions in guinea-pigs with Ringworm and came to the conclusion that animals which have once had Tinea, give a positive reaction to injection of Trichophytin.

950.
TOMASCZEWSKI working with Achor. Quinck. on guinea-pigs, rabbits, cats, dogs and hens, found that guinea-pigs developed lesions with scutula which rapidly fell off with intense local inflammatory signs. One such attack left a lasting immunity behind.

Whereas/

Whereas with rabbits, cats, dogs and hens more frequently he got a more or less long-standing Favus with much less inflammatory reaction. Therefore he concludes that the duration of the lesion depends on the intensity of the reaction.

LOMBARDO'S [895.] experiments on animals with many kinds of Ringworm fungi on the whole confirm the results obtained by others. He obtained, after a positive inoculation, a condition of allergy which was manifested by symptoms of reaction and an atypical short lived lesion on later inoculation. He never produced a true immunity by inoculation. The allergy persisted long after the lesion had healed (even after 18 months) but gradually tended to diminish. It was found not to be strongly specific to the fungus which first produced it. It is not transmissible from mother to young and showed itself most distinctly in grown animals after puberty and Castration did not modify it. No allergy could be produced either by injection of living or dead fungus under the skin or by intramuscular or intravenous injection of toxines or culture filtrates.

SABOURAUD inoculated guinea-pigs with different Ringworm fungi and found that it was impossible to use the same animal twice, as the first attack/

attack had sensitised the animal. From his researches he came to the conclusion that the greater the inflammatory reaction produced by a given Trichophyton in man, the greater the immunity it confers when inoculated in the guinea-pig and probably also in man.

Analagous experiments to those with Ringworm fungus were done by RIBBERT,[927] who worked with Aspergillus. He showed that rabbits which had been previously injected intravenously with Aspergillus Spores showed a milder reaction, when the Aspergillus Spores were injected into the anterior chamber of the eye, than occurred in rabbits not previously injected. The reaction in the eye appeared sooner than in the animals not previously injected and was manifested by the lesser number of leucocytes in the inflammatory reaction.

MARTENSTEIN[901, 902.] demonstrated that the skin epithelial cells as well as the blood serum of a guinea-pig infected with Achor. Quinck. contains certain specific "bodies", which if brought into contact with the living spores of Achor. Quinck. in vitro produce a toxic substance. This toxic substance if injected intradermally into a normal animal produced a local inflammatory infiltration at the seat of/

of inoculation. This toxic substance was found to be thermolabile whilst the specific bodies are thermostable. A later investigation by the same author showed that, in a guinea-pig infected with Achor. Quinck. for the first time, the specific bodies appear at the injected area after 6 days; in the blood serum after 7 days and in the unaffected epidermis after 8-9 days. If the injection area is excised in toto (within 1-4 days) the specific bodies appear first in the unaffected epidermis after 8 days and then later in the blood serum. The duration of the reaction produced in a guinea-pig which has been injected intradermally with the toxic substance corresponds to the length of time which the animal has been infected with Achor. Quinck. The oftener the toxic substance is injected, the shorter the duration of the reaction. In animals, which have gone through an infection with Achor. Quinck. the reaction is very slight. By repeated intradermal injection of this toxic substance, it is possible to produce an ever increasing immunity in a normal guinea-pig and repeated subcutaneous injection of the toxic substance leads to a reaction in the subcutaneous tissues which runs a chronic course.

This work of MARTENSTEIN'S therefore seems to show that Achor. Quinck. produces a specific antibody/

antibody first at the seat of injection, and this antibody is carried by the blood serum to the cells of the rest of the skin. Whenever fungus elements are introduced and come into contact with the specific antibody, a toxic substance is produced which leads to an inflammatory reaction. This would account for the local and focal Trichophytin reactions, for the cutaneous Trichophytin reaction and for the Trichophytides.

I have given the foregoing rather detailed account of inoculation experiments with Ringworm and Favus, because I feel that except to those who have worked at the subject, they are very little known. From a survey of them all, it may be safely concluded that in animals at least and probably also in man, infection with Ringworm always leads to a more or less marked sensitisation. Whether this is associated with a real immunity is more difficult to determine, but all the evidence goes to show that given a deep-seated Ringworm lesion, it leads to an immunity. The lesion often produced on reinoculation is not a true reinfection. It is to be looked upon as a hypersensitive reaction in an immune animal, and when PRYTEK and others speak of a relative immunity because they obtained a modified lesion on reinoculation, the whole question of/

of the relation of sensitisation to immunity is raised. This question will be discussed later under the cutaneous tests which occur not only on a sensitised skin, but in an immunised one as well.

LOCAL /

## LOCAL IMMUNITY of the SKIN to RINGWORM.

As already mentioned all the workers who inoculated animals with Ringworm found that after an animal had passed through an attack of the disease, its skin on reinoculation either showed a complete immunity or reacted in a different manner from the first occasion. This was found in all cases not to be a local immunity or altered reaction, but a general one affecting the whole skin.

I have only been able to find three references to local immunity in Ringworm. The one was a discussion on this subject in 1910 by BLASCHKO[840.], who brought forward the theory that Ringworm spreads in circles and heals in the centre because a local immunity occurs in the infected centre. He quotes a case of extensive Tinea on the chest and back which spread always outwards and never recurred on the previously infected areas. He suggests that there may be a local immunity produced in the skin cells where the parasite has been. Against this theory is the fact that one may get cases (~~see cast no.~~ ) where there are numerous concentric rings, the fungus still being active in the central rings whilst it still spreads at the peripheral ones. It is not often that one sees two/

two Ringworm lesions so close together that they run into one another but I have no recollection of ever having seen two completely ringed lesions over-lapping one another. The more usual result is for the patches to fuse and form one larger one with a circinate outline.

CITRON[866], doing experiments on mice with mouse Favus which heals with scar formation, found that if one injects into this scar after complete healing, a not too large amount of Favus emulsion, the infection either does not take place or is very slight. He thinks this is probably not a local immunity but is due to anatomical changes in the scarred skin.

KUSONOKI[889] quotes MENSCHEN as having found after Trichophytosis that there remains a local immunity, but he does not give the source of his information. JADASSOHN[885] suggested that in superficial Tineas which had healed in the centre, the central area should react more strongly to Trichophytin than normal skin, if the central one heals as a result of sensitisation there, but he found this not to be the case. As recurrence often occurs in such central healed areas, he thinks that the healing in the centre is due to the nutritive material being used up in the central area rather than to any local immunity. If recurrences do occur in a central healed area they do not cause any specially/

specially intense inflammatory reaction such as one would expect if that area were hypersensitive. The fact that the disease may recur in a previously affected area is against any local immunity being present.

ACTIVE/

## ACTIVE IMMUNITY in RINGWORM and FAVUS.

Several observers have attempted to produce an active immunity in animals. BLOCH and MASSINI[849] injected animals with the juice of the fungus and culture filtrates previous to infection, but found it did not prevent infection taking place.

CITRON[866] also found that in guinea-pigs, injection with dead cultures or filtrates before inoculation or simultaneous injection at the same time as inoculation, had as a rule no effect on the development of the lesion, but in one case the lesion seemed to heal more quickly than usual. He also did a series of experiments on white mice with mouse Favus (Achor. Quinck.) Human Favus and Microsporon. He found that previous injection of dead culture emulsions caused a certain increase of resistance in susceptible animals when inoculated later with emulsions of living cultures. These above experiments were done by intraperitoneal injection of both dead and living cultures. He also did another series of experiments to see whether immunity could be produced by subcutaneous injections, and obtained similar results.

Therefore he concludes that an active immunisation is to a certain degree possible in Ringworm and Favus as in Tuberculosis.

KUSONOKI/

KUSONOKI[889], in spite of different modifications of technique never succeeded in producing active immunisation with Trichophytin or dead fungus extracts but in a few cases a mild or abortive form of the disease was to be seen in immunized animals.

PECORI[909] also failed to produce an active immunity by injection of Trichophytin.

But BLOCH succeeded in partially immunizing guinea-pigs by repeated prolonged rubbing of the skin with fungus killed by heat. He therefore concludes that immunity in guinea-pigs to Trichophytosis can be produced through the skin and it was found to be immaterial whether living or dead fungus is used.

SUTTER[946] similarly found that prolonged rubbing of sterilised fungus into the skin of normal guinea-pigs leads to a partial immunity, but the same result can be obtained by repeated intradermal injection of a concentrated Trichophytin. The result produced is the same as in an animal which has become partially immune after a slight ringworm infection.

PASSIVE/

## PASSIVE IMMUNITY TO RINGWORM AND FAVUS.

As in active immunity several observers have done work in an attempt to produce passive immunity. BLOCH and MASSINI[849.] were unsuccessful in producing passive immunity with serum and skin extracts of immune animals.

CITRON[866.] tried to get a serum against fungus infections. He began with intraperitoneal injections into rabbits of dead culture emulsions, and then later gave intraperitoneal injections of living cultures, and from time to time towards the end of the immunising process intravenous injections of culture filtrates. The animals stood intraperitoneal injections well, but some died after the intravenous injections. Some of the animals were treated thus for eight months. The serum in numerous experiments on mice showed neither a protective nor a healing effect.

CHANGES/

## CHANGES in the BLOOD in RINGWORM and FAVUS.

MIESCHER[904.] in 1915 found that in the deep forms of Ringworm, as was to be expected, there is a more or less marked leucocytosis. The leucocytosis is a polymorphonuclear leucocytosis with an absolute diminution of lymphocytes. The superifical forms of Ringworm show no such change in the blood picture. Injection of Trichophytin either intradermically or subcutaneously in Ringworm cases also produced the characteristic polymorphonuclear leucocytosis. This occurred markedly in deep seated Ringworm cases and with Trichophytin made from a fungus which produces a deep lesion. In superifical Tineas it is less constant, but if present, is the same as in deep cases. Persons who had not had Ringworm previously, may react to Trichophytin injection with a leucocytosis, but in this case it is always due to an increase of lymphocytes. BLOCH had previously shown that if Trichophytin be injected subcutaneously into a patient with Ringworm, general symptoms of illness, swelling of glands, local and focal reaction occur and also a leucocytosis in the blood.

The blood changes described by MIESCHER and BLOCH[847.] in Ringworm and after Trichophytin injections were confirmed and extended by SUTTER[946.] (Weitere Beitrage). He found that in healthy individuals during the/

the incubation stage an injection of Trichophytin produces a slight lymphocytosis. In ringworm cases and immune persons it produces a polymorphonuclear leucocytosis which gradually diminishes on repeated injections. In cases of Ringworm when there is an already existing polymorphonuclear leucocytosis, each intradermal injection of Trichophytin caused a further increase of polymorphonuclear leucocytes in the blood.

945.
In 1916 STRICKLER examined the blood in 60 cases of Tinea capitis and 4 of Favus. He found that in Tinea cap. there is an increase of the small lymphocytes in the blood. The average differential count showed 37·4% of lymphocytes. This lymphocytosis was present in 80% of the cases. In the 4 cases of Favus a small increase of lymphocytes was also found. STRICKLER considers that this lymphocytosis is sufficiently constant to be of value in the differential diagnosis of Tinea-capitis.

SERUM/

## SERUM CHANGES in RINGWORM AND FAVUS.

As the deep seated Ringworms produce an immunity, one would expect that it would be possible to demonstrate the presence of antibodies in the blood serum of such cases. The fact that in animal experiments, the injection of Trichophytin causes local, focal and general reactions also points in the same direction.

CITRON[866.] examined the serum of animals for the presence of agglutinins and precipitins. He found it impossible to do agglutination tests because the fungus was in masses and could not be separated easily. But he infers that agglutinins are present because when the fungus is injected intraperitoneally, as a rule it is found massed together in clumps and not floating loose in the peritoneal fluid. He found the presence of precipitin in the serum. The reaction did not occur if the serum was very diluted but normal serum caused no precipitation. It was also found that the reaction was not specific. The serum of an immunised animal gave a positive precipitation test with all ringworm and favus fungi but the one, with which the animal was immunised showed itself more sensitive than/

than the others. This fact also supports the conclusion already come to as a result of inoculation of animals that the different varieties of Ringworm and Favus fungi are very closely related biologically.

SUTTER[946.] found that in isolated cases of deep seated human Tinea at the height of the disease the serum contains complement fixing substances and precipitins. In his investigations he used Trichophytin as Antigen. In the majority of cases in man, however, and in all cases in animals the results were negative.

He also exposed Trichophytin to the blood serum of Ringworm patients and healthy individuals for some hours. This Trichophytin was used for intradermal skin tests in Ringworm and normal individuals and the results found to be the same as those produced by ordinary Trichophytin. Therefore he concludes that the presence of antibodies in the serum of Ringworm cases has not been demonstrated. He further tried to see if he could get any better results in "vivo". He froze an area of skin with $CO_2$ snow in normal and ringworm cases. The serum was then drawn off from the blisters produced by the freezing and Trichophytin was injected into the blister and again withdrawn some hours later. This was used to do skin tests, but the results/

results were exactly the same as when ordinary Trichophytin was used. Similarly negative results were obtained by using the fluid obtained by puncture of lymphatic glands of healthy and ringworm cases, mixing this with Trichophytin, and doing skin tests with it. The results were all negative.

He also did experiments, similar to those done by DALE and others, on the intestine of animals. A guinea-pig immune to Ringworm was killed and the intestine suspended in RINGER'S solution. Even although 3 cc. of Trichophytin were added to the RINGER'S solution, no contraction of the bowel occurred. SUTTER therefore failed to find in the blood or serum of Ringworm cases or in Ringworm hypersensitive animals or man (apart from a fairly strong complement fixation in the serum of a few highly allergic ringworm cases) the presence of specific antibodies. He therefore concludes that Ringworm hypersensitiveness is not a true anaphylaxis and quotes in support of this the fact that immunity or allergy to Ringworm have not been passively transmitted; nor can active immunity be produced by Trichophytin injections; Whereas BLOCH only succeeded in producing a partial immunity by repeated prolonged rubbing of dead or living fungus into the skin. It would seem therefore that the hypersensitive or immune condition produced in Ringworm is due not to a serum reaction, but to some/

some local change in the skin cell itself. This will be referred to again later when BLOCH'S transplantation experiment is discussed.

PECORI[909.] like SUTTER obtained weak but definitely positive complement fixation and precipitation reactions in some cases of human Tinea using Trichophytin as antigen.

CAROL[860.] tested the serum of eighteen cases of Ringworm and found that in marked cases of deep seated Ringworm it was possible to get a positive complement-fixation reaction with a Trichophytin antigen. In superficial forms of Ringworm, which had existed for some time, a partial fixation may occur. In Favus capitis and corporis the reaction was always negative. The serum should, if possible, be examined within 24 hours after withdrawal and should be used undiluted or half diluted. Serum from normal individuals and individuals suffering from other diseases always gave negative results.

Using a mass of emulsified fungus KUSONOKI[889.] found that complement-fixation and precipitation tests with sera of men and animals with Ringworm gave only uncertain results.

