

OBSERVATIONS ON SCARLET FEVER

AND ITS SPECIFIC THERAPY

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OBSERVATIONS ON SCARLET FEVER
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I. INTRODUCTORY.

Few diseases, exhibiting themselves in their typical symptom-complexes are more readily diagnosed than is Scarlet Fever. No disease, occurring in mild or atypical forms, taxes the acumen of the clinician to a greater degree than does this particular pathological entity. The more intimate one's experience of Scarlatina, the more respect one has for its protean manifestations.

In the past, the Specialist in Infectious Diseases has done much to lighten the onus of diagnosis for those whose duty it is to secure the best possible treatment of illness, but, until comparatively recently, it was impossible to combine laboratory and clinical methods in an attempt to elucidate the cause of a departure from the normal, when suspicion pointed to the possibility of Scarlet Fever.

With the exception of the last few years, the treatment of Scarlatina has been empirical and symptomatic. Hospitalisation has made expert nursing available for cases of the disease and at the same time has tended to reduce the spread of infection. The specialised/

specialised knowledge of those entrusted with the care of sufferers has helped to minimise the likelihood of permanent ill-health or physical crippling which may result. But there has been no specific treatment, which, because it is directed against the cause of the illness, is bound to have an influence for good, even if incomplete knowledge concerning it and its rational application may be responsible for results far from ideal.

Because of the co-operation between the clinician and the laboratory worker, it is now possible to predict with accuracy certain things when dealing with scarlet Fever in a given community. For example, susceptibles may be separated from insusceptibles by a simple intra-cutaneous test. Or, again, previous knowledge that a person was not immune to Scarlet Fever at the beginning of an indefinite illness may be the very detail required to establish a diagnosis of Scarlet Fever.

The laboratory has come to the aid of the clinician, too, in the supervision of contacts of Scarlatina and the possibility of producing a definite, if transitory, passive immunity to the disease in those persons exposed to it and not immune, is a powerful weapon in dealing with hospital communities, when accidental mixed infection has been introduced.

New diagnostic methods and therapies call forth both protagonists and antagonists. Some workers are willing to give unqualified praise, while others are critical, but, with the criticism of a mind already biassed against the innovations. As in other realms, so in Medicine the middle path is not uncommonly found to be the one trodden by those observers most capable of rational deduction. Whatever may be the merits or demerits of the comparatively new diagnostic and therapeutic agents in Scarlet Fever, one thing is certain and that is, that only prolonged tests and their common-sense interpretation can decide whether the new régime is a definite advance on the old, or whether the laboratory is so far impotent to lend material aid in combating a disease which is still far too common.

The causative organism of Scarlet Fever has been debated for many years, even though it has been known since 1885 that haemolytic streptococci could be recovered from the throats of scarlatinal patients. It was not until 1923 that a very definite fillip was given to the laboratory investigation of the disease. In that year, the classical experimental work of Drs George and Gladys Dick was carried out, establishing almost at once and practically beyond reasonable doubt the specific relationship between a haemolytic streptococcus/

streptococcus and Scarlet Fever. Pursuing their scientific work, the same observers experimented with the toxin found in the filtrate from cultures of the already isolated organism and they elaborated the technique of the intradermal test now bearing their name.

Some seven years before the Dicks produced experimental Scarlet Fever in volunteers, very important and now universally recognised observations had been made by Schultz and Charlton. Interest in these researches was now revived and the two sets of experiments were correlated. Several points are noteworthy, as for example, the demonstration that the blood_serum of persons giving a positive Dick Reaction does not have the quality of causing blanching of a scarlatinal rash. On the other hand, persons who do not react to the Dick Test are possessed of blood_serum which will give a positive Schultz_Charlton Reaction. It is also true that blood serum with the property of blanching the scarlatinal eruption need not necessarily be obtained from persons convalescent from Scarlet Fever, the phenomenon being observed sometimes when the reagent is obtained from ordinary healthy individuals with no history of an attack of Scarlet Fever. The very interesting observation that the disappearance of the rash at the site of injection does not occur when/

when the serum of patients in the early stages of scarlet fever is used, shows clearly that the reaction is due to the development of a special quality, as a result of having overcome an attack of scarlet fever or of having otherwise acquired an immunity to it.

Since the time of the experiments of Schultz and Charlton and the Dicks, a tremendous amount of research work has been done on the relation of streptococci to scarlet fever. The problem is not entirely, nor even principally, an academic one, for the clinical aim of the work is twofold, namely, to enhance the treatment of patients suffering from scarlatina and to protect susceptible persons against an attack of the disease, either by the production of an active immunity or, in emergencies, by bestowing a temporary passive immunity.