SAEVES[932.] tried to prove the presence of ferments from the Ringworm fungus in the serum of men allergic to Ringworm. He used the Abderhalden test but/

but failed to find any evidence of the presence of defensive ferments. COSTA and FAYET[867] did agglutination and complement-fixation tests with the serum of horses which had suffered from Ringworm, but the results were all negative. This was to be expected as the disease in these cases was a superficial one and was shown, by successful reinoculation not to have produced any immunity.

KOLMER and STRICKLER[888] examined the sera of 27 cases of Tinea capitis due to Microsporon Audoini, 3 of Favus capitis due to Achorion Schönleinii and one of Pityriasis versicolor. He found that with a polyvalent antigen of Microsporon Audoini, complement - fixation was found to occur in 78% of patients suffering from Tinea capitis. This is rather surprising in view of the fact that small spored Tinea capitis is a superficial invasion of the hair follicle only. KOLMER and STRICKLER think that it is conceivable that the fungus produces soluble products which are capable of absorption and of stimulating the local and general body cells to produce antibodies.

The sera of 2 cases of Favus out of 3, gave positive complement-fixation reactions using achorion schönleinii as antigen. This is not to be wondered at as Favus is a much deeper infection than small-spored Tinea capitis, the fungus actually growing in the skin itself.

The/

The degree of reaction to both ringworm and favus was found to depend on the severity and duration of the infection. The ringworm and favus antibodies (amboceptors) fixed complement best with their respective antibodies but with relatively large doses of serum this specificity was not observed. Here again a biological relationship between the Ringworms, even small spored, and Favus, was demonstrated.

A culture from the scales of the case of Pityriasis Versicolor which K. & S. regarded as a doubtful culture of microsporon furfur, reacted weakly or irregularly with the sera of ringworm and favus patients and negatively with the serum of a case of Pityriasis Versicolor.

In all these tests the authors used the sera of syphilitics, and that of persons suffering from scabies, impetigo contagiosa, eczema, acne vulgaris and other diseases as controls, but in no case did the sera give any complement-fixations with the antigens of the fungi.

Like CITRON and others, VERROTTI[956.] found a want of specificity in the complement fixation test. He obtained a culture of Microsporon Lanosum from a case of Ringworm of the scalp. A dog was infected with/

with this fungus. The dog's serum gave a positive reaction with several fungus antigens, and curiously enough a more marked reaction with Trichophyton Gypseum, Tr. Rosaceum and Tr. Accuminatum as Antigen than with Microsporon Lanosum. Complement-fixation tests were also done by BLUMENTHAL and HAUPT.[850] They examined the sera of patients with deep-seated Ringworm and in the majority of cases found the presence of complement fixing antibodies. They used the ordinary technique the same as in the Wassermann test, but with fungus antigens which they prepared themselves. In superficial Tineas antibodies were found only exceptionally. Usually the quantity of antibody was proportional to the severity of the disease. An interesting point was that allergy reactions and antibody formation did not always run parallel. Cases previously treated with Trichophytin all showed complement fixation. It was also found that the complement fixation reaction was just as little specific as the allergy reactions. It occurred also in sycosis and in gland tuberculosis. From their results BLUMENTHAL and HAUPT conclude that one cannot speak of the immunity which occurs in deep seated Ringworm as a cell immunity. Humoral immunity changes play a part in the defensive mechanism.

SCHREUS and GOEHL obtained similar positive complement/

complement fixation reactions in deep and superficial Ringworm cases. "Trichon" (Hochst) was used as antigen, but no details are given and only a few cases were tested. That the serum change was not due to any reaction or absorption from the X-rays used in the treatment was shown by the fact that a positive reaction was usually obtained before the cases were X-rayed as well as afterwards.

NATHAN[906.] also came to the same conclusion. He obtained non specific complement fixation reactions in 3 deep Ringworm cases using the different preparations of Trichophytin, and in 5 cases (superficial ringworm, gonorrhoea and syphilis at various stages) the reaction was negative. These negative results on the controls however were only obtained when a special Trichophytin prepared by HOCHST was employed as antigen. Precipitation tests were also made, using the special preparation of HOCHST Trichophytin, and in 12 sera from Trichophytosis profunda, 7 were positive, 2 doubtful and 3 negative. Two sera from superficial Ringworm were negative. Here also the precipitation tests were non specific as the sera of 4 syphilis patients gave a positive reaction. Different samples of Trichophytin gave different results.

Therefore NATHAN'S results together with those of BLOCH, PECORI, SUTTER, CAROL and BLUMENTHAL and HAUPT show that at least in deep seated Tineas in men/

men the immunity processes are not dependent exclusively on the formation of a skin allergy and immunity. but that antibody formation in the blood serum plays a part.

The general symptoms such as fever, swelling of glands and spleen and the leucocytosis in the blood in deep Tinea cases also point to the probability of fungus elements circulating in the blood and coming into contact with antibodies in the blood, thus leading to the production of toxic substance which cause the general symptoms. KUSONOKI, SAEVES, and SUTTER all noticed general symptoms in guinea-pigs which had been repeatedly inoculated with Tinea. They went out of condition and often died. SUTTER too noticed that some of his animals died a day or two after reinoculation with Ringworm and on post mortem no gross pathological lesions were to be found. SUTTER thinks these were probably chronic anaphylactic deaths.

He also quotes the fact that Trichophytides occur as a point in favour of the presence of antibodies in the blood just as the rashes in the specific fevers are probably due to the same cause and thinks that the circulation carries the antibodies and gives them up to the skin tissues and saturates them so that if fungus elements again circulate, a reaction takes place between this circulating fungus and the allergic skin with the production of the Trichophytide.

The/

The fact too that man and animals after an attack of deep seated Ringworm show an allergy of the whole skin means that the substances necessary to produce this allergy must have been carried there by the circulation. This subject will be referred to again later under Trichophytides.

CUTANEOUS/

## CUTANEOUS REACTIONS in RINGWORM and FAVUS.

Although NEISSER and PLATO [407] in working with Trichophytin in human beings in 1902 had shown that in addition to a general reaction a local one was often produced in Ringworm cases at the seat of inoculation, it was not till some years later that investigations were carried out by several observers as to the nature of these local reactions.

BLOCH, and BLOCH with MASSINI, as already mentioned, obtained on reinoculation in animals and men who had suffered from deep seated tinea, a modified lesion which ran a rapid course and which they rightly attributed to the fact that the skin was allergic to the fungus. They also showed that in man every deep Tinea leads to a heightened sensitiveness which was shown by a positive cutaneous reaction to filtrates of Ringworm cultures. The reaction is exactly analogous to the Pirquet reaction with old Tuberculin in Tuberculosis. BLOCH found that it appeared in 7-8 days after first inoculation with the disease and remained long after the disease is healed (up to 3 years) It occurs both after injection of living fungi and after inoculation with culture filtrates. AMBERG [831] in 1910 did a number of cutaneous tests with Trichophytin, and pointed out the far-reaching analogy between the cutaneous/

cutaneous Trichophytin reaction and the Tuberculin Pirquet reaction. Both may persist for a long time after the active disease has ceased to exist, indicating that the infection has left the body in a state of altered reactivity or allergy. He found that a person who had had a deep Tinea 29 years previously still gave a positive cutaneous reaction with Trichophytin. He thinks that the skin test may be of value in diagnosis, but in view of the fact of its long persistence after the disease is healed, as with the Tuberculin Pirquet reaction, a negative reaction may be of greater value than a positive one, thus enabling one to exclude ringworm. He suggests its value to distinguish the circinate syphilides of the face from Ringworm.

AMBERG also in one case tested with Trichophytin obtained, as is sometimes seen in Tuberculin Pirquet tests, a delayed reaction on the 8th day. This he considers as analogous to the so-called accelerated reaction in cases of revaccination against smallpox. The explanation is that the organism has an insufficient amount of antibody at its disposal with which to react immediately. The injection of the Trichophytin leads to a renewed formation of antibody which later reacts with the Trichophytin still left at the seat of injection. BLOCH obtained regularly positive skin reactions/

reactions to Trichophytin in cases of Kerion and Tinea Barbae. The degree of reaction was proportionate to the intensity of the infection. The deeper and more inflamed it was, the greater the reaction. Very superficial Tineas gave a slight or no reaction. There was no reaction in cases where only the nails or hair were affected. That is what one would expect because in the latter cases the fungus is growing more as a saprophyte on the surface than as a parasite in the tissues.

HANAWA[380] did intracutaneous tests in animals immune from previous inoculation with Ringworm and found that positive results were obtained. The reaction was similar to that produced by reinoculation with living fungus viz. a marked partly necrobiotic inflammation which occurs as a nodule in the centre with a surrounding inflammation. KUSONOKI[389] did both cutaneous and intracutaneous tests with Trichophytin and found the intracutaneous method is more certain than the cutaneous. He obtained positive results by the intracutaneous method both in deep-seated and superficial cases. After intracutaneous injection in deep Trichophytosis the temperature usually rose to 39·8 C. but not in superficial Ringworm. Trichophytin produced a stronger reaction, the more virulent the kind of fungus used to make it. The older the broth culture

of/

of ringworm, the more potent is the Trichophytin produced. Ringworm cases usually gave a positive reaction with "Favin", but the reaction was weaker in Ringworm than in Favus, and Favus cases seldom reacted positively to Trichophytin. By this method it was found that mouse Favus (Achorion Quinck.) stands nearer to the Ringworm fungi than Human Favus (Achor. Schönleinii). Repeated intracutaneous injection leads to a gradual weakening of the reaction.

The reaction was found to be always negative in other diseases and in normal persons. In immune animals it is irregular and in normal animals sometimes positive. In cachectic and young animals it is always absent.

SUTTER[946.] also did cutaneous and intracutaneous tests with Trichophytin made from Achor. Quinck. For the intracutaneous test he injected 0·1 cc. Maltose broth was used as a control. He did the control, cutaneous and intracutaneous tests side by side and obtained rather astonishing results in 150 healthy persons. 123 were positive and 27 negative by the intracutaneous test. In 5 cases only was the cutaneous test weakly positive and that in the cases which gave very strong positive intracutaneous tests. Other observers have obtained positive skin reactions in normal persons. AMBERG[831.] reports four cases and

KUSONOKI/

KUSONOKI one. In these cases no previous history of Ringworm was to be obtained.

SUTTER thinks that the intradermal reaction to 0·1 cc. Trichophytin can produce a certain degree of reaction which can only be quantitatively distinguished from a specific Trichophytin reaction. The question is whether all those apparently normal individuals had had an attack of some mycotic disease previously. AMBERG'S case giving a positive reaction 29 years after a deep Tinea shows that the reaction may persist for a long time but it is not at all probable that all these persons could have had some form of Tinea in childhood without knowing it. Another and more likely explanation is that the reaction is not a specific Trichophytin reaction but a general Antigen one. As SUTTER points out Trichophytin is not a pure substance, and the reaction might be due to trace of the peptone and maltose in which the fungus was grown. It might be analogous to the Agar reactions to be referred to later on. That it is a quantitative rather than a qualitative reaction is shown by the fact that dilution to 1 in 1000 gave far more marked reactions in Ringworm cases than in healthy individuals.

These results would also tend to prove that the intracutaneous method is not suitable as a diagnostic test and that the cutaneous is to be preferred as/

as it is more specific.

SUTTER also tested the degree of reaction at different age periods in healthy individuals. 140 cases were tested and it was found that the younger the individual the fewer positive reactions obtained. Infants hardly ever reacted at all. The majority of positive reactions were obtained between the ages of 15-65 years. SUTTER[946.] thinks that the probable explanation is that given by MORE and FEER, who have shown that in the first years of life the faculty of reacting is almost absent from the skin. That is in accordance with what one would expect. The infant has not yet suffered from any infection and its protective mechanism has not been stimulated, whereas in adults, who have passed through various infections, their tissues have become sensitised to various chemical substances, bacterial and otherwise. As the intradermal Trichophytin reaction has been shown to be a relatively non-specific one, one would expect a high percentage of positive results in adults who were already sensitised from attacks of various acute or chronic diseases.

This effect of acute and chronic diseases on the Trichophytin reaction was specially studied by SUTTER. He tested 13 cases of pneumonia, 4 of scarlet fever, 2 of measles and 2 of typhoid fever, none of whom

whom had previously had Tinea, and found that the intradermal Trichophytin reaction was negative in all during the fever, but later on all gave positive reactions. He also quotes PECORI who tested with Trichophytin injections 6 cases of Ringworm, who had measles. They were all negative at the height of the disease and while the rash was out but later on were positive. This corresponds with what has been known for some time regarding the Tuberculin Pirquet test in measles and other fevers. PIRQUET, HAMBURGER and ROLLYS found that the Tuberculin Erquet, if present before, disappeared during the attack of these fevers and returned again later on recovery. HAMBURGER likewise found that there was a marked diminution of the reaction to vaccinia during measles. Pirquet attributes the temporary loss of the reaction during fevers to the temporary absorption of the antibodies to Tuberculosis. SUTTER also did a number of Trichophytin tests in chronic diseases and found that in arthritis, chronic nephritis, tuberculosis, diabetes, arteriosclerosis, Carcinoma, endocarditis, pernicious anaemia, gastritis, Tabes Dorsalis, and Gonorrhoea, the reaction is practically the same as in healthy individuals except that in cachectic patients it is absent. In three cases of hemiplegia the reaction was much weaker on /

on the paralysed than on the other side. These results also are what one would expect as in all these infections and toxaemias the tissues are already sensitised and as the reaction persists during a chronic infection and long after its disappearance, practically everyone on reaching adult age will react. The absence of the reaction in cachectic cases also corresponds to the well known fact that the Tuberculin skin test disappears in the late cachectic stages of Tuberculosis.

735.
SCHOLTZ like SUTTER did numerous intradermal tests with Trichophytin (HOCHST). He used it on dilutions of 1 in 50 and 1 in 100. Positive reactions occurred within 24 hours producing a slightly raised flat papule with a halo of erythema about the size of a sixpence. Smaller areas of erythema even although slightly papular were cohsidered negative. He found that non-specific reactions occurred with these dilutions but not sufficiently frequently to interfere with the value of the test. Cases of Lupus Vulgaris reacted almost without exception positively but patients with Tuberculosis of the lung did not react positively. The reaction in Lupus was so constant that SCHOLTZ considers it useful in distinguishing between Lupus and tertiary syphilis, which does not give the reaction.

FUHS/

874.
FUHS, using a Trichophytin produced by previously digesting a culture of Trichophyton, found that 4 cases of superficial and 8 of deep Ringworm were all negative to the cutaneous Erquet Test. But by the intracutaneous method in superficial forms of Ringworm the results were negative and in deep cases a positive reaction was obtained beginning in 6-12 hours, reaching its height in 24-48 hours and slowly fading leaving pigmentation.

910.
PEDERSON did a number of experiments to see if the cutaneous Trichophytin reaction was more marked on areas where Trichophytides (see later) had been present. He assumed that the skin in such areas should be more sensitive to Trichophytin than in other areas. Nine cases of Kerion without secondary Trichophytides were tested by Erquets method on the abdomen, upper arm and leg in each case. All were positive on the abdomen some of them markedly so; seven were positive on the arm and four on the leg. PEDERSON therefore concludes that Trichophytin tests should always be done on the abdomen near the umbilicus. Now that is the region where Trichophytides are most constantly found. He also tested similarly six cases of Kerion with Secondary Trichophytides. All were positive on the abdomen and upper arm i.e. where the trichophytides were present and only two were positive on the leg, where there were no trichophytides.

In/

In order to see whether the skin round a lesion was more sensitive than elsewhere, four cases of Kerion were Pirqueted near to and at a distance from the lesion. He found that the reaction was always stronger on or around areas near the lesion where secondary superficial Tinea lesions had been or were. SUTTER repeated these experiments and obtained the same heightened reaction around the ringworm lesions. He also inoculated cases with living fungus both in the neighbourhood of the existing lesion and at a distance, and found that he obtained an early reaction with a papular eruption, with a rapid disappearance of fungus from the area and later the lesion became spinulous, but no actual Trichophytosis developed. In areas at a distance a typical early reaction was absent and a short-lived Trichophytosis developed showing that the skin in these areas was not so sensitised as it was near the lesions.

A great many intradermal Trichophytin tests were also performed recently by Arnold,[833.] both in healthy children and children with Ringworm. In 130 healthy children with no previous history of Ringworm, 14 gave positive reactions to a polyvalent Trichophytin (HOCHST) diluted 1 in 10. Forty one cases of Ringworm were also tested. With Trichophytin (1 in 100) no healthy children and 58% of children with superficial Tinea/

Tinea reacted. The age of the child (up to 14 years) had no influence on the specific reaction. ARNOLD found when the reaction did occur, no difference in intensity or duration between the non-specific reaction in healthy children and the specific reaction in Ringworm cases. He agrees with SUTTER that the difference between specific and non-specific reactions is a quantitative one only and if the results are to be of any value the Trichophytin must be diluted to between 1 in 50 and 1 in 100. He could find no special difference between the reactions in deep and superficial Tineas. Many superficial forms (Tinea cap.) gave more marked reactions than the deep.

He also found that feverish diseases such as Measles and Varicella cause an absence of the specific reaction. The non-specific reaction with high concentrations of Trichophytin was diminished and with lower concentrations disappeared in measles, scarlet fever, diphtheria and typhoid fever. The reaction to injection of carbolic acid, distilled water and hypertonic salt solution injections, analogously to the fungus reactions were also found to be diminished in fevers; so also the reaction due to trauma from injection of 0·2 cc. of fluid into the skin. Cachexia either diminishes or prevents the reactions to Trichophytin, carbolic acid or trauma. Daily intracutaneous Trichophytin reactions in Ringworm cases caused a diminution in the degree of reaction./

reaction. In small spored ringworm of the scalp there was at first an increase in the reaction. This ARNOLD attributes to the fact that all cases were epilated by X-rays. This increased reaction is later followed by a diminished one. ARNOLD concludes that Trichophytin is less specific than Tuberculin. It shows a greater toxicity and a greater dependence on the condition of the skin. But he thinks it is more specific than the non-specific bacterial toxines such as typhoid and diphtheria toxines etc.

CUTIREACTIONS/

## CUTIREACTIONS IN FAVUS.

In Favus Capitis BLOCH[846] found the cutireaction to Trichophytin (from Achor. Quinck.) almost always negative. The Achorion Schonleinii has no great power of allergising and therefore Human favus is a chronic disease and does not tend to heal spontaneously.

KUSONOKI[889] also found that Favus cases seldom react positively to Trichophytin, but Favus cases always and Ringworm cases sometimes react positively to Favin made from Achorion Schönleinii. These results again point to Achor. Quinck. (Mouse Favus) which has been so much used to produce Trichophytin, being much more nearly related to the Ringworm than the Favus fungi.

Recently STEIN[943] did intradermal tests with a mixed polyvalent Trichophytin (containing 6 kinds of Trichophytons and 3 Achorions) diluted 1 in 10. Fifty one cases of Favus Capitis all due to Achor, Schönleinii were all negative even although the Trichophytin contained one ninth part of Achor. Schönleinii. Similarly 17 cases of Favus Corporis (12 with scutula) all due to Achorion Schönleinii all showed negative cutireactions, but two cases of Favus Corporis due to Achor./

Achor. Violaceum both reacted positively. One case of Favus Corporis due to Achor. Quinck. and another due to Achor. gypseum, both reacted positively.

Therefore out of 67 cases of Favus, only 4 reacted positively and these 4 were all due to animal Achorions. STEIN thinks that one must make a distinction between the Achorion Schönleinii of human Favus and other Achorions. He suggests that the Achorion Schönleinii has in the course of centuries become accustomed to the human skin always being transmitted from man to man; whereas the other Achorions are normally animal parasites and if they infect man set up an immunising process which causes a skin allergy and a tendency to spontaneous cure such as never occurs in human Favus.

AUTHOR'S/

## AUTHOR'S EXPERIMENTS with CUTIREACTIONS to FUNGUS EXTRACTS.

In 1909 I undertook some experiments to see whether a skin test could not be obtained for diagnostic purposes in cases of Tinea and Favus capitis. As the results were disappointing they were not published at the time. It is however thought advisable that they should be recorded. Extracts of the fungus were made in the following manner.

(1) EXTRACTS from a Small Spore Fungus = "MICROSPORIN". (See Plate 17.)

A pure culture of Microsporon Audoini, from a case of Tinea capitis was used. With this culture, an Erlenmeyer's flask containing liquid 4% maltose peptone medium was inoculated. It was kept at room temperature. In 3-4 weeks time the surface of the medium was covered with a pellicle of fungus which gradually increased in density and thickness. Growth was allowed to go on for 9 months, when the mass of fungus was removed and dried in the oven in a sterile Petri's dish. It weighed 1·135 grm. In the dry state it was pounded in a mortar as finely as possible and 15 cc. sterile saline added and the masses of fungus again crushed in a mortar. The fluid mass was filtered through sterile filter paper and the slightly turbid filtrate containing any soluble toxins labelled Microsporin/

Microsporin B. The residue containing the undissolved mass was mixed with other 15 cc. sterile saline and labelled Microsporin C. Microsporin B and C were both sterilised by heating at 65°C. for one hour. Twenty drops of 1 in 20 carbolic were then added. Cultures were made from both preparations on SABOURAUD'S proof medium and found to be sterile.

By the above means 2 Microsporins were obtained.

Microsporin B. containing any soluble toxine

Microsporin C. containing the dead crushed mycelium and spores.

(2) EXTRACTS from large spore fungus = TRICHOPHYTIN.

As in the case of the small spore fungus, cultures were made on liquid maltose peptone medium and allowed to grow at room temperature for 4 months. Two varieties of large spore fungus were used - a Trichophyton Acuminatum from a patient named Richardson (Plate 18) and a Tr. Crateriforme flavum from a patient named King (Plate 18.) Both were treated similarly. The felted mass of fungus was taken from the surface of the medium and the subjacent fluid filtered through sterile filter paper. The filtrate, which contained any soluble toxine which had been dissolved out into it during the process of growth of the fungus was/

was labelled Trichophytin A.

The mass of fungus was then washed in sterile saline and then pounded up in a mortar with 20 cc. sterile saline and filtered through sterile filter paper. The filtrate which contained any soluble toxine obtained by crushing the fungus was labelled Trichophytin B. The residue consisting of the crushed masses of fungus was again, more thoroughly than before, pounded in a mortar, mixed with 15 cc. sterile saline and labelled Trichophytin C. All three preparations of Trichophytin were sterilised for 1 hour at 65°C. and to each 20 drops of 1 in 20 carbolic acid added, and cultures made to test their sterility.

Thus six Trichophytin Extracts were obtained, viz:-

Trichophytin A. (Richardson).
Trichophytin B. ( " ).
Trichophytin C. ( " ).
Trichophytin A. ( King ).
Trichophytin B. ( " ).
Trichophytin C. ( " ).

(3) EXTRACTS from FAVUS fungus = FAVIN.

A typical culture of Achorion Schönleinii (Plate 19.) was inoculated on liquid maltose peptone medium /

medium and allowed to grow for 4 months. The same procedure as in the preparation of the Trichophytin Extracts was followed and Favin A Favin B. and Favin C. obtained.

Favin A. contained the soluble toxin in the liquid medium.

Favin B. contained the soluble toxin in the liquid after crushing the fungus.

Favin C. consisted of the crushed mass of fungus.

With the above 2 preparations of Microsporin, 6 of Trichophytin and 3 of Favin, cutaneous tests were done as in Pirquet's Tuberculin test. The tests were all done on the left upper arm. Three small scratches were made with a needle and across these 3 similar scratches and a drop of the fungus extract rubbed gently in with a glass rod. Controls were done in every case using liquid peptone maltose medium with the addition of 5% carbolic acid. The arms were examined at intervals of twenty four hours for 4 days.

The following tables give the results.

| SEX | AGE in YEARS | DISEASE | DATE | EXTRACT USED | | RESULT in DAYS. 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|---|---|
| M. | 7 | Tinea cap. small spore | July 22 1909 | Microsporin B.&C. | Control<br>M.B.<br>M.C. | −<br>−<br>− | −<br>+<br>+ | −<br>+<br>+ | −<br>−<br>+ |
| M. | 11 | Tinea cap. small spore | July 22 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| F. | 8 | Tinea cap. small spore | July 23 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | −<br>±<br>± | −<br>±<br>± | −<br>±<br>± | −<br>−<br>− |
| M. | 9 | Tinea cap. small spore | July 24 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | −<br>±<br>± | −<br>±<br>± | −<br>−<br>− | −<br>−<br>− |
| M. | 11 | Tinea cap. small spore | July 24 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− | −<br>−<br>− |
| M. | 7 | Tinea cap. small spore | July 26 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | −<br>−<br>− | −<br>±<br>± | −<br>±<br>± | −<br>−<br>± |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| F. | 5 | Tinea cap. small spore | Aug. 4 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | –<br>–<br>– | –<br>+<br>± | –<br>+<br>± | –<br>+<br>± |
| F. | 3 | Tinea cap. small spore | Aug. 4 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. 1 | –<br>–<br>– | –<br>–<br>– | –<br>–<br>– | –<br>–<br>– |
| M. | 6 | Tinea cap. small spore | Aug. 10 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | –<br>–<br>– | –<br>–<br>– | –<br>–<br>– | –<br>–<br>– |

| SEX | AGE in YEARS | DISEASE | DATE | EXTRACT USED | | RESULT in DAYS 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|---|---|
| M. | 7 | Tinea cap. et.. corp.( Small spore ) | Aug. 10 1909 | Microsporin B. & C. | Control<br>M.B.<br>M.C. | –<br>–<br>± | –<br>–<br>± | –<br>–<br>– | –<br>–<br>– |
| M. | 14 | Tinea cap. ( small spore ) | Aug. 24 1909 | Microsporin | Control<br>M.B.<br>M.C. | –<br>–<br>– | –<br>±<br>– | –<br>±<br>± | –<br>±<br>± |
| F. | 9 | Tinea cap. large spore. ( Kerion ) | July 23 1909 | Trichophin (King) A.B. etc. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>–<br>±<br>± | –<br>–<br>±<br>± | –<br>–<br>±<br>± |
| M. | 11 | Tinea cap. Large spore | July 24 1909 | Trichophytin (Richardson) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– |
| M. | 11 | Tinea cap. Large spore. | July 26 1909 | Trichophytin (Richardson) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– |
| F. | 4 | Tinea cap. et. corp.( large spore ) | July 26 1909 | Trichophytin (Richardson) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| M. | 59 | Tinea Barbae (large spore) | July 23 1909 | Trichophytin (King) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>+<br>± | –<br>–<br>+<br>+ | –<br>–<br>–<br>– | –<br>–<br>–<br>– |
| M. | 39 | Tinea Barbae st. corp. (large spore - ectothrix) | July 27 1909 | Trichophytin (King) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– | –<br>–<br>–<br>– |
| M. | 12 | Tinea corp. (large spore) | July 26 1909 | Trichophytin (Richardson) A. B. & C. | Control<br>T.A.<br>T.B.<br>T.C. | –<br>–<br>–<br>– | –<br>+<br>+<br>+ | –<br>+<br>+<br>+ | –<br>+<br>+<br>+ |

| SEX | AGE in YEARS | DISEASE | DATE | EXTRACT USED | | RESULT in DAYS 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|---|---|
| M. | 7 | Favus cap. | July 22 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | − | − | − |
| | | | | | F.B. | − | − | − | − |
| | | | | | F.C. | − | − | − | − |
| F. | 9 | Favus cap. | July 22 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | − | − | − |
| | | | | | F.B. | − | − | − | − |
| | | | | | F.C. | − | − | − | − |
| M. | 10 | Favus cap. | July 23 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | ± | − | − | − |
| | | | | | F.B. | − | + | + | ± |
| | | | | | F.C. | + | + | − | − |
| M. | 11 | Favus cap. | Nov. 2 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | ± | ± | ± | − |
| | | | | | F.B. | ± | ± | ± | − |
| | | | | | F.C. | ± | ± | ± | − |
| M. | 8 | Favus cap. | Nov. 2 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | − | ± | − |
| | | | | | F.B. | − | − | − | − |
| | | | | | F.C. | − | − | − | − |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| M. | 6 | Favus cap. | May 11 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | − | − | − |
| | | | | | F.B. | − | − | − | − |
| | | | | | F.C. | − | − | − | − |
| F. | 7 | Favus cap. | May 2 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | − | − | − |
| | | | | | F.B. | − | − | − | − |
| | | | | | F.C. | − | − | − | − |
| M. | 6 | Favus corp. | Aug. 2 1909 | Favin A. B. & C. | Control | − | − | − | − |
| | | | | | F.A. | − | ± | − | − |
| | | | | | F.B. | − | ± | − | − |
| | | | | | F.C. | − | ± | − | − |

From these tables it will be seen that in 11 cases of ordinary small-spore Tinea Capitis all due to Microsporon Audoini, in 4 the results were absolutely negative. In 6 doubtful reactions were seen and those were considered as probably negative. In judging the reaction, no reaction was considered positive unless a definite papule was formed with an area of erythema around it at least twice the size of the control. 5 of these doubtful reactions occurred to both Microsporin B and C and in one to Microsporin C only. In one case only was there a definite positive reaction to both Microsporin B and C.

In 3 cases of ordinary Tinea cap. due to large spore fungus tested with Trichophytin A. B. and C. (Richardson) all were completely negative. One of these cases in addition to having Tinea cap. also showed small lesions on the body.