Unfortunately, the scientific exactness of the laboratory cannot always be observed in the clinical application of bacteriological and serological methods. Tests which are constant in vitro, may be very difficult to interpret or may even be quite useless on occasion in the hospital ward. For instance, one sees cases of scarlet fever, where the course of the disease ultimately establishes the diagnosis, but in which the Dick test is already negative on admission and in which the rash is so faded and characterless that/

that the Schultz Charlton reaction is very unsatisfactory. When one remembers, too, that in adults particularly, the appearance of the tongue and throat may be much modified in comparatively mild forms of the disease, it is easy to understand that in certain cases, usually, the very ones where definite tests would be of paramount value, laboratory methods may fall short of the ideal. Sometimes, in cases which are clinically Scarlet Fever on admission, a perfectly good rash is not blanched by the Schultz Charlton test. But it must be admitted that one seldom sees instances in which a diagnosis of Scarlet Fever is later confirmed by the clinical course, where all the laboratory tests are negative. Perhaps the most useful test is the Repeated Dick Test, the changing from a positive, in the early stages, to a negative reaction later being absolutely diagnostic of Scarlet Fever. Such repeated tests presume, of course, that in the meantime, the patient has not been treated by the injection of Specific Anti-Serum.

The control of diagnostic tests is admirable, test and control being carried out on the same person, but the same cannot be said for the therapeutic aspect of the question. All scientific tests must necessarily be controlled, but the real point at issue seems to be:— Is the clinical application of a laboratory recommendation/

recommendation strictly a scientific test? In the series of cases included in this thesis, the earlier work of collection included "controls", which I discarded later for reasons noted below.

It is pre-eminently in the realms of Tuberculosis that we consider the "soil" as fully as the "seed", but in all diseases the invader is only one element in the combination which allows of varying clinical manifestations in the same disease. If the type of disease-producing organism is a constant, as it most probably is in Scarlet Fever, then the only justifiable means of interpreting the value of any agent specifically modifying the action of that constant, is by comparing the clinical course of the disease in a "natural" subject with the clinical course in a specifically modified, but otherwise identical, subject. For example, it seems useless to say that the administration of Scarlet Fever Anti-Serum showed that cases so treated had only one-third of the number of complications found in untreated cases, unless it is known that before the attack of Scarlet Fever, both treated and untreated groups were physiologically and pathologically identical. One finds in actual practice that patients who, before admission, suffered from enlarged tonsils and adenoids are more likely to develop such complications as Rhinitis and Otitis than/

than patients whose throats were hitherto apparently normal. Similarly, it seems unfair to compare, either as a serum-treated case or as a control, the course of the disease in a child with obvious Congenital Syphilis with that in an apparently normal child. Again, children with Tuberculous Adenitis show, in one's experience, a greater tendency to suppurative conditions of the glands of the neck during the course of Scarlet Fever, than do ordinary, apparently healthy, children.

One could multiply instances of the incongruity of many reputed clinical "controls", but perhaps the following three cases may bear witness at least to the cogency of the arguments given above.

(1) A boy of 8 years was admitted to one of the Diphtheria Wards from a General Hospital. At this time, the particular ward of that General Hospital was infected with Scarlet Fever, Measles and Diphtheria and the Fever Hospital for the City had to accommodate the cases. Incidentally, it was not known at this time that there was mixed infection in the General Hospital Ward. It was believed that the cases were from quite separate wards. The boy had Diphtheria quite definitely, but was not a serious case. Two days after his admission, a diphtheria patient lying next to him and from the same General Hospital Ward developed Scarlet Fever and was of course appropriately dealt/

dealt with at once. The Medical Officer of the ward did not passively immunise those susceptible. Four days later, our patient developed Scarlet Fever, the case being, to all appearances, the mildest possible. During the course of the disease, there were Otitis, followed by Mastoiditis requiring surgical interference, Empyema, also requiring operation, and cardiac failure of a degree causing great anxiety. The case had been treated at once by specific therapy, but no doubt the second infectious disease being consequent on Diphtheria had much less than the usual resistance offered by the tissues which were already crippled by the diphtheritic toxins. But such an experience is no argument against the efficacy of Scarlet Fever Anti_Serum, although admittedly, it would compare badly with other mild cases receiving no specific therapy and yet presenting no complications.

(2) The second case was one of well-marked Congenital Syphilis admitted with typical, but not severe, Scarlet Fever. The child was given Anti_Serum and did quite well until Rhinitis made its appearance. This child was over five months in hospital, all kinds of treatment, including removal of tonsils, being tried to clear up the condition. Like the first case, this one affords no evidence at all against the usefulness of specific therapy.

The/

(3) The third case was one in which there were quite definite Tuberculous Glands in the neck, but without the slightest sign of breaking down when the patient was admitted with Scarlet Fever. Serum therapy was not used at all in this Hospital and the patient developed suppurative adenitis which necessitated a stay of over 4 months in hospital.

It may be said that since patients in whom previous pathological conditions existed are found both among serum-treated cases and "controls", there is no need to take special notice of them at all; the one will balance the other and the percentage results will remain unaltered. But even if they do, the whole comparison is a very unscientific one and the "control" loses its significance in dealing with comparatively small numbers.

It is not necessary, however, to cite cases of Scarlet Fever in which the physical condition of the patient prior to the attack played a part in modifying the course of the disease, in order to realise the impossibility to ensuring real control cases in the average Fever Hospital. Probably in very large Fever Hospitals such as those under the London County Council, it is possible during one epidemic to have such a wealth of cases that they can be paired off, one for specific therapy and one for "control", each pair/

pair comprising clinically identical cases. But even this is doubtful, when one remembers the abandon with which Scarlet Fever pursues its clinical course. All who have had a fairly wide experience in Fever Hospital Practice can call to mind numerous cases which defied anything resembling a definite prognosis. Sometimes the apparently mildest case possible, exhibits more than one troublesome and even dangerous complication; sometimes patients who, on admission, are extraordinarily ill, make an absolutely uncomplicated recovery. If there is one disease, other than Pulmonary Tuberculosis, in which, having made a definite diagnosis, it is unwise to venture a prognosis, it is Scarlet Fever.

Another factor which renders "controls" almost useless is relative overcrowding of Fever Hospitals during epidemics. By the term "overcrowding" no implication of failing to observe the Ministry of Health's Regulations as to cubic space per patient is intended; it merely signifies that a ward is fuller than usual. At such times it is not uncommon to get "Ward Epidemics" of Rhinitis or Otorrhoea or Cervical Adenitis. In my experience, such "epidemics" flourish particularly among cases which have not been treated by specific serum, but that does not invalidate the argument that it was principally the comparative congestion/

congestion of the wards and not Scarlet Fever to blame for the per centage of complications occurring.

It has long been known that the chief complication of measles, namely Broncho-Pneumonia, is most evident in "overcrowded" wards, but it is probable that this particular observation has been stressed because its dramatic significance sharpens our powers of deductive reasoning; whereas a few extra cases of Otitis or Adenitis cause little commotion in hospital routine and may fail to excite our curiosity.

If, then, controls are to merit the real meaning of the word, what conditions are necessary for selecting them? The following, at least, require consideration. First of all, the previous physical condition of the patient should be known. In this respect, I believe the School Medical Service could be of infinite value in the scientific investigation of clinical therapeutics. Every school child's medical record is carefully kept and the results of physical examinations are accurately recorded. Co-operation between School Medical Departments and Infectious Diseases Hospitals would do much to raise the standard of clinical "controls".

Secondly, only very large Fever Hospitals, where one epidemic will give several hundreds at least of "treated" cases and "controls", can hope to be able to/

to make selections of cases in pairs which can be said to be reasonably free from gross error.

Thirdly, hospital wards which are being used for experimental therapy should never be allowed to be filled to capacity, for if they are, the difficulties arising from "Ward Epidemics" of complications will upset the accuracy of results.

But surely the work in smaller Fever Hospitals has some value, even if a control system is, in the writer's opinion, unscientific. I think there is no doubt of that, but one must look elsewhere for a means of comparison between the results of "treated" and "untreated" cases. If Scarlet Fever Anti_Serum is specific, and apparently it has fulfilled all the conditions for such a description, cases treated with it should compare favourably with the text_book picture of the disease and its clinical course. After all, statistics which have been collected for years and whose averages are based on hundreds of thousands of observations must have a very small margin of error. There will be included, cases whose previous histories were definite liabilities as well as others whose physiological conditions prior to the attack were definite assets. There will be among the number, numerous instances of the apparently initially mild but eventually seriously complicated disease as well/

well as of cases which at first looked unusually severe but made straight for restored health without a single untoward incident. Good environment and bad environment previous to attack will be represented. Indeed, all manner of combinations of factors and fates will have subscribed their quota to the tabulated records.

Granting that the text-book error of averages is very small and assuming that Scarlet Fever Anti-Serum is specific and that only clinically or serologically definite cases of Scarlet Fever have been included in the experimental therapy, one should find that the clinical course of "treated" cases compares very favourably with the traditional records. If, in the discussion which follows, it cannot be shown that the administration of Scarlet Fever Anti-Serum increases the usefulness of the ordinary comparatively small Fever Hospital by reducing the Length of Stay in Hospital per average case as well as by minimising the incidence of complications both as regards number and severity, then it would seem that the therapy falls far short of the ideal.

It must be remembered, that the real value - if any exists - of specific treatment in Scarlet Fever can only be assessed with the passage of years. Two points are particularly important in this connection:- (1) Will the temporary passive immunity conferred/

conferred by the serum prevent the development of an active immunity to the disease, thereby rendering future attacks more likely in the same persons? Some authorities assert that the passive immunity obtained from Anti-Diphtheria Serum hinders the production of an active immunity as can be demonstrated by the number of antitoxin-treated patients who are subsequently Schick-positive. (2) Will the type of the disease change, as the result of the much modified environment to which the causal organisms are suddenly subjected with the institution of specific therapy? It must be admitted that this is more likely in connection with Active Immunisation, but the constant subjection of invading organisms to an induced specifically antagonistic environment appears to justify the hypothesis that alteration in virulence in one direction or the other may occur. And such change may not necessarily imply a parallel mutation in infectivity, so that epidemiological complications, at present entirely unforeseen, may arise.

But for the present thesis, only the immediate effects of treating definite cases of Scarlet Fever with a definite serum are being dealt with. A comparatively novel treatment, especially one which is strengthened by advocacy from the laboratory, at once calls forth criticisms, some well-informed and some worthless/

worthless. The layman deprecates "new fashioned" ideas and strongly objects to his children being the victims of experiment. It is of little use pointing out to him that what is experiment to-day may be routine to-morrow. Statistics are so confusing that even educated citizens are doubtful whether an advance has really been made.

On the other hand, the medical profession and Hospital Authorities are disappointed that Scarlet Fever is still a prevalent disease, in spite of the notification and isolation of cases and in spite of all the precautions consequent on these. Scarlet Fever is not a serious disease in the sense of being responsible for a large proportion of the death-rate, but failure to diminish its incidence appreciably and consciousness of the expense incurred in its treatment have made it expedient that new methods of attack on the disease should be made.