One case of inflamed large spore Tinea cap. (Kerion) tested with Trichophytin A. B. & C. (KING) gave a doubtful reaction to Trich. B. & C.

One case of large spore Tinea corporis also gave doubtful reactions to Trichophytin A. B. & C. (RICHARDSON).

In two cases of Tinea Barbae due to large spore fungus one of which also had Tinea corp. the latter was negative and the former gave doubtful reactions/

reactions to Trich. B. & C.

Seven cases of Favus Capitis all due to Achorion Schönleinii were tested with Favin A. B. & C. and 4 were negative, 2 doubtful and one positive. Similarly one case of Favus corporis due to Achorion Quinckeanum (Plate 19.) gave a doubtful reaction to all three forms of Favin.

Therefore out of 26 cases tested only 2 (8%) gave positive cutaneous reactions, one ordinary small spored Tinea and one ordinary Favus capitis. 13 were definitely negative and 10 doubtful, but I think the doubtful cases should also be considered as negative. The following shows the results in tabular form.

| KIND of CASE | NUMBER of CASES TESTED | NEGA-TIVE | DOUBT-FUL | POSITIVE. |
|---|---|---|---|---|
| Small spore Tinea Cap. | 11 | 4 | 6 | 1 |
| Large Spore Tinea Cap. | 3 | 3 | 0 | 0 |
| Large Spore Tinea Cap. Ker-ion. | 1 | 0 | 1 | 0 |
| Large Spore Tinea Corp. | 1 | 1 | 0 | 0 |
| Large Spore Tinea Barb. | 2 | 1 | 1 | 0 |
| Favus Capitis | 7 | 4 | 2 | 1 |
| Favus Corporis | 1 | 0 | 1 | 0 |
| Total | 26 | 13 | 11 | 2 |

These results are rather disappointing but agree to some extent with SUTTER[946.], who only obtained 5 positive reactions in 150 cases tested (i.e. nearly 4%) by the cutaneous method. These results however do not agree with the results of BLOCH, AMBERG, SUTTER and others in so far as my one positive case in Ringworm was in an ordinary small spored Tinea capitis and negative results were obtained in all the suppurating cases such as Kerion and Tinea Barbae.

A positive reaction, in one case of Favus capitis out of 7 cases (i.e. about 8%) is more than was usually obtained by BLOCH, KUSONOKI and others. Also the one case of Favus corporis tested was doubtful and probably negative, even although it was due to Achor. Quinck. and was spreading rapidly. The fact that my Favin was made from Achor. Schönleinii and not Achor. Quinckeanum may have had something to do with the result. No great difference was found between the reactions to A. B. and C. extracts of fungus. On the whole the A. extracts (i.e. Toxines in fluid medium before fungus crushed) gave very few even doubtful reactions, whereas the B. extracts (i.e. toxines in fluid medium after crushing of fungus) and the C. extracts (i.e. masses of crushed fungus) in practically all cases gave similar results.

My/

My Microsporin B. Trichophytin B. and Favin B. corresponded to the Trichophytins used by other workers and also to Old Tuberculin, and therefore in comparing my results with those of others the reactions to the B. extracts were those which were adopted.

TRANSPLANTATION/

## TRANSPLANTATION EXPERIMENT in RINGWORM.

A most interesting experiment was performed by BLOCH[849.] in order to see whether, in a sensitised person, the sensitiveness was in the skin cell itself or not. A man with a chronic leg ulcer, which required skin grafting, was made use of. Two pieces of skin were grafted on to the ulcerated area, the one a piece of BLOCH'S own skin, the other a piece of skin from a man who had never had Ringworm and whose skin gave no cutaneous reaction to Trichophytin. BLOCH had previously infected himself with a deep Tinea and he gave a well marked cutaneous reaction to Trichophytin. After the two pieces of skin had "taken" and the ulcer healed, cutaneous tests with Trichophytin were done on a healthy area of skin and also on the two grafted pieces of skin. The only area which reacted was the area where BLOCH'S own skin had been grafted. The other two areas gave no reaction at all.

This experiment is most important as it demonstrated that the sensitiveness belonged to the skin cell itself and when that cell was implanted on a non-sensitive individual, it still retained its sensitiveness. This will be referred to again later on, when the mechanism of the cutaneous tests is discussed.

The/

## THE EFFECT of RINGWORM and FAVUS FUNGUS in TISSUES OTHER THAN the EPITHELIUM and HAIRS.

In cases of superficial Tinea corporis and ordinary Tinea capitis the fungus grows on the epithelium and hairs. Very little reaction is produced and microscopically a slight small-celled infiltration or no infiltration at all is observed. But whenever the fungus gets more deeply into the tissues, either into the true skin or deeper, a much more marked reaction takes place. This has been long recognised in the inflamed ringworms such as Kerion (Plate 15.) and Tinea Barbae (Plate 16.) where large lumpy lesions are present. A good deal of experimental work has been done to show the result of infecting the body with various fungi. As far back as 1870 SEMMER[938.] injected the spores of penicillium mixed with distilled water into the jugular veins of animals, but on killing the animals later no lesions were found. But in 1885 NAEGELI[905.] found that injection of fungi into animals lead to the formation of granulomatous masses with giant cells in the internal organs. Similar lesions have long been known to occur in infections with actinomycosis and more recently cases of Sporotrichosis (Plate 21.) were published and in these large granulomata were demonstrated as the result of the invasion of the fungus.

Similarly/

Similarly when the Ringworm fungus gets out of the hair follicles into the true skin, a marked reaction takes place with suppuration. These swollen areas, if excised, were found by FORLANINI[872], PELLIZARI[913] and others to show a mass of round cells together with abundant giant cells such as are seen in all the granulomata. Those Kerion cases are much more commonly due to a large spore fungus but, SABOURAUD[929], LEWANDOWSKY[891] and others have described Kerion due to Microsporin Audoini. In Edinburgh Kerion is a fairly frequent condition, and it is not at all rare to find it due to the small spore fungus.

Tinea Barbae also in the deep seated form with pustules and large raised bluish-red lesions also shows this same granulomatous formation (Plate 16.).

These conditions (Kerion and Tinea Barbae) have been known clinically for a long time, but there is another type of lesion which is very much rarer, viz. Granuloma Trichophyticum. This condition was first described in 1883 by MAJOCCHI[898] in Italy. Most of the cases have been recorded in Italy. MAJOCCHI, VIGNOLO-LUTATI[957], SORRENTINO[940], PINI[916], MAZZA[903], CHIRIVINO[865], CAMPANA[858] have all reported cases. The only case recorded in this country was one by SEQUEIRA[939] in 1912. The condition is quite distinct from Kerion. It is characterised by dermic, rounded, indolent swellings which are painful /

painful or tender and covered with normal or slightly red skin. The lesion is not scaly, is of elastic consistence; usually the centre softens, fluctuates and may burst on the surface leaving a chronic indolent ulcer. Microscopically it shows all the characteristics of a subcutaneous granuloma with plasma cells, epithelioid and giant cells. MAJOCCHI found that this granulomatous lesion might be due to different kinds of fungus such as Tr. Violaceum, Tr. Rosaceum, Tr. Cerebriforme and Tr. Plicatile but was usually due to Tr. Violaceum. MAZZA and SABOURAUD each found the Tr. Violaceum in one case, PINI found a Trichophyton with a yellow powdery culture which SABOURAUD thinks was Tr. Cerebriforme or regulare; and in another case PINI obtained a snow white culture, probably Tr. gypseum. Therefore this peculiar formation is not due to any special kind of fungus causing a special kind of lesion.

SEQUEIRA'S case in this country was a peculiar one, in a boy aged 14, who had suffered from Tinea corporis for 8 years. His sister aged 21 had also been affected with the same disease for 15 years. The boy, when the disease first started had no treatment. The disease gradually spread till the whole trunk and parts of the limbs were affected with a scaly brownish eruption which, on close inspection, showed raised red papules/

papules in rings. The finger nails were all rough, thickened and opaque. The eruption itched a good deal. A year after he became affected a swelling appeared near the umbilicus. This broke down and formed an ulcer. This ulcer healed under treatment, but broke down again and began to enlarge. When seen by SEQUEIRA the boy had a reniform ulcer near the umbilicus 3 inches by 1½ inch with thickened indurated margins and undermined edges. The base was covered with a moist yellow-brown slough. There was a thin yellowish purulent discharge. On the right wrist was a circular infiltrated patch the size of a penny which had never ulcerated and resembled a local tuberculous infection. Scrapings from the scales and nails and the exudate from the ulcer near the umbilicus all yielded pure cultures of a fungus, which was identified by SABOURAUD as Trichophyton Plicatile. There seemed little doubt that the ulcer was caused by the fungus. The boy was in hospital for nearly two years, and during that time a very large number of flat button-like lesions varying from 2 to 2·5 cm. in diameter developed. Many of these were cured by the injection of carbolic acid. Some were scraped away and strong antiseptics applied to the base. Iodine, chrysarobin and many other antiseptics were used for the skin lesions and finally they all cleared up, the umbilical ulcer healing after prolonged immersion in a boracic/

boracic acid bath. The nails were all removed and the nail-bed dressed with weak Iodine solution. The granulomatous eruption left extensive scars. At no time was the hairy scalp affected except when the disease extended from the left auricle which showed a raised indurated lesion which led to considerable sloughing.

The boy remained well for 3 years except for the nail lesions. These were again treated but not cured and after another three years he had a fresh outbreak of granulomata with dry scaly areas of skin as before. He had extensive lumpy lesions in right axilla and left groin. The reinfection was probably from the finger nails. Microscopically the tumour-like lesions showed giant cells, lymphocytes, plasma and eosinophile cells. Filaments of fungus were seen in the giant cells.

SEQUEIRA on discussing the case expresses the view that "it is rather curious considering what is known of the granulomata caused by sporotrichia and other allied fungi, that granulomatous reactions are not more common from trichophytic infection". He also suggests that it may be difficult for the Trichophyta to develop deeply in the tissues.

903.
MAZZA did experiments by injecting cultures of Ringworm and hairs with Ringworm subcutaneously into man and animals. He succeeded in producing granulomata/

granulomata which were the very same as those produced when foreign bodies are introduced into the tissues.

As in Ringworm so in Favus a deep infection may occur. MAJOCCHI first described Kerion due to Favus in 1877. TRUFFI [953.] found that the Achor. Schonleinii may determine a morbid lesion identical clinically with Kerion and also that it may produce in the skin of man and in the subcutaneous tissues of the guinea-pig a granuloma analogous to that produced by the Trichophytons. BUKOWSKI [856.] in 1900 injected Achorion intravenously into rabbits and produced in the lungs nodules with a granulomatous structure with giant cells. In these giant cells were portions of the fungus. He also found that Favus and Trichophyton fungi, if injected intraperitoneally, produced pseudotuberculous nodules. The fungus is phagocyted by the cells and often causes necrosis of the cell. The same results were obtained by injecting dead as by injecting living fungus. BUKOWSKI doubts whether these results were due to the toxines of the fungus, because no lytic substances were found in the peritoneal exudate. He suggests that the whole reaction might be a mechanical one due to pressure or the result of the introduction of a foreign body.

SABRAZES [931.] previously in 1893 had produced very/

very similar lesions by injection of fungi, but CARINI[859] obtained no results by injecting rabbits intravenously with Achorion. Quincke, in 1886, produced nodules in the lungs of rabbits by injecting Achorion Schonleinii intravenously. These nodules were found to contain the fungus.

RADAELI[923] also confirmed this work. A pure culture of Achorion Schönleinii, inoculated into the vein of a rabbit, caused the formation of nodules in the lung. These nodules microscopically were granulomata with areas of necrosis. In the centre of these nodules masses of fungus with radiating filaments resembling what is seen in Actinomycosis, were found. Similar lesions were also found to be produced in the lung by intravenous injection of Trichophyton Violaceum

More recently in 1910 DARIER and HALLE[869] reported a case of Favus capitis which clinically showed no peculiarity, but on excising a piece of skin with scutula, pseudo-tuberculous nodules with giant cells were found in the corium. This case they describe as a "granulome favique".

From these observations therefore there seems no doubt that both Trichophytosis and Favus may in certain cases lead to a granulomatous formation. These formations are similar to those seen in Tubercle, Syphilis, Sporotrichosis etc. They are to be looked upon as reactions to the invasion of the fungus in individuals/

individuals who are sensitised to the infections and as they can be produced equally well with dead as with living fungus, they are analogous to the reactions produced by subcutaneous injections of Tuberculin in Tubercle-sensitive individuals. Whether the fungus spreads by local growth in the skin tissues or is carried to the skin by the circulation, there is no evidence one way or the other to show; but it is a question whether they should not be regarded more as large "Trichophytides" analogous to the lesions in BAZIN'S disease or the gumma in tertiary syphilis. Both of these latter conditions contain the causal organisms in small numbers and the relatively large lesion is due to the patient being highly sensitised to the infection thus leading to a marked reaction.

THE/

# THE TREATMENT of RINGWORM and FAVUS WITH FUNGUS EXTRACTS.

It has already been shown that NEISSER and PLATO, BLOCH and others obtained local and general reactions by injection of Trichophytin. From that it is natural to assume that results might be obtained by Trichophytin injections in the treatment of Ringworm.

BLOCH[844.] succeeded by giving injections of Trichophytin in causing the healing of a case of Ringworm without any local treatment. He also, in a case of Kerion due to Tr. Rosaceum, succeeded in healing it by inoculating another healthy area of skin with Achorion Quinckeanum . These results were obtained in deep seated lesions, but in the chronic superficial small-spore Tineas and in Favus he found that fungus injections did not cause healing.

BRUCK and KUSONOKI[852.] found that injections of Trichophytin had no paracitide effect on the fungus but that they had a specific effect in stimulating the tissues to expel it. Whilst the lesion was fading, the fungus could still be found and cultivated. Therefore the effect of Trichophytin was not to kill the fungus but to make the tissues unsuitable for its growth/

growth. Three cases of deep seated Tinea Barbae, in which the cutaneous Trichophytin test was negative and the intracutaneous test positive, were each cured in about ten days by Trichophytin injections. He found intracutaneous injection better than subcutaneous, as it avoided the general and other disturbances produced by subcutaneous injection. No focal reactions were seen. Two cases of superficial Tineas were treated similarly but with no result.

These results show that in cases of Ringworm where the patient is hypersensitive and gives a positive intradermal reaction, the intracutaneous administration of antigen at intervals assists the natural tendency to healing and results in a cure of the disease. Whereas, as already shown, injection of Trichophytin will not sensitize an animal but infection with the disease will. That therefore explains why Trichophytin injections do not cure superficial Tineas because a sensitization has not taken place.

In cases repeatedly treated with intracutaneous Trichophytin injections BUCK and KUSONOKI found that the local reaction becomes weaker and weaker. On the other hand STEIN 941. observed that every additional intracutaneous administration of antigen led to a local and focal reaction.