The best treatment for any disease is prevention, but apart from the avoidance of infection, it is difficult to sway the public mind in this direction. The "Dick Test", followed where necessary by Active Immunisation is the ideal method of attacking Scarlet Fever, but until the time comes when specific prophylaxis against Scarlet Fever becomes part of the routine existence of a child, there will be many cases of/

of Scarlet Fever requiring treatment and better treatment than has been possible hitherto.

This prompts the question of how infection occurs. One cannot always associate present cases of Scarlet Fever with a definite source of infection. Certainly nothing resembling actual contact is necessary. No doubt fomites play a not unimportant part; but chain infection by a system of carriers may be much more important than is sometimes thought. About 4% of discharged Scarlet Fever Patients, free from all complications, still retain virulent streptococci in the naso-pharynx. Their temporary or permanent immunity to these germs makes such persons a real source of danger to others. I believe this percentage to be a very conservative estimate, for it is quite astonishing, when one has ample opportunity of following up discharged cases, as those medical officers combining Public Health and School Medical Work have, to note, especially in winter, the number of cases of rhinorrhoea apparently dating from about a week or so after discharge from hospital.

Missed cases may also be more commonly associated with the spread of infection than is commonly allowed. During the past three years, at Routine Medical School Inspections, I have seen quite a number of children with definitely desquamating palms and soles. On careful enquiry/

enquiry, a history which was strongly suggestive of recent Scarlet Fever could be obtained in nearly every instance.

Another, and I think quite considerable cause of the spread of infection, is the person who has gained an active immunity from sub-infective doses of the causal organism. The large percentage of "Dick-Negative" reactions obtained in testing adults who have no history of an attack of Scarlet Fever strengthens such an argument. Pilot and Davis⁽⁶³⁾ found haemolytic streptococci in over 90% of a large number of persons in the bacteriological examination of normal throats. Cases of Scarlet Fever occur, too, where one is almost forced to the conclusion of auto-infection, namely a few days after the removal of adenoids and diseased tonsils. Patients who have been thus operated on appear to have harboured virulent haemolytic streptococci without developing an immunity to them or at least having only developed a very low degree of immunity which counted for very little when massive infection occurred through the fresh throat wound. The same relationship of enlarged infected tonsils to Scarlet Fever seems to be inferred by Hamer,⁽²⁷⁾ when he says that the removal of enlarged tonsils and adenoids in children who have not had Scarlet Fever is a measure which affords a considerable degree/

degree of protection.

Direct evidence of the infectivity of desquamated scales is lacking. Moore of Huddersfield, along with many others, holds that the presence of desquamation may be disregarded as evidence of infectivity in persons otherwise clinically convalescent from Scarlet Fever. He places great emphasis of the persistence of the infective agent in the nose and accessory sinuses. There seems to be little doubt that desquamation is simply the end result of a pathological proliferation of the skin layers in response to the dilatation of the peripheral bloodvessels; the latter is occasioned by the toxins of the disease. In favour of the infectivity of desquamated scales it is sometimes argued that the most evident desquamation occurs in parts where the rash has not been seen - namely the palms and soles. Such is simply due to the skin in those regions being so dense as to make changes in the underlying capillaries and skin papillae imperceptible and does not mean that identical changes do not occur. As a result of failure to demonstrate the infectivity of desquamated skin, most Hospitals now discharge patients who are otherwise apparently normal on the 28th day and several, since the institution of specific therapy, consider 21 days a sufficient period of isolation for the uncomplicated case.

In/

In order to show that a "return" case had been infected by the scales of a patient discharged while still desquamating, it would be necessary to demonstrate that the discharged patient gave negative bacteriological results from swabs of the naso-pharyngeal region.

The streptococcus of Scarlet Fever clings heroically to life, thus rendering necessary the utmost care in dealing with utensils, garments and bedding in scarlet fever wards. Unless nurses are particularly careful, they may be unwilling carriers of the disease to persons outside the Hospital, for Ruth Tunicliff⁽²⁷⁾ states that she has found the streptococcus on the masks worn by nurses. In this connection, all nurses do not wear masks and therefore it is likely that their nasal, buccal and pharyngeal secretions retain the organism for some time after contact with cases.

Milk has several times been closely associated with an outbreak of Scarlet Fever, and local epidemics where no other evident source of infection is found, should occasion suspicion of the milk supply.

But it must be admitted with regard to the spread of infection that practically in no instance is it possible to exclude chain infection - either direct or indirect - or at least to show that there has not been close association between the case and some person harbouring/

harbouring virulent haemolytic streptococci capable of causing Scarlet Fever, as a result of having had the disease, or of having been in close contact with some person who has recently "recovered" from the disease, or of being an immune chronic carrier.

Reverting for a moment to the question of auto-infection, one reads in all the text-books of the association of Scarlet Fever with Burns and I have been interested in quite a few definite cases during the past few years. I have never seen the disease follow minor burns and in this connection I think that in extensive burning it is not necessary to postulate the wounds themselves as the site of entry into the deeper tissues of streptococci already present in the skin, for I have convinced myself that there is a wide-spread inflammation of the mucosae and secretory tissues of the body - whether sympathetic or as the result of the general toxæmia or both, I am not prepared to argue - and keeping in mind the very high proportion of healthy throats harbouring haemolytic streptococci, it is not unreasonable to presume an enhancing of virulence and a resulting attack of Scarlet Fever.

Confronted as we are with innumerable difficulties in relation to Scarlet Fever; the expensiveness of its treatment, the inability to prognose with any degree/

degree of certainty, the reluctance on the part of the public to submit their children to Active Immunisation, we should welcome a new era in the treatment of the disease. Now that the specificity of the causal organism is beyond all reasonable doubt, as was, for all practical purposes, conclusively demonstrated by the Dicks in 1923, we look to Anti-Serum Treatment to revolutionise our statistics on Scarlet Fever, pending the time when public opinion will accumulate sufficient enthusiasm to take the final step in the complete ousting of a cause of much suffering and in some cases, considerable consequent physical disability; that step is Universal Active Immunisation.

It is therefore proposed to discuss in this Thesis:-

The effect of the Specific Therapy of Scarlet Fever on:-

- (a) Initial Toxaemia.
- (b) Incidence of Complications.
- (c) Length of Stay in Hospital.
- (d) Per centage of Return Cases.
- (e) Contacts (as a prophylactic).

OBSERVATIONS ON SCARLET FEVER
AND ITS SPECIFIC THERAPY.

II. HISTORICAL:- PART I.

Sydenham first described Scarlet Fever in 1675, differentiating it as a clinical entity distinct from Measles. Nothing of its bacteriology was known until 1885, when Haemolytic Streptococci were discovered in the throats of Scarlet Fever patients. Apparently, little interest was created in any possible specific relationship between this organism and the disease with which it had been found in association, for ten years elapsed before Marmorek⁽⁶⁶⁾ prepared an "antitoxic" serum by actively immunising a horse against the Haemolytic Streptococcus recovered from Scarlet Fever. There are no exact details of the potency of this serum as compared with that of present day preparations, but probably its antitoxic value was relatively low, for we are told that the results of treatment were very indefinite.

Other workers copied the example set by Marmorek and notable among these was Moser, who, in 1902, made a similar preparation and gave a favourable report of its usefulness in cases of Scarlet Fever. His findings were not upheld by other observers.

It is interesting to note that almost the first contact/

contact with the bacteriology and immunology of Scarlet Fever opened a controversy over the causative agent and arguments for and against a specific relationship with one of the Haemolytic Streptococci continue right up to the present.

(66)

Jockmann reviewed the work done in those early years and in 1905 he published a critical survey, expressing the opinion that the haemolytic streptococcus was not the cause of Scarlet Fever, but was a secondary invader. This work must have been considered of some merit, for the bacteriology of the disease was not further investigated by anyone of repute until nine years had elapsed.

(47)

In 1914, Mallory described certain bodies to which he gave the name *Cyclasterion scarlatinale*. They were polymorphic in form and occurred inside the epidermal cells of the Scarlet Fever patient as well as in the lymph spaces and lymph vessels of the skin proper. No confirmation was forthcoming that those bodies were in any way the specific cause of Scarlet Fever. Mallory later reported the finding of a small bacillus which he considered had some claim to being the causative organism.

An important advance was made in 1917, when Schultz and Charlton experimented on the rash of Scarlet Fever, using serum from convalescent patients. They/

They found that the intradermal injection of such a serum in acute cases of the disease, caused the disappearance of the rash at the site of the injection. Incidentally, a point which is often insufficiently stressed is that the rash does not appear again in the slightest degree in the tested area. Schultz and Charlton further found that the blood serum from a considerable percentage of ordinary individuals who had never, to their knowledge, suffered from Scarlet Fever, gave the same blanching phenomenon, but in no case could a positive reaction (blanching) be observed if the serum from early cases of the disease was used. At the time of discovery, comparatively little interest was taken in those clinical serological experiments, though now the Schultz Charlton Reaction is known to every student of Medicine. Two things at least were very clearly demonstrated by the two observers mentioned:— (1) That the blood of patients convalescent from Scarlet Fever contained an antitoxin which counteracted in a clinically specific manner the local toxic effects of Scarlet Fever on the skin. (2) That this clinically specific antitoxic property was developed in the blood_serum of many persons who, apparently, had never suffered from Scarlet Fever.

In this connection, it was mentioned in the introductory chapter that the part played by immune chronic/

chronic carriers in the dissemination of the disease should not be underestimated. Here is evidence, sufficiently accurate to be clinically valuable at least, that a considerable percentage of healthy individuals have developed such a degree of immunity to the disease that they can, without detriment to themselves, carry virulent Strept. scarlatinae and thus be a real danger to others.

(18)

Two years later, in 1919, Dochez, along with Avery and Lancefield divided the haemolytic streptococci into groups by the direct agglutination method. They worked on cultures of haemolytic streptococci prepared after swabbing the throat and naso-pharynx of soldiers in camp and they decided that six distinct groups could be made out. All six were toxigenic entities and antitoxins for each group were specific. During the next year, Gordon experimented with haemolytic streptococci recovered from cases of Scarlatina and he reported that 80% of these showed identical agglutination characteristics. But Park and Williams⁽⁶¹⁾ found, on experimenting with haemolytic streptococci isolated from 60 early cases of Scarlet Fever, that only 28% of the strains fell into one serological group, as tested by complete cross absorption. They also found that 15% of strains of non-scarlet fever cases fell into the same group as the above.