STEIN/

STEIN points out that CITRON has shown that the Hyphomycetes form no toxines. Mice injected intraperitoneally or subcutaneously with filtrates of cultures of Ringworm show no noteworthy disturbances, even in relatively large doses. Therefore we must conclude that the pathogenic fungi are not in a position to form an extra-cellular toxine. This is not surprising as Ringworm even although it produces an intense skin lesion does not cause any general symptoms such as are seen in diphtheria and other infections with organisms which produce toxines. STEIN argues therefore that extracts of the fungus and not filtrates should be used. Just as with attempts to produce immunity to ringworm all strains of fungus do not immunise equally well, so all extracts do not act equally well. BRUCK and KUSONOKI used Tricho. gypseum but STEIN found that the cultures were very thick and did not rub up easily. He obtained the best Trichophytin from Achor. Quinck. The effect of the treatment does not depend on treating the patient with the Trichophytin from his own fungus but on the preparation which is most richly saturated with the decomposition products of the fungus. This is the case in Trichophytin prepared from Achor. Quinck. Although the preparation is really a "Favin", as already pointed out, the Favuses and Trichophytons are very closely related biologically.

STEIN/

STEIN treated 15 cases of deep-seated Ringworm. A diagnostic cutaneous test was done first to see whether the patient reacted promptly to Trichophytin. The more marked this reaction the better the prognosis. Injections of 0·1 cc. Trichophytin were given intradermically every ten days. Two such doses may be enough to effect a cure. Local and focal reactions were seen and also reactions in previously injected areas. Out of the 15 cases treated 10 were rapidly cured without local treatment; Two were improved and three showed little tendency to heal. In these cases the cutaneous reactions were very feeble. Five cases of Favus capitis were treated similarly. The local reactions were less than in the deep Tineas and focal reactions were absent. Two children with Favus corporis contracted from a cat and due to Achor. violaceum also reacted promptly to Trichophytin treatment.

941.
STEIN also used a Trichophytin ointment for therapeutic purposes on the same principle as the Histopin ointment in Staphylococcal infections used by WASSERMAN, 1295. LEDERMANN and 1293. BECK. He used a 30% ointment of Trichophytin in lanolin. 889. KUSONOKI had used a similar 10% ointment for diagnostic purposes but obtained no reactions. STEIN used his

30% /

30% ointment by local application to the lesions with good results. This ointment alone, without Trichophytin injections, was not successful in curing cases, but it was found to be very useful in preventing recurrences if the injections had been stopped too soon. He claims that Tinea Barbae and Kerion Ringworms can be healed more quickly by intradermal injection of Trichophytin and local application of Trichophytin ointment. In superficial Tineas, which do not react to Trichophytin, he recommends the Trichophytin ointment alone. He also suggests the use of Trichophytin ointment for rubbing the heads of healthy children to prevent the spread of small spore Ringworm of the scalp during epidemics.

935. SCHOLTZ found that both deep and superficial Ringworms healed rapidly with repeated injections of Trichophytin (HÖCHST) without any local treatment. Injections were given every 4-5 days and the Trichophytin was diluted 1 in 100. The best results were obtained by giving the Trichophytin intradermally and the dose was split up and given in 3-4 places 0·1 cc. being injected in each area.

874. FUHS used a digested culture of Trichophyton fungus analogous to JOANOVIC'S Tubercle Bacillus preparation. Twenty-six cases of Ringworm were treated with doses up to 0·5 cc. Intradermal and subcutaneous/

subcutaneous injections were found to produce the same result. The treatment was beneficial in the deep forms of Tinea Barbae. It assisted and shortened the healing process and acted similarly to BLOCH'S and SCHOLTZ'S Trichophytin. The almost constant dry absorption of the infiltration of the lesions without outward sign, was different from what occurs when other Trichophytins are used.

ROZSAVÖLGYI[928.] treated over 100 cases of Ringworm, chiefly Tinea Barbae, with injections of Trichophytin. He used a dilution of 1 in 100 and at first gave the same doses as SCHOLTZ, in the same way intradermally, dividing the dose up into 3 and injecting $\frac{1}{3}$ into 3 different areas. Later he gave the undiluted Trichophytin in the same way and only diluted it for children with Kerion and in cases where he got a very marked local or focal reaction. He also gave the injections every second day and sometimes daily. At first he often produced large oedematous painful swellings with hyperaemia and oedema at the seat of injection. But the results on the whole were favourable and no important drawbacks were found to the method.

Trichophytin was also used fairly extensively by TRUFFI[954.] for therapeutic purposes. He was disappointed in the results and thinks its therapeutic value very slight whereas its diagnostic value is quite definite./

definite. He used the Trichophytin by subcutaneous injection to get a focal and general reaction, but a great drawback to the method was the marked local reaction produced at the seat of injection.

A somewhat modified form of inoculations with fungus elements was reported by PERSSON; 914. The case treated was an extensive Favus corp. on body limbs, finger and toe nails. The disease had lasted for 23 years. There is no mention of the scalp being affected. Microscopically the scales from the lesions showed fungus and cultures on agar-contained Achor. Schönleinii and Staph. aureus. Cultures of this Achorion, in 80 parts sterile salt water, together with 20 parts of a 5% Sol. of nucleinic acid, were incubated for 72 hours and diluted with physiological salt solution to give a suspension representing 5 million individual segments or spores to each cc. This was sterilised at 180° F. for 45 minutes. The patient received in all 77 inoculations varying between 500 and 5,000 million. At first injections were given daily, then, twice a day and later every second day. By the 27th day the disease was practically healed and six months later the patient was still well. The opsonic index gradually rose from 0.3 to 3·6 in 35 days.

Last/

908.

Last year NOVAK published the results of treatment of cases of Ringworm with Fungus extracts. He used two preparations,

(1) Trichophytin prepared in the State serological Institute in Vienna, and

(2) "Trichon" prepared by SCHERING in Berlin, and consisting of a polyvalent Trichophytin made according to the formula of Prof. BRUCK.

The injections were given subcutaneously and were found to be useful as an aid to the usual local treatment with 1% hot resorcin solution. In severe cases the injections hastened the cure. If used alone they were found insufficient to overcome a ringworm infection. The Trichophytin (Vienna) was found to be a weaker preparation than Trichon. (Berlin) but was easier to handle and its administration caused less pain and less local reaction. NOVAK recommends "Trichophytin" for superficial infections and "Trichon" for deep cases.

As having a bearing on this subject mention must be made of the result of treating cases of deep Tinea Barbae with a non-specific vaccine. LOEB 894. treated 12 cases with injections of Leukogen (HÖCHST) which is a vaccine containing staph. aureus and citreus. LOEB found that by intracutaneous injection of Leukogen and by rubbing it into the skin no reaction is produced but in all cases by subcutaneous injection an /

an oedematous tender swelling was produced, but as it occurred in non-ringworm persons it has no significance. Focal reactions were frequently observed especially after the second to fourth injection. The cases received on the average 10 injections each of from 10 to 500 million every 3-10 days. All healed in a relatively short time without other treatment. In eight cases of more superficial Tineas similarly treated, four were cured, one improved, one left before treatment finished and one recurred in 14 days after apparent healing. LOEB thinks that deep Tinea Barbae is due to the Ringworm fungus and staphylococcal infection and that therefore the vaccine acts specifically. I cannot agree with this view. Doubtless the lesions are contaminated with the Staphyloccus, but the facts that no reactions were produced by intracutaneous injection or rubbing into the skin produced no reaction and the subcutaneous injection produced a non-specific reaction, are all in favour of the method acting non-specifically. LOEB also admits that the treatment has no immunizing effect as in many cases new spots appeared in the course of treatment and recurrences occurred after apparent cure. Deep Tinea Barbae also tends to produce its own immunity whether treated or not and once the sensitising process has begun it is quite likely that/

that injections of any bacterial substance would stimulate that process, and therefore the results were probably similar to those produced by non-specific bacterial therapy.

AUTHOR'S/

## AUTHOR'S EXPERIMENTS WITH "MICROSPORIN".

In 1915 I treated 5 cases of ordinary Tinea capitis with "Microsporin" prepared as already described (p. 239. ) from a culture of Microsporon Audoini. Details of the cases are as follows:-

CASE 1. R. P. age 7. Tinea Capitis for one month. Several areas. Small spore fungus found.

Aug. 23. '15. Vaccine 0·5 cc. Microsporin.
Aug. 26. '15. " 1 cc.
Aug. 30. '15. " 1 cc.
Sept. 3. '15. " 1 cc.

No local reaction produced, but patient not looking well. General condition improved again as soon as injections stopped. Left without treatment and on Nov. 22. '15. fungus again found in hairs. Result, negative.

CASE 2. A. R. age 9. Tinea capitis for 3 weeks. Large area near crown 3" x 4" and small spot on right side of head. Small spore fungus present.

Aug. 11. '15. Vaccine 0·5 cc. "Microsporin"
Aug. 16. '15. " 1 cc.
Aug. 19. '15. " 1 cc.

Aug./

Aug. 23. 15. Vaccine 1 cc. Diseased areas look dry and dusty.

Aug. 26. 15. Injection area on left arm swollen red and tender. No injection given.

Aug. 30. 15. Swelling on arm gone down. Vaccine 1 cc. No spread of disease on scalp.

Sept. 2. 15. Suph. praecip. ℥i. Hydrar. ammoniat. ℥ss in Lanolin and Vaseline aa ℥i. started locally.

Sept. 7. 15 Vaccine 1 cc.

Sept.14. 15 " 1 cc.

Sept.17. 15 " 1 cc.

Sept.21. 15 " 1 cc.

Sept.24. 15. " 1 cc.

Sept.28. 15. " 1 cc.

Oct. 1. 15. " 1 cc.

Oct. 5. 15. " 1 cc. Each of the last eight injections caused some local swelling and tenderness.

Oct. 12. 15. Vaccine 1 cc.

Oct. 15. 15. " 1·5 cc.

Oct. 26. 15. " 1 cc.

Oct. 29. 15. " 1·5 cc.

Nov. 1. 15. " 1·5 cc.

Nov. 5. 15. " 1·5 cc.

Nov. 8. 15. Last injection area very sore, swollen, red and tender to touch. All the previous six injections caused some swelling specially the last one. Fungus found in hairs from scalp. The seats of previous injections in many cases swelled up after subsequent injections.

Nov./

Nov. 15. 15. Swelling on back not so red.

Nov. 25. 15. " " " almost disappeared Local treatment with ointment only continued till Feb. 14. 1917 when he was X-rayed. Finally cured on Nov. 29. 1917.

CASE 3. R. T. aged 4. Tinea capitis for some months. Several areas all over scalp. Small spore fungus found.

Aug. 23. 15. Vaccine 0·5 cc. "Microsporin"

Aug. 26. 15. " 1 cc. Local treatment with Sulphur and Ammoniated mercury ointment.

Oct. 5. 15. Patient was not brought back till to-day. Mother reports that he had diarrhoea after the first two injections. Diarrhoea now well. Vaccine 1 cc.

Oct. 26. 15. Vaccine 1 cc.

Oct. 29. 15. " 1 cc.

Nov. 1. 15. " 1 cc.

Nov. 4. 15. Vaccine stopped as mother reported diarrhoea recommenced as soon as vaccine injections were resumed. Local treatment only continued. Diarrhoea stopped again within 2 days of stopping vaccine. Case finally cured by ointment on July 18. 1916.

CASE 4. J. H. age 10. Tinea capitis for 2 years chiefly on left side of head. Several areas. Small spore fungus found.

Aug. 21. 15. Local treatment with Sulphur and ammoniated mercury ointment started

Aug. 23. 15. Vaccine 0·5 cc. "Microsporin"

Aug. 26. 15. " 1 cc.

Sept./

Sept. 9. 15. Vaccine 1 cc.

Sept. 13. 15. " 1 cc.

Sept. 16. 15. " 1 cc.

Sept. 20. 15. " 1 cc.

Sept. 27. 15. Mother reports that child getting very thin and not eating well. Vaccine stopped. Diseased hairs found on scalp. Case eventually cured on Nov. 6. 1917. after X-ray treatment.

CASE 5. R. S. age 12. Tinea capitis for 3 weeks. Several areas scattered over scalp. Small-spored fungus found.

Sept. 2. 15. Local treatment with Sulphur and ammoniated mercury ointment started.

Sept. 3. 15. Vaccine 0·5 cc. Microsporin.

Sept. 7. 15. " 1 cc.

Sept. 14. 15. " 1 cc.

Sept. 17. 15. " 1 cc.

Sept. 21. 15. " 1 cc. Spots on right side of scalp, redder than formerly.

Sept. 24. 15. Vaccine 1 cc.

Sept. 28. 15. " 1 cc.

Oct. 1. 15. " 1 cc.

Oct. 5. 15. " 1 cc.

Oct. 12. 15. " 1 cc.

Oct. 26. 15. " 1 cc.

Nov. 5. 15. " 1 cc. Disease still present on scalp. After the third and subsequent injections there was some local swelling and tenderness and in some cases sites of previous injections swelled/

swelled up. As the patient ceased to attend the later history is not known.

As will be seen from the above the results were very disappointing and therefore the method of treatment was discontinued. The local reactions at the seat of injection was always very marked and in most cases the seats of previous injections reacted to subsequent ones. All injections were given subcutaneously into the back between the scapulae. In no case was any focal reaction produced in the scalp lesion. At no time was any temperature seen, but as the cases were out-patients and only seen on the days injections were given there might have been rises of temperature following the injections. In cases 1 and 4 there was a distinct effect on the general health, and I think in Case 3 one must attribute the diarrhoea to the injections. My own impression is that the symptoms were possibly not due to the fungus elements in the Microsporin but to traces of maltose and peptone which could not very well be eliminated in the preparation of the microsporin.

The only other reference which I can find to the treatment of small spored Tinea capitis with a vaccine is an article by STRICKLER[944.] published in 1915. In this article he describes how he made his "microsporin"/

"microsporin". He lays great stress on the use of a vaccine containing the fungus elements themselves as he considers the failure of PLATO'S Trichophytins was due to the culture suspension being filtered. When I made my microsporin, the great difficulty I found was to get the fungus elements separated from one another. The cultures formed a felted mass of fungus which it was very difficult to rub up so as to separate spores and myceliuminto sufficiently small pieces to allow of injection with the syringe. STRICKLER got over this difficulty by rubbing up the culture growths with crystals of chemically pure Sod. chloride. By this method all the elements became separated so finely that filtration was unnecessary. After rubbing up the cultures, the sodium chloride was diluted with sterile distilled water to the strength of normal saline. STRICKLER gave his vaccine in doses of 0·5 cc. up to 4 cc. As it was found no advantage to employ the larger doses, the usual dose varied from 1 to 2 cc. Injections were given at intervals of three days, in the back between the scapulae or into the buttock. After 6 or 7 injections had been given infiltrated areas appeared sometimes at the seat of injection. In one instance an abscess formed. In no case did he find any constitutional reaction. The number of injections varied from 7 up to 17 in number. Seven cases were treated, 6 of which were ordinary cases of small spored Tinea/

Tinea capitis and the other was a Kerion (fungus not stated). Six were cured in about a month and one in 3 months without local treatment. Therefore STRICKLER concludes that Tinea capitis can be cured by vaccine and suggests its use together with ordinary local treatment.