Drs/

Drs George and Gladys Dick carried out most valuable experimental work on the relation of Haemolytic Streptococci to Scarlet Fever in 1923. The throats of nine volunteers were swabbed with a pure culture of haemolytic streptococci isolated from the pus of a sore on the finger of a nurse, who developed Scarlet Fever. Two of the nine developed the typical disease. None of the subjects used for experiment had previously had Scarlet Fever, but it has to be remembered here, that the Dick Test was not yet discovered and there is therefore no proof that all or any of the seven, who did not develop symptoms, were in fact susceptible to Scarlatina.

(46)
Mair was at this time experimenting with the Schultz Charlton phenomenon and read a paper on the subject before the Ulster Medical Society on Dec. 3, 1925. He records in the Lancet that serum obtained for the test from a convalescent diphtheria patient gave a negative reaction in the blanching phenomenon. Thirty-eight days later, serum from the same patient, who had contracted Scarlet Fever four days after the initial test, gave a positive Schultz Charlton Reaction when injected intradermally in cases of Scarlet Fever. Mair suggested that the blanching is a toxin-antitoxin reaction and that the rash disappears because of the neutralisation of the local toxin which has been responsible/

responsible for the abnormal dilatation of the peripheral capillaries. He further states that no such blanching quality is found in the serum of infants unless it has been present in the mother's blood when the child was born, and that this specific quality is acquired as the result of an attack of Scarlet Fever. He notes, however, that at the time, the case may not have been diagnosed as Scarlatina.

In his 1925 paper quoted above, Mair⁽⁴⁶⁾ states that "The negative reaction (Schultz Charlton) of the sera of acute cases of scarlet fever is simply due to the fact that antitoxin has not yet developed".

Drs George and Gladys Dick, still pursuing their work on the strain of streptococcus isolated by them and which they considered had a specific relationship to Scarlet Fever, published in the Journal of the American Medical Association in 1924, the identification of a toxin, which gave a positive skin reaction, akin to the Schick Test in Diphtheria, in early cases of Scarlet Fever. Such a reaction was absent in convalescent Scarlet Fever patients and could be prevented in early cases of the disease by the previous intradermal injection of convalescent serum at the site of experiment. Park and Williams⁽⁶¹⁾ corroborated their findings.

So far, then, experimental evidence had given some/

some very suggestive results, making it highly probable that a haemolytic streptococcus had a very definite relationship to Scarlet Fever; that it produced an exotoxin capable of antitoxic neutralisation by means of a specially prepared antiserum. The practical therapeutic value of a possible specific anti-serum suggested itself at once. Already the serum or whole blood from convalescent patients had been used in various parts of the world in the treatment of early toxic cases of the disease. Experience had so far been rather limited, but results suggesting a wider clinical application had been obtained. Reiss and Jungman suggested that convalescent serum, after being carefully tested to exclude Syphilis, and the donors minutely examined to obviate the possibility of their being tuberculous, should be pooled and that 50 cc. to 100 cc. should be given intravenously in the treatment of severe cases of Scarlet Fever. Zingher used whole convalescent blood and advocated intramuscular administration, which has obvious advantages and apparently causes little local disturbance. He reported the effect of his therapy in 15 very toxic cases treated at the Willard Parker Hospital; 5 cases were strikingly improved, 6 others made an ultimate recovery and 4 died from various septic complications.

Soon/

Soon after describing their experiments with a toxin produced from the Berkefeld filtrate of media in which a certain haemolytic streptococcus isolated from a case of Scarlet fever had been grown, the Dicks published a report on the production of an anti-toxin, prepared by the active immunisation of the horse with increasing doses of media filtrate. Apparently, the therapeutic results of its use were very satisfactory.

In the same year (1924) Dr Dochez of New York contrived, by a most ingenious method, to produce an antitoxic serum against the *Streptococcus scarlatinae*. He succeeded in introducing an agar culture medium into the cellular tissues of a horse's neck and after allowing solidification to occur, this was inoculated with *Streptococcus scarlatinae*. The bacteria produced a toxin which, on reaching the circulation of the horse, excited the formation of an antitoxin. After allowing the antitoxin-forming process to continue for six months, the horse was bled and clinical tests of the potency of the serum made.

(66)

Blake, Trask and Lynch reported very good results from Dochez Serum, a single intramuscular injection in early cases being followed by a rapid convalescence without complications. They also noted that the intra-dermal/

intradermal injection of the serum in cases with early scarlatinal rash, gave the Schultz Charlton phenomenon. The rapidity with which the toxins of early scarlet fever blood serum were neutralised was also demonstrated by periodically bleeding the patient before treatment with the antitoxic serum and at short intervals afterwards. Negative Dick tests with the serum of treated cases were obtained as early as four hours after the administration of the serum. Robb, of Belfast, gives some interesting details of the application of Dochez's original antiserum in cases of Scarlet Fever; they will be discussed in the appropriate place.