TRICHOPHYTIDES/

## TRICHOPHYTIDES and MICROSPORIDES.

In 1912 a new light was thrown on our conception of the changes taking place in Ringworm infections by the description of Trichophytides by JADASSOHN.[885.] He noticed on several occasions in children with Kerion, specially in the healing stage, that there suddenly appeared small pale red follicular papules on the trunk. These resembled Lichen Scrofulosorum very closely but did not react when rubbed with Tuberculin as Lichen Scrofulosorum always does. Occasionally the lesions showed small horny projections resembling the clinical picture of Lichen Spinulosus. JADASSOHN named them Lichenoid Trichophytides, and this conception was further strengthened by the fact that by rubbing Trichophyton fungus into the skin of children suffering from Kerion exactly similar Lichenoid eruptions, which remain for some time, are produced. JADASSOHN considered the lichenoid eruption in Kerion cases as due to external autoinoculation and as a hypersensitive reaction analogous to Lichen Scrofulosorum, and because no fungus was found in the lesions he concluded that the reaction was probably due to the toxines of the fungus.

Since/

Since JADASSOHN'S publication numerous similar cases have been recorded by GUTH,[878] SAEVES,[933] CHABLE,[862] SUTTER,[947] BLOCH,[848] RASCH,[924] PEDERSEN,[910] HERXHEIMER,[883] and KOSTER,[921] PULVERMACHER,[832] AMBROSOLI, ARZT and FUHS,[835] JESSNER[887] and WILLIAMS.[959].

At first these eruptions were only described in cases of large spored Tinea and usually in deep seated cases, but recently they have been described in cases of small spored Ringworm constituting the so-called "Microsporides".

In addition to the papular eruptions, several other kinds of eruption have been described so that the Trichophytides may be divided into several clinical types.

(1) Papular eruptions. Lichen Trichophyticus or Lichenoid Trichophytides.

(2) Vesicular Trichophytides.

(3) Pustular Trichophytides (Impetigo Trichophytica).

(4) Eczematoid Trichophytides.

(5) Scarlatiniform Trichophytides - (Erythema Scarlatiniforme Trichophyticum).

(6) Nodular subcutaneous Trichophytides (Erythema nodosum Trichophyticum).

(7) Erythema multiforme Trichophyticum.

PAPULAR/

## PAPULAR LICHENOID TRICHOPHYTIDES - LICHEN TRICHOPHYTICUS.

This seems to be the commonest form of Trichophytide and the majority of cases reported by the authors already mentioned were of this type. The exanthem is characterised by the sudden appearance of numerous lichenoid papules of flat or conical form. The papules are disseminated over the skin of the trunk, on the extremities, and more rarely on the face and generally, but not always, localised in association with the follicles. They are widely distributed and often arranged in groups. The lesions are pale red, bluish or brownish in colour and the apex of the lesion may show a small scale, crust or pustule. They appear in crops and may disappear rapidly or persist for weeks. If they are closely set together a scaly area may be produced resembling a seborrhoeic eczema (eczematoid Trichophytide). Many of the papules develop a horny spine at the mouth of the follicle producing the clinical lesion of Lichen spinulosus and as JADASSOHN pointed out many cases described as Lichen Spinulosus are really cases of Lichen Trichophyticus. In 1905 LEWANDOWSKY[890.] described a case of Lichen Spinulosus in a girl who had Kerion on the scalp. The lesions were those of Lichen Trichophyticus but/

but LEWANDOWSKY did not recognise the connection between the eruption and the scalp Kerion. Of course it is not to be assumed that all cases of Lichen Spinulosus are due to Ringworm as the disease has been reported by ADAMSON,[830] COLCOTT FOX,[873] GRAHAM LITTLE,[872] MACLEOD,[897] AUDRY,[836] HALBERSTÄDTER[879] and many others in cases where no ringworm existed. But it throws light on the possible origin of these cases of Lichen Spinulosus and suggests that in all cases the lesion is due to the reaction produced at the follicles by some toxine or organism coming either through the circulation or by external application into contact with a sensitized skin.

GUTH[878] examined the lichenoid lesions microscopically and found the same histological changes as LEWANDOWSKY described in his so-called Lichen Spinulosus, namely a follicular inflammation with oedema, vacuolation of the epithelial cells of the outer root sheath of follicle and a small-celled infiltration in the surrounding corium. In places the epithelium of the follicle is destroyed and a small intrafollicular pustule is formed surmounted by a mass of horny cells. The adjacent skin epithelium shows acanthosis. In the later stages the pustulation and signs of acute inflammation largely disappear and the/

the follicle shows a parakeratosis, which leads to the formation of the horny spine. This parakeratosis may be so marked as to prevent the hair getting out. The connective tissue around occasionally shows a mucoid degeneration, but the elastic tissue is never affected. In the eczematoid forms where the changes are not limited to the neighbourhood of the follicles GUTH found spongiosis of the epithelium, vesicle formation, parakeratosis with more or less acanthosis.

In all cases the cell infiltration in the corium consisted entirely of small round cells with no sign of giant cells. A special form of the Lichenoid Trichophytide is the Corymbiform Trichophytide described by JADASSOHN[885.] and SAEVES.[933.] The latter's case was that of a man who was infected with cattle Ringworm on the body. Around the larger deep seated lesions were numerous smaller ones arranged in a corymbiform manner. The smaller lesions were bright red follicular nodules. In addition, on the body and limbs, were numerous small red lesions of Lichen Trichophyticus. In the large central lesions fungus was found but not in the small follicular ones. The large lesions had been present for 18 days before the small lichenoid ones appeared. The latter also disappeared without treatment. These corymbiform lesions are similar to those seen in syphilis/

syphilis, in tubercle and scrofuloderma lesions and in leprosy (JADASSOHN). SAEVES discusses the pathogenesis of these corymbiform lesions. There are three possibilities.

(1) Blood spread.

(2) Lymphatic spread.

(3) External autoinoculation.

As JADASSOHN has shown in syphilis the lymphatic spread is the most probable in that condition, the area immediately around the lesion being relatively immune. In the corymbiform Trichophytide a similar explanation is possible but there is still the possibility of an external spread. If Trichophytin is rubbed into a sensitized skin a lesion exactly like Lichen Trichophyticus can be produced, and SAEVES suggests that the patient whilst rubbing an ointment into a ringworm lesion may rub the fungus into the sensitized skin round about and so produce the corymbiform appearance. SAEVES considers that the lymphatic or external route is the probable one in the corymbiform cases and that the generalised eruptions are probably produced by a blood spread.

PEDERSON[211] found that the skin around deep seated Ringworm lesions reacted more strongly to Trichophytin than did the skin of more distant areas.

One/

One might argue that that supports the external origin of the corymbiform trichophytide, but PEDERSON thinks that it does not necessarily support that theory because if the reaction occurs through a blood infection the more sensitive area around the lesion would react more readily than other areas.

## VESICULAR TRICHOPHYTIDES.

RASCH[924] describes 5 cases in which he saw eruptions generally consisting of vesicles or vesico-pustules the size of a pin's head. In another case he found a similar eruption in large groups on the buttocks, once on the arms and once on the toes. This eruption was found twice on the scalp and adjacent parts of the forehead and temples.

It is a question whether these lesions should not be included under those to be next discussed, viz. the pustular trichophytides.

## PUSTULAR TRICHOPHYTIDES.

As already mentioned some of the lesions in the lichenoid Trichophytides may show pustulation, but BLOCH[846] described a case of extensive scalp Kerion in a child who developed on the body and extremities a symmetrical rash consisting entirely of pustules on an/

an inflammatory base. They were arranged sometimes in groups, at other times in large irregular patches, but the majority of lesions were isolated and some showed a follicular distribution. The contents of the pustules were sterile. The general condition of the child was gravely affected. There was shivering, rise of temperature, swelling of the lymphatic glands, and a leucocytosis in the blood. The intradermic Trichophytin test was strongly positive on three occasions and on each occasion the day after the injection there appeared round the seat of injection, an erythemato-pustular eruption exactly similar to that on the body. For fifteen days the child's general condition was alarming and only improved as the Kerion lesions began to subside. As the Kerion became better, the pustular lesions gradually disappeared.

ECZEMATOID TRICHOPHYTIDES have been described by JADASSOHN and others. They are really a sub-variety of the lichenoid form in which the lesions are so closely set together that they form scaly patches not unlike a seborrhoeic dermatitis. GUTH also describes one case of Kerion, which showed a rash on the body resembling pityriasis rosea.

SCARLATINIFORM/

## SCARLATINIFORM TRICHOPHYTIDES.

947. SUTTER describes a case of a girl of 10 years of age with a Kerion of scalp due to Trichophyton granulosum. On the 15th day of the disease and 5 days after the head had been X-rayed the child suddenly complained of headache and vomited. A scarlatiniform rash appeared all over the body and limbs. The exanthem consisted of a punctate erythema beginning in small patches which rapidly coalesced and resembled scarlet fever very closely. The mucous membrane of the palate pharynx and gums showed a diffuse redness. The conjunctivae were slightly reddened. The temperature rose and remained up for 8 days. There was marked swelling and tenderness of the cervical, supra-and infra-clavicular and axillary glands. The right retro-auricular and cervical glands were swollen and fluctuating. On puncture of these glands, pus was obtained and although no fungus was seen microscopically, cultures from the gland contents gave a pure growth of Tr. granulosum, the same as had been obtained from the Kerion scalp lesions. The spleen also was enlarged and the blood showed a polymorphonuclear leucocytosis of 16,800 per cmm. The diazo reaction was positive. The child also complained of pain and swelling of the joints especially of the right/

right foot and left knee. The joints were painful on movement and showed an increase of fluid in them.

As the temperature fell the rash altered in character. It became more papular and papulo-pustular and follicular and in places annular or eczematoid like the cases of lichenoid trichophytides already described. In the subcutaneous tissues of the legs there appeared several swellings tender to pressure, and resembling erythema nodosum (See nodular Trichophytides later).

At this stage the softened retroauricular gland was excised and found to show a necrobiosis in the centre with masses of leucocytes all round among which were numerous mycelial threads. Several giant cells were also visible.

The Trichophytin intradermic test and the Moro test with 20% Trichophytin ointment were both positive. Four papules were excised from the exanthem and from these cultures of the Trichophytȯn granulosum were also obtained. Therefore in this case the same fungus as caused the Kerion was found in the skin rashes and lymphatic glands. The fungus was obtained culturally from the surface of lichenoid lesions 48 hours after their appearance but not later on either in the scales or crusts on the lesions.

SUTTER /

SUTTER also describes two analogous cases one, with a Kerion of scalp in whom a rash like that of scarlet fever appeared on the body and mucous membranes but without swelling of glands or spleen. This rash later became papular and spinulous. The other was a Kerion case in whom an injection of 0·1 cc. Trichophytin subcutaneously resulted in a rigor with a rise of temperature and a macular rash on the chest, abdomen and mucous membranes. This rash was exactly analogous to those sometimes produced in Tuberculous cases by the injection of old Tuberculin (vide infra).

## NODULAR TRICHOPHYTIDES.

(Erythema nodosum trichophyticum)

This form of Trichophytide was first described by BLOCH[846] in a case with an extensive Kerion, together with a very marked Lichen trichophyticus on the body and arms, associated with fever, leucocytosis, enlargement of lymphatic glands and spleen. Then, rather suddenly, on the extensor aspect of the legs there appeared numerous cutaneous and subcutaneous nodules, of firm consistence, tender on pressure and of a reddish or bluish colour. Clinically the lesions were indistinguishable from an ordinary erythema nodosum. After injection of Trichophytin a very definite /

definite focal reaction occurred in the nodules. One of the nodes in excision showed an inflammatory infiltration of the derma and hypoderma.

Since this case was published BLOCH[848.] has recorded another case, and cases have been reported by SUTTER,[947.] PULVERMACHER,[921.] GUTH[878.] and BRUUSGAARD.[855.] In all, eight cases have been published. All cases occurred in the course of a severe infection with Ringworm associated with general symptoms. All except one case (which occurred in a Tinea Barbae) were in children with Kerion. With the exception of PULVERMACHER'S case, in which the arms and buttocks were involved, the nodules were situated on the lower extremities and usually on the anterior aspect. The eruption came out suddenly and lasted for weeks. Both BLOCH'S cases gave a positive focal reaction on injection of Trichophytin. The view that the lesion probably starts from a vein was supported by one of PULVERMACHER'S cases in which there was a hard string of nodules in the course of the great saphenous vein. The question naturally arises as to whether these cases are to be regarded as nodular trichophytides or as cases of Kerion with Erythema nodosum in addition. The fact that they showed Lichen Trichophyticus as well is a point in favour of their being Trichophytides. A positive focal reaction on injection of Trichophytin is/

is also in favour of the same view. The question is ~~will be~~ further discussed under Erythema nodosum.

But the final proof of their trichophytic origin was given recently by BRUUSGAARD who excised one of the nodules in his case. He selected a fresh nodule scarcely 24 hours old. Histologically the lesion showed a marked inflammation with numerous polymorphonuclear leucocytes in the pars-reticularis of the corium with oedema and proliferation of the connective tissue cells. The papillary blood vessels were very congested and haemorrhages had taken place. Among the cell infiltration of the corium numerous deeply stained spore-like elements were seen, either isolated or in groups. From the node also a pure culture of the Tr. gypseum was obtained - the same fungus which had previously been grown from the original Tinea Barbae lesion in this case.

ERYTHEMA/

## ERYTHEMA MULTIFORME TRICHOPHYTICUM.

Two cases of this condition have been described by BLOCH.[848] The one was a female patient with chronic gonorrhoea who was inoculated on the left arm with Achorion Quinckeanum, and soon developed a vesicular and scaly spreading lesion of the size of a florin. ,After an intradermic injection of Trichophytin (0·1 gr.) a very marked local reaction was produced at the seat of injection. This inflamed area spread during the following days producing a large swollen area with raised edge over the greater part of the arm. Three days later an eruption appeared on the backs of both hands in the form of flat rounded erythematous areas. These enlarged, spread to the backs of fingers and palms, elbows and face and showed the usual rounded lesions of erythema multiforme with bluish centre and red edge. This eruption took about six days to spread and then gradually disappeared.

BLOCH also refers to but gives no details of another analogous but less extensive case.

Although BLOCH claims these as a trichophytides of erythema multiforme type, in the first case at least it seems to me there might be some doubt as to the correctness of that opinion. The marked swelling at the seat of injection and its spread to the greater part/

part of the arm like a lymphangitis suggests that the area of injection might have become infected with some septic process and from that the multiforme rash might have proceeded.