In 1925, Messrs Parke, Davis & Co. claimed to have produced an anti-serum which was antibacterial as well as antitoxic, by immunising horses with injections of both toxin and of the living organisms. Reports of treating some thirty cases of Scarlet Fever with such a serum in Detroit have been published but the day of disease on which the serum was administered in each case is not stated, thus detracting from the clinical value of the work.

The experimental work of inducing an attack of Scarlet Fever in a manner identical to that employed by the Dicks in 1923 was repeated by various workers and results confirmatory of the original experiment were announced from Russia in 1925. Park also records an/

an accidental infection in one of his laboratory workers, who developed the typical disease.

The bacteriology of the complications of Scarlet Fever has not escaped notice. O'Brien,⁽⁵⁷⁾ after a convincing argument in favour of the existence of a streptococcus scarlatinae, goes on to say that Steven and Dochez and other workers obtained Haemolytic streptococci, identical with those found in Scarlet Fever, in such septic complications of the disease as Otitis and Septic Adenitis.⁽⁵⁸⁾ Okell takes the view that the rôle of the Streptococcus in Scarlet Fever is a dual one; it is toxic and pyogenic. The toxic effects are the result of the local infection, whereas the pyogenic results occur when the organism has reached the general circulation.⁽⁵⁸⁾ Okell states that anti-serum therapy has no effect once septic complications have been established, but that it appears to be valuable in the toxic phase of the disease.

From the foregoing summary of the historical investigation of the cause of Scarlet Fever, combining with that study the experiments to try and discover an anti-serum which will have a definite clinical value, the consensus of opinion seems to be in favour of a specific haemolytic streptococcus (or toxigenically identical group of haemolytic streptococci) as the cause of the disease and that antitoxic serum prepared/

prepared by special means therefrom is an important therapeutic agent in the treatment of Scarlet Fever. Birkhaug⁽⁸⁾ gives very strong evidence in favour of this specific relationship when he records that he isolated *Streptococcus scarlatinae* from 97% of the throats of 500 cases of Scarlet Fever and he says, "The significance of *Streptococcus scarlatinae* in its relation to Scarlet Fever is an established fact". He also believes that in scarlatinal antitoxic therapy we have a highly curative method of treatment. His early observations with Dochez's serum brought him to the conclusion that, given early in the disease, it hastened recovery and cases were uncomplicated.

⁽⁶¹⁾
Park and Williams, reviewing the history of the bacteriological and serological investigations of the causative organism of Scarlet Fever and problems resulting therefrom, have made the following deductions, which appear to provide an apt ending to this portion of the historical survey.

" 1. They (Haemolytic Streptococci) are found more frequently and in larger numbers early in scarlet fever throats than early in other diseased throats."

"2. They subside with the disease, but more sequelae produced by streptococcus occur after scarlet than after other diseases."

"3./

- "3. Serum from scarlet fever convalescents agglutinates
" streptococci from Scarlet fever throats".
- "4. Serum from animals after multiple inoculations with
" haemolytic streptococci from scarlet throats agglut-
" inates the majority of strains from other scarlet
" throats, and not strains from other diseases."
- "5. The serum from a horse inoculated in a special way
" by a haemolytic streptococcus from scarlet fever,
" produces blanching in scarlet fever rashes on intra-
" cutaneous inoculations just as does human convalescent
" serum (Schultz-Charlton reaction). Some normal
" serums blanch scarlet rashes but only from those
" who have had scarlet fever, or who give a negative
" Dick test."
- "6. A toxic filtrate from cultures of haemolytic
" streptococci from scarlet fever gives a positive
" intracutaneous reaction in beginning scarlet fever
" cases and a negative one in convalescents from
" scarlet fever. It is neutralised by convalescent
" scarlet fever serum and by serum from horses
" inoculated with the toxic filtrate. Many more
" investigations must be made before we can consider
" the relationship of haemolytic streptococci to
" scarlet as proved. We have already corroborated
" the Dicks' observations".

HISTORICAL:- PART II.

The very exact methods of the laboratory are apt to detract from the gradual unfolding of such clinical skill as is evidenced by reference to the general records of the disease. As was pointed out at the beginning of the introductory chapter, there is probably no disease which tries harder, and unfortunately, sometimes with success, to elude clinical ability in diagnosis than does Scarlet Fever. But this very difficulty has been a great urge to more detailed knowledge and this in turn has pointed the way to more successful treatment and more elaborate precautionary methods anent the spread of the disease. Probably, too, the tremendous obstacles in finally elucidating the bacteriology of Scarlet Fever are in part due to experimental complications which must arise when the laboratory worker seeks the co-operation of the clinician. If one could separate susceptibles from insusceptibles simply by their having a negative or positive history of a diagnosis of Scarlet Fever, quite apart from the added difficulty of assessing those who may have become immune by repeated or hoarded sub_infective doses of the causative organism, there would at least be a much greater percentage of young/

young children in whom the uniform clinical experimental results in the realms of prophylaxis and therapeutics would be very convincing. There must be very many cases of Scarlet Fever missed; perhaps because medical aid has never been sought; perhaps because of unfamiliarity with the very early or very late signs and symptoms; perhaps because the case was atypical or some localising sign (e.g. endocarditis or arthritis) compelled the attention, to the exclusion of a zymotic cause.