924.
RASCH also describes a case of a deep-seated Tinea Barbae which showed on the backs of the hands, lower arms and knees an eruption of erythematous lesions with a small vesicle in the centre of each. RASCH considered it typical of erythema multiforme.

MICROSPORIDES/

## MICROSPORIDES. (LICHEN MICROSPORICUS)

In addition to the Trichophytides in infections with large-spore Ringworm, similar lesions have been described in association with small-spore infections, but the reports are much less numerous than in large spore cases. The first report of such a case was made in 1917 by CHABLE[862.] in a child aged 3½ years who had a typical Kerion from which Microsporon Audoini was cultivated. Five days after the Kerion developed the child complained of pains in the joints and vomited. The temperature rose to 38°. 4 C. and next day almost all the body was covered with a small papular eruption (Lichen microsporicus). The limbs were slightly affected. This eruption remained for about three weeks, gradually fading and becoming brownish in colour. Some of the papules showed some hyperkeratosis at the mouths of the follicles but some became definitely spinulous. An intracutaneous injection of Trichophytin, a few days after the rash appeared, produced a marked local reaction at the seat of injection. The scalp lesion in this case began as an ordinary small-spore Tinea and developed into a Kerion after the head had been X-rayed ~~and~~ when the hair was partially out after the raying.

In/

835.
In 1921 ARZT and FUHS published reports of cases of Lichen Trichophyticus together with one case of ordinary small-spored Tinea capitis due to Microsporon Audoini who showed a lichenoid rash.

834.
In 1922 ARZT in an epidemic of 250 cases of small-spore Ringworm saw exanthemata on the body in twelve of them. Two of the cases showed an ordinary scaly Tinea capitis with no signs of inflammation. Five showed slight inflammation with red scaly areas and five showed marked inflammation with pustulation and crusting, but without any definite Kerion lesions. Clinically the exanthem was not quite the same in all cases. Usually the body or body and limbs were affected and occasionally the face. In most cases the rash was lichenoid in character but small vesicular lesions going on to pustules and eczematoid lesions were also seen. In two cases the lymphatic glands were enlarged. All twelve cases had been X-rayed and the rash came out after that and usually in from 2 to 3 weeks after raying. In all cases Trichophytin (he had no microsporin) in doses of 0·1 - 0·3 was injected intracutaneously. Five cases showed an exanthem 24 hours later, and in 5 cases a rise of temperature was seen. ARZT also succeeded in finding the fungus in scales and by culture from the lichenoid lesions. In excised lichenoid lesions he did not succeed in finding the fungus microscopically. Blood cultures were also made/

made but were negative.

From the above it is evident that in small-spore Tinea Capitis, even in cases not differing from the ordinary scaly variety, general exanthemata may occur similar to the Trichophytides.

## FAVIDES.

8 Cases of Favides similar to Trichophytides and Microsporides have recently been recorded by Italian observers. MARTINOTTI (a) reports three cases, all occurring in patients with Favus Capitis due to Achorion Schönleinii. All were of the small papular type and indistinguishable from Trichophytides. In two of the cases the eruption appeared after X-ray applications for treatment. AMBROSOLI (b) reports one case of Favus Capitis due to Achorion Schönleinii in which, six days after the head was X-rayed, a papulo-squamous eruption appeared suddenly on the trunk and proximal parts of upper and lower extremities. There was a slight rise of temperature, a lymphocytosis in the blood and swelling of all the lymphatic glands. The Achorion was demonstrated both microscopically and culturally in the eruption on the first day or two after its appearance.

PERSONAL/

(a) MARTINOTTI Recerche sui processi immunitari della cute dei tignosi. Giorn. Ital.d.mal. ven e. della pelle 1923. Fasc. II. p.132.

(b) AMBROSOLI "Favide" Reazione cutanea generalizatta alla tigna favosa. Ibid. p. 147.

# PERSONAL EXPERIENCES of TRICHOPHYTIDES and MICROSPORIDES.

During the last year or two I have been on the look out for generalised rashes in cases of Ringworm of the scalp. In hospital practice where very large numbers of cases are to be examined, it is hardly feasible to examine the whole body in every case of Ringworm of scalp but all the inflamed Ringworms have been stripped and examined. There are two types of inflamed cases seen in Edinburgh. First the true Kerion which although sometimes due to a Trichophyton is quite frequently due to the Microsporon Audoini and secondly a more widely distributed inflamed condition of the scalp with superficial pustulation. In only a very few cases has any rash been noticed, so that the condition cannot be at all frequent.

CASE I. This was seen in the early stage and was one which occurred in the private practice of Sir Norman Walker, who kindly allowed me to see it. The child was a boy of 10 years of age, the son of a farmer. He had suffered from a deep seated Ringworm on the nape of the neck for six weeks. There were no other affected children but one of the bullocks on /

on the farm suffered from Ringworm. In three weeks after the first skin lesion appeared, other diseased areas occurred in the neighbourhood and a week before the boy was seen numerous spots appeared on the body. The lesions on the back of the neck were swollen, pustular and resembled Kerions and in them hairs containing large-spore fungus were found. The rash which came out suddenly was distributed more or less all over the body, and consisted of lichenoid papules, some of which showed a necrotic centre covered with a crust. Some of the lesions were larger and might be described as nodules. On the sides of the body they were so closely set together as to form patches like seborrhoeides or an early psoriasis. They resembled very closely the rash of Lichen scrofulosum and I think there is no doubt that this was an example of a papulo-nectrotic Trichophytide. The boy's general condition was apparently unaffected.

CASE II. A boy aged 7 years showed on the scalp red scaly areas which were almost bald when first seen. The father said that the areas had been swollen red and tender when they first appeared. They were obviously areas of healing Kerion. No fungus was to be found now in the lesions. On the back and both sides of the chest especially the right side were several oval areas/

areas very slightly red and covered with small spines which projected from the follicles. The father had not noticed these before but I think they must be considered as the later stage of the lichenoid and eczematoid trichophytide which had gone on to the spinulous stage. They resembled scaly seborrhoeides except for the marked horny spines. Had the child been seen earlier be would probably have shown the lichenoid stage of the lesions.

CASE III. A boy 7½ years of age was seen in private with a Kerion which had lasted for four weeks. The Kerion lesions were numerous but less inflamed than they had been. His mother said that a fortnight before I saw him the child suddenly developed a rash all over the body and legs. For some days the child was feverish and out of sorts. When I saw him, this rash had completely disappeared from the body, but the lower limbs still showed several scaly red areas resembling seborrhoides. I think this case also may be considered as an eczematoid trichophytide, which was disappearing.

CASE IV. A boy aged 3 years showed a Kerion on the top of the head with numerous pustular lesions on the rest of the scalp. After this had lasted for 2 weeks he suddenly developed a small red scarlatiniform rash all over the chest, abdomen and proximal parts/

parts of limbs. It remained out for 3 or 4 days and then faded. The child had no sore throat nor temperature and the face was not affected. The tongue also was normal. The rash did not develop into lichenoid lesions, as SUTTER'S case did, so that it is doubtful whether this case was a scarlatiniform trichophytide or a septic rash due to absorption from the pustular lesions on the scalp.

CASE V. A girl aged 11 years developed Kerion lesions on the scalp 16 days after being X-rayed for a scaly Tinea capitis due to infection with small spore Ringworm from a cat. A few days later she showed numerous scaly red papules on the neck, body and arms. These persisted for about ten days and gradually became browner in colour and faded. There was no disturbance of the general condition. No fungus could be found in the papular lesions. I think they are to be regarded as microsporides and as they were much more numerous on the neck, shoulders and upper chest than elsewhere, it suggested that they were due to an exogenous spread from the infected hairs, which had fallen out after the raying, and had been rubbed into the skin.

CASE VI. I have to thank Dr. F. GARDINER for kindly allowing me to record this case. The patient was a boy aged 5 years who showed one very large typical round Kerion lesion near the crown of the head with/

with a smaller one on the left side of head. The Kerions had been present about three weeks. On examination the neck, trunk, upper parts of upper and lower extremities were found to be covered with a papular eruption. The papules were pale bluish-pink with a brown tinge in places. They were arranged follicularly and fairly evenly distributed over the skin surface, but with a tendency to grouping. Most of the lesions had a small scale at the apex but quite a number showed a definite horny spine projecting from the mouth of the follicle. They were not itchy. The glands at the back of neck, axillae and groin, were slightly enlarged. The father, who came with the child, said the eruption had not been noticed but on being questioned said the boy did not seem to be very well and was off his food about a week previously.

There is no doubt the above case was a typical example of a lichenoid Trichophytide. Cast (N° 14.) and Plate 20. show the appearance of the lesions on the right shoulder region.

There are two other points which I have noticed with regard to trichophytides and to which I should like to refer.

Firstly in a considerable number of cases of Kerion when the body was examined here and there especially/

especially on the sides of the chest, isolated spiny projections were seen sticking out of the follicles. There was no history of any rash being noticed in these cases but it is possible that a rash might have occurred and passed unnoticed, and that these spinulous lesions were the only visible remains of it.

Secondly, a very considerable number of cases of ordinary scaly Ringworm of the scalp, mostly due to the small spore fungus, develop an extensive pustular eruption all over the scalp about a fortnight or so after exposure to X-rays. The pustules are rounded and slightly flattened on the top and have a very red inflamed base and are always associated with enlarged tender glands in the occipital region. The pustulation persists long after the hair has completely fallen out. When it first begins the lesions are very tender and the child often looks out of condition. No fungus has ever been found in the pus. Are these lesions due to a secondary infection with a septic organism or are they Trichophytides or Microsporides? As they remain more or less localised to the scalp and do not spread except to the adjacent forehead, temples and neck, it suggests that they are septic in origin. These cases also seem to occur in epidemic form, especially in the children who are attending the special Ringworm school, suggesting an infection/

infection which spreads from case to case. On the other hand the lesions look extraordinarily like the vesico-pustular trichophytides figured on the scalp by RASCH. The fact that they nearly always arise just as the hair is beginning to come out after X-rays is also significant. They might be due to the loose hairs containing fungus getting rubbed into the scalp in the process of rubbing in the ointment used in treatment, and if the child is sensitized to the infection, in that case a vesico-pustular or pustular reaction would take place. This reaction would not take place in a non-sensitized case.

PATHOGENESIS/

# PATHOGENESIS of TRICHOPHYTIDES and MICROSPORIDES.

In the first place it would be well to satisfy ourselves that these various eruptions described are really Trichophytides and directly associated with the Ringworm infection. That being determined, it has to be shown how they arise.

The fact that they always occur in cases of Ringworm and usually in deep seated suppurating cases would at once suggest the connection. Then all these cases show a well marked allergic condition of the skin as is shown by the presence of a positive cutaneous or intracutaneous Trichophytin reaction as shown by GUTH,[878] SAEVES[932] and others. This, as one would expect, is essential to the production of Trichophytides. PEDERSEN[910] showed by Trichophytin skin tests that this hypersensitiveness of the skin was specially marked in the skin round the lesions and on the arms where trichophytides usually occur, and SUTTER[947] confirmed this, using the living fungus instead of Trichophytin. JADASSOHN and BLOCH by rubbing in Trichophytin ointment into the skin in these cases produced a lesion indistinguishable from Lichen trichophyticus. The fact also that fungus has been seen microscopically and grown from the lichenoid lesions and enlarged glands further proves that it is the causal agent. Therefore/

Therefore I think there is no doubt that the various lesions described as Trichophytides are the result of the Ringworm infection.

Let us now consider how they are produced. There are three possibilities.

(1) Lymphatic spread.

(2) Exogenous spread.

(3) Haematogenous spread.

1. LYMPHATIC SPREAD. This naturally could only be possible in localised Trichophytides and could never explain the widespread lesions found in most cases, but as already indicated, that might be the means of spread in the corymbiform Trichophytide.

2. EXOGENOUS SPREAD. This method is suggested by the fact that lesions identical with Lichenoid Trichophytides can be produced by rubbing Trichophytin into the skin of patients allergic to Ringworm. DU BOIS examined the skin of patients suffering from scalp Ringworm and found that from practically any part of the apparently healthy skin surface the fungus can be obtained. The clothes rubbing on the skin might rub such fungus into the follicles and so produce the follicular lichenoid lesions. That however is rather unlikely to occur all over the body at once as the Trichophytides usually develop suddenly and simultaneously all over. It might however and doubtless does account/

account for some of the less extensive Trichophytides and especially those that occur on skin areas near the Ringworm focus. This would explain especially those cases where the lesions occur on the neck and shoulders where broken hairs containing fungus are likely to fall down and become rubbed into the skin.

3. HAEMATOGENOUS SPREAD. A spread through the blood stream is the one which naturally suggests itself as the most likely one. The eruption comes out suddenly and has a symmetrical distribution. The resemblance of the lichenoid and scaly forms to Lichen scrofulosum, and of the nodular forms to erythema induratum both of which are generally allowed to be haematogenous in origin, support this view too. The presence of fever, headache, joint pains, a blood leucocytosis, with a general enlargement of the lymphatic glands throughout the body and of the spleen, and a positive diazo reaction, all point to a general infection. The finding of the fungus in the lesions by GUTH[878.] and SUTTER[747.] also shows that in some, if not all cases, it is present. The fact that some workers did not find fungus is of no great importance. Analogous negative results were sometimes obtained in Tuberculides, yet that does not in any way detract from/

from the value of other positive findings.

The time at which the lesion is excised is probably also important. It is only in cases where the lesion is excised within 48 hours or so of its appearance that one would expect to find the fungus, as the reactionary processes going on in the skin are designed to destroy and eliminate the fungus. The finding of fungus in the cervical and retroauricular glands does not necessarily prove that it got there through the blood stream as it might have spread from the scalp by the lymphatics. It is a valuable contribution to our knowledge, however, as that may be the route by which the fungus reaches the circulation eventually. It might spread, as the Spirochaete in syphilis does from the primary, by the lymphatics to the nearest glands and from there get into the circulation. SAEVES [933.] by injecting intracardially an emulsion of Ringworm spores succeeded in producing foci in the skin from which the fungus was recovered. The most important advance, however, in these investigations was made in 1921 by AMBROSOLI [932.]. The case was a Kerion in a child aged 11 years. From the Kerion lesion the Trichophyton gypseum asteroides was cultivated. After 5 or 6 days in hospital the child developed/

developed a temperature of 38·5° C. and on the sides of the neck small follicular papules appeared. These were bright red in colour at first and showed small vesicles. During the next two days the rash spread to the thorax, abdomen and outer aspects of upper extremities. Repeated examination of scales, etc. from the surface of these lesions were negative. The inguinal and cervical glands and the spleen were slightly enlarged. The blood showed an increase of the polymorphonuclear leucocytes. Therefore he was dealing with a typical case of Trichophytide.

Whilst the rash was at its height blood cultures were made. Several cc's. were withdrawn from the median cephalic vein with antiseptic precautions and put on SABOURAUD'S maltose medium in four tubes 2-3 cc. into each. Cultures were similarly made again next day from blood similarly withdrawn and four tubes were again inoculated. The first set of cultures were negative but in the second set after eight days a typical culture of Trich. gypseum asteroides grew. This, therefore, definitely proves that in Trichophytides, the fungus is actually circulating in the blood stream.

This observation of AMBROSOLI was confirmed in the same year by JESSNER.[887] His case was in a boy, aged/

aged 10 years, who suffered from the ordinary superficial Tinea capitis. This boy suddenly developed a Lichenoid Trichophytide with some eczematoid lesions all over the body, face and neck. The cervical glands were enlarged and puncture of one of the enlarged glands was negative as regards fungus both microscopically and culturally. The blood showed a polymorphonuclear leucocytosis of 16,000 per. cmm. There were no mucous membrane lesions and no fever. Slight bronchitis was present in both lungs. Five days after the eruption appeared, blood cultures were taken. 20 cc. of blood were withdrawn from a vein and plated on maltose and glucose agar. In these a culture grew exactly the same as the one obtained from the scalp hairs. This culture was a little difficult to identify. At first it looked like Tr. granulosum but later JESSNER was more doubtful. PLAUT, who saw it, said it belonged to a kind of Botrytis, which grows as a saprophyte on dead plants and vegetation, but it belongs morphologically to the Trichophytons. Inoculated into 2 guinea-pigs, 2 adults and 2 children the results were negative but when inoculated on a colleague who was allergic after an attack of deep seated Ringworm it gave a positive reaction. This fungus also when inoculated on the skin of a female colleague produced a/

a superficial erythemato-squameous Ringworm from which the fungus was again obtained by retroculture.

JESSNER also describes a second case in a boy of 11 years of age with a Kerion. He could not get a pure culture from the Kerion. The cultures were all spoilt by contaminations. This child developed a Lichenoid trichophytide on the body with a leucocytosis of 28,000 per. cmm. The Trichophytin skin reaction was positive. Blood cultures showed one colony of Tr. gypseum which on inoculation on two men produced typical superficial Tinea corporis. Therefore, from these observations there can be no doubt that, if cultures are taken early enough, the fungus can be obtained from the circulating blood.

Comparing the different routes by which Trichophytides may arise we may conclude, therefore, that in the majority of cases especially the generalised ones, the spread is by the haematogenous route but in less extensive ones, near the lesion, the spread may be externally, or in some cases as in the corymbiform lesions by the lymphatics.

Although we have seen that the lesions produced by haematogenous spread are due to the fungus itself circulating in the blood, some of the Trichophytides may not be produced by the fungus elements circulating in the blood and sticking in the skin capillaries of/

of the allergic skin and there producing a reaction which is seen as the Trichophytide. They may be due to the skin cell becoming sensitized to the fungus infection and the toxines of the fungus absorbed from the Kerion lesions producing a reaction when circulating in the allergic skin. This is especially suggested in the Scarlatiniform Trichophytide which looks so extraordinarily like the rash sometimes seen on injection of old Tuberculin in tuberculous cases. In such cases the rash may be due to the lighting up of a previous Trichophytide. BLOCH thinks that the fungus emboli do not act as parasites in the tissues but that the endo-toxines which they contain and which are set free by the rapid lysis of the spores and mycelium in the skin, produce the lesions. BLOCH had a case of Kerion of the scalp in a boy, aged 16 years, with numerous superficial foci of ringworm on the face and arms. In addition he had fever, swelling of the cervical glands, blood leucocytosis, and on the body a lichenoid trichophytide. The trichophytin skin reaction was strongly positive. After complete disappearance of all symptoms BLOCH began giving the patient intravenous injections of Trichophytin. He received in all 3 ccm. pure Trichophytin in 20 days. There appeared at first a scarlatiniform erythema and later on the trunk and limbs a typical lichenoid trichophytide.

In/

In another case which had a pustular trichophytide, after its complete disappearance, subsequent intravenous injections of Trichophytin produced a typical lichenoid trichophytide.

Thus it is possible that some Trichophytides especially the scarlatiniform and small lichenoid ones may be due to the toxines of the fungus.

From this general survey of the whole subject of Ringworm and allied fungus infections it is evident that these infections are not, as used to be supposed, purely local ones. In a great many cases the infection has great analogies with what occurs in infections like Tubercle, syphilis, etc. When sensitisation occurs the whole reactive mechanism of the body is brought into play with the production of a marked skin hypersensitiveness which leads to the production of the various skin reactions and rashes, which have been described.

## S U M M A R Y.

1. Ringworm, especially the deep seated varieties, produces general as well as local effects.

2. Injection of an extract of Ringworm fungus (Trichophytin) in cases of deep seated Ringworm in human beings leads to a local reaction at the seat of injection, a focal reaction in the lesion with a general reaction with rise of temperature and signs of intoxication.

3. These reactions are not as a rule present in cases of Superficial Ringworm.

4. Animals such as the guinea-pig and rabbit can be readily infected with certain kinds of fungus especially Trichophyton gypseum and Achorion Quinckeanum.

5. The lesions in animals heal spontaneously leaving behind a sensitiveness of the skin as evidenced by a positive cutireaction and a lasting immunity.

6. Neither the sensitisation nor immunity is specific for the fungus employed.

7/

7. Immunity is only produced by skin inoculation. Intraperitoneal and subcutaneous inoculation do not produce the same result.

8. Immunity is only produced by an actual infection. Injection of Trichophytin or Favin does not cause immunity.

9. The immunity is not in all cases absolute but may be only relative.

10. In animal experiments a second infection with Ringworm always runs a modified course from the first infection usually with a shortened incubation period and more rapid course. The lesion produced on a second inoculation is to be considered as a hypersensitive reaction rather than as a true reinfection.

11. Immunity produced by infection in animals can be inherited both when the mother's immunity is acquired before conception and during the pregnancy.

12. There is no evidence of any local immunity of the skin in areas which have been affected with Ringworm.

13/

13. Active Immunity to Ringworm and Favus has been produced by some workers by injection of Trichophytin and by rubbing dead fungus extracts into the skin. The immunity produced is only a partial one.

14. Attempts to produce passive immunity to Ringworm were unsuccessful.

15. In deep seated Ringworm the blood shows a polymorphonuclear leucocytosis. The same change also occurs in the blood in ringworm cases and immune persons after injection of Trichophytin. Healthy persons injected with Trichophytin show a lymphocytosis in the blood. A similar lymphocytosis was found in superficial small-spore Tinea capitis and in Favus capitis.

16. In deepseated Ringworms and to some extent in superficial Ringworms and in Favus, precipitins, agglutinins and complement-fixing bodies are present in the serum. All these reactions were found not to be specific for the fungus causing the disease but to occur more or less markedly with all fungus antigens.

17/

17. Cases of Ringworm, especially the deep seated varieties, give a positive cutaneous and intracutaneous reaction to fungus extracts (Trichophytin). This reaction may still be present as long as 29 years after an attack of Ringworm. Some observers found the reaction, especially the intradermal one, to be non-specific as it occurred in normal individuals and persons suffering from other chronic diseases. The intracutaneous reaction was also found to be quantitatively rather than qualitatively specific. In young infants the reaction was absent. It was also absent in the exanthemata and cachexia. This corresponds with the absence of the Tuberculin skin tests in these conditions

The trichophytin skin reaction is more marked on areas such as the abdomen where the trichophytides occur and in the skin round ringworm lesions, than elsewhere. Repetition of the test causes a gradual decrease in the severity of the reaction.

18. In the majority of cases of Favus cutireactions to Trichophytin and Favin were absent.

19. The author tested 11 cases of small spore Tinea capitis, 7 of large spore ringworm and 8 of Favus. The method used was the cutaneous Pirquet method. In each case extracts of the same fungus which caused the disease were used.

Extracts (A). (Containing toxines in fluid medium before fungus crushed).

Extracts (B). (Containing toxines in fluid medium after crushing of fungus).

Extracts (C). (Containing masses of crushed fungus)

were used. The A. extracts in no case produced a positive reaction. The B. and C. extracts in practically all cases gave similar results. Doubtful reactions were considered negative.

With B. and C. extracts in small spore Tinea capitis one case out of 11 gave a positive reaction, i.e. in about 9%.

In 8 cases of Favus one reacted positively, i.e. 12·5%. All the large-spore cases were negative.

20. A transplantation experiment by BLOCH demonstrated the fact that the skin cell itself is sensitised after an attack of deep seated Ringworm.

21. In certain cases the fungus of Ringworm and Favus may produce large cutaneous and subcutaneous granulomatosis masses consisting of round cells, epithelioid cells and giant cells. (granuloma trichophyticum (MAJOCCHI) and granuloma favicum). These granulomata differ from Kerion and the "lumpy" lesions of Tinea Barbae in that actual ulceration takes place.

22. Cases of Ringworm can be cured, without local treatment, by injections of Trichophytin. Intradermic injection was usually found to be more efficacious than subcutaneous injection. Rubbing in a Trichophytin ointment was also successful in some cases. Extracts of the actual fungi were much more potent than culture filtrates. Good results were obtained in both superficial and deep Tineas and in Favus but especially in deep lesions. Certain Trichophytins such as the one prepared from Anchorion Quinck. gave much better results then others.

23/

23. Encouraging results were also obtained by LOEB in the treatment of deep and superficial Tineas with a staphylococcal vaccine.

24. The author obtained disappointing results in the treatment of a few cases of small spore Tinea capitis with Microsporin. STRICKLER, however, claims to have cured similar cases by this method.

25. Generalised rashes may occur in cases of Ringworm both superficial and deep seated, and specially the latter. These are known as Trichophytides and Microsporides. They may be papular (Lichenoid Trichophytide or Lichen Trichophyticus) with or without horny spines (Lichen Spinulosus) vesicular, vesicopustular, pustular, eczematoid, scarlatiniform, erythematous (erythema multiforme trichophyticum) or nodular (erythema nodosum trichophyticum). A more localised corymbiform Trichophytide may also occur.

26. These trichophytides and microsporides are due in the widespread cases, to a haematogenous spread of the fungus but on the less/

less extensive cases the spread may be exogenous and in the corymbiform lesions may be lymphatic. In all cases an allergic condition of the skin is essential.

27. Favides may occur.

SENSITISATION/

# SENSITISATION AND IMMUNITY TO SPOROTRICHOSIS AND OTHER FUNGUS DISEASES.

Sporotrichosis resembles Ringworm in that it is due to a fungus - the Sporotrichum (Plate 21. ) which produces lesions in the skin very similar to the Granuloma Trichophyticum already described. It differs however in being a more widespread infection and in affecting internal organs as well as the skin. Only one case of this disease has been described in Scotland and that was a case reported in 1911 by the late Professor JAMES RITCHIE and Sir NORMAN WALKER.[974] This case was typical of the local inoculation of the fungus (Plate 21.) producing a primary lesion on the finger from which a spread took place up the arm by the lymphatics leading to the formation of numerous indolent swellings which suppurated and ulcerated. Besides this localised form numerous cases have been described, especially in France, where a generalised infection took place either following the local infection or without any previous visible point of inoculation. Multiple gummatous lesions may occur on the skin, mucous membranes, bones, muscles, joints, eyes and internal organs such as lungs etc.

As would be expected, cases of sporotrichosis /

sporotrichosis cause marked general reactions in the tissues. WIDAL and ABRAMI[967] and BEURMANN and GOUGEROT[967] have shown that the serum gives positive complement fixation reactions using the fungus as antigen. Positive agglutination reactions are also present. WIDAL, SICARD and GOUGEROT[967] showed the presence of precipitins in the serum and MILHIT[167] the presence of opsonins , Indicating that the patient is allergic, in sporotrichosis, intracutaneous and subcutaneous injection of dead fungus also leads to positive reactions. But all these reactions are not specific. The presence of any other fungus infection will cause these reactions to be present. BEURMANN and GOUGEROT also showed that an active immunity can be produced to sporotrichosis in animals by inoculation of dead or living cultures of the fungus. An anti-sporothrix serum can also be produced which has both immunising and curative properties.

The changes in the blood serum and tissues generally are much the same as can be produced by some Ringworm fungi but there is this difference that no general rashes resembling the Trichophytides have ever been described. Why this should be is rather curious because, as the cutireaction is present in these/

these cases, one would expect "Sporotrichides" to occur. Of course the multiple gummatous lesions which occur in general infections with Sporotrichosis might be looked upon as analogous to the nodular trichophytides, but they do not show the same tendency to spontaneous healing which the latter do. They are exactly similar to the lesions in granuloma trichophyticum, which also, as in SEQUEIRA'S case, do not tend to heal spontaneously. It is possible that in sporotrichosis and in granuloma trichophyticum there is too much fungus present in the lesions or it is too active in its growth to allow of the tissues destroying it easily.

Sporotrichosis although it leads to a sensitisation of the tissues, as evidenced by the cutaneous and blood serum reactions, does not confer a good immunity. The patient never seems to get beyond the sensitised stage.

In BLASTOMYCOSIS of the skin, GILCHRIST [967] found that the serum of the patient gave a positive agglutination and a positive complement fixation test with the parasite obtained from the lesions. These reactions as in Sporotrichosis are not specific, but may be useful to distinguish the lesion from others not/

not due to a fungus. So far as I can find, no cutaneous tests have been done in Blastomycetes. Where a general infection has taken place and been treated, the disappearance of the complement-fixation reaction may be useful in determining whether cure has taken place in the internal lesions or not. This also applies equally well to sporotrichosis and other general fungus infections.

In ACTINOMYCOSIS (Plate 22.) the researches of WIDAL and ABRAMI[967] have shown the value of the complement fixation and agglutination tests in such cases. ABRAMI, BRISSAUD and JOLTRAIN[967] have also shown that an anti-actino-mycotic serum which has a therapeutic value can be obtained. In this condition also I have been unable to find any report of cutaneous tests having been made.

HEMISPOROSIS is a fungus infection due to the Hemispora stellata which may produce cutaneous gummatous lesions as reported by GOUGEROT and CARAVEN[969] and AUVRAY.[961] Like all the other fungus diseases, general infections especially of the bones may occur. GOUGEROT and CARAVEN also found that the blood serum gives positive agglutination and complement-fixation tests with the fungus. As in all the fungus infections already described these reactions are not specific/

specific, but their presence in hemisporosis indicates that the fungus, if found, in the lesion, is the cause of the condition and not an accidental contamination.

In all those fungus infections therefore, there are evidences of sensitisation as shown by cutaneous and blood serum reactions. Although not specific these reactions may be of assistance in diagnosis. An attack of one of these diseases does not produce any marked immunity. The production of active immunity and the curative effect of anti-sera indicate that there is possibility of a considerable degree of immunity being produced, but the body never seems to go beyond a stage of hypersensitiveness. In this respect they resemble closely the other granulomatous diseases such as syphilis, in which the hypersensitive condition leads to a marked reaction on the part of the tissues, but not of sufficient intensity to cause a complete destruction of the invading virus.