A few notes on atypical cases of Scarlet Fever during the last hundred years may be edifying, especially as some were quite severe but without any rash, and others which in the infecting case had a typical rash gave rise to instances with no exanthem whatever. All of which goes to strengthen the writer's opinion that although the "seed" is very important, the "soil" is of even more moment in deciding what characters the acquired disease may exhibit and to what complications the attack is likely to give rise.

In 1839, ⁽⁷²⁾ Taupin described five cases of Scarlet Fever from a common infective source; two of the patients exhibited no eruption. Shortly before this ⁽²²⁾ (1838), Eiselt published details of a case of severe Scarlet Fever in a woman of twenty, where there was no rash although marked desquamation occurred later.

(13)

Buttura, in 1857, described a series of cases, the first of which had a copious eruption, which had followed very protracted throat symptoms and signs. Four days after the appearance of the rash, another member of the family developed a sore throat, the disease being later diagnosed Scarlet Fever, although there was at no time, during its course, the slightest evidence of erythema. Another member of the family became ill, with very marked throat symptoms, but in this case too, no eruption ever made its appearance, although the case proved itself to be Scarlet Fever.

(13)

In the same treatise, Buttura reviews reports of cases of Scarlet Fever without rash dating from 1829.

It is not intended to detail all the historical accounts of cases of Scarlet Fever without eruption, such being only one of the anomalous forms of the disease. Afebrile Scarlet Fever is not so uncommon as is generally believed. McClanaghan described several such in a report of 150 cases of Scarlet Fever. The skin disease Erythema Scarlatiniforme probably exists as a clinical entity, but one cannot help feeling that some at least are cases of Scarlatina without rise of temperature.

(21)

Fourth Disease, as described by Clement Duke in the Lancet in 1894, need only be mentioned, as its existence/

existence is not now regarded as having been established.

From the above extracts of the literature, it is abundantly clear that:-

- (1) Scarlet Fever is at times a difficult disease to diagnose.
- (2) Cases may show a well developed rash without any co-existing abnormality of temperature.
- (3) There may be marked pyrexia and serious intoxication followed by troublesome complications, although no exanthem has been noted throughout the disease. In this connection, the peripheral hyperaemia observed during the rash of scarlet fever does not appear to be a necessary antecedent of desquamation, the occurrence of which is repeatedly described in cases of the disease exhibiting no eruption.

Although the disease cannot be said to be a serious one at the present time, the average case mortality being between 1 and 3 per cent, the disease was not always so benign and indeed, judging by the long and short periodicities of other comparable diseases, it may be that scarlet fever is passing through a phase of low virulence in its cycle. Its prevalence, infectivity and comparatively high case mortality occasioned great concern 60 or 70 years ago/

ago and were responsible for its inclusion in the various Acts of Parliament dealing with the notification and prevention of Infectious Diseases. Hospitalisation of cases and the investigation of the source of the disease as well as the supervision of contacts followed as natural sequences. Infectious Diseases Hospitals sprang up all over the country as well as in other countries and attempted by segregation of the patients to decrease the percentage number of deaths; to minimise the number of complicated cases and to curtail the spread of the disease. The first hospital for Infectious Diseases in London was opened by the Metropolitan Asylums' Board in 1871. At the present time there are nine such hospitals under that Body. In 1895, the first large Hospital for Infectious Diseases in Boston (U.S.A.) was opened; previous to this, there had only been such accommodation for cases as was provided by the erection of a pavilion by the trustees of the Boston City Hospital.

The Public Health Act 1875 provided in some measure for the prevention of the spread of infectious diseases. Sanitary Authorities were given power, subject to the necessary certificates having been completed, to cleanse and disinfect any house or part of a house so filthy as to endanger health or likely to promote the spread of infectious diseases.

Hospital/

Hospital accommodation could also be provided, as well as suitable apparatus for dealing with the disinfection of articles removed from the infected patient and his dwelling.

Further powers to facilitate the hastened subsidence of epidemics of infectious diseases were conferred on Sanitary Authorities by the Epidemic and Other Diseases (Prevention) Acts 1883. The Infectious Diseases (Notification) Act 1899 made the corresponding adoptive Act of 1889 compulsory, so that it was now the duty of anyone in attendance on a case of certain scheduled Infectious Diseases, of which Scarlet Fever was one, to notify the case to the Medical Officer of Health of the district in which the disease occurred.

At first, the compulsory notification of cases of Infectious Disease was not viewed with favour by some sections of the medical profession; it was regarded by many as a breach of confidence, while others considered that the fee offered was not commensurate with the time and trouble involved. Nowadays, no practitioner thinks of notification as other than one of the details of the day's routine.

OBSERVATIONS ON SCARLET FEVER
AND ITS SPECIFIC THERAPY.

III. AETIOLOGY AND DIAGNOSIS.

The strict division of diseases into "epidemic", "endemic" and "sporadic" has become more difficult as science and its philosophic interpretation have advanced. More and more it is realised that natural processes - and even disease may be included in the most comprehensive meaning of that term - progress in curves. Not only are there long periodic curves, but, if these be represented graphically, it is also found that each one is itself made up of a series of curves, each of which constitutes a minor period. In the case of Scarlet Fever, it appears that at intervals of something like thirty years there has been completed a cycle of the infective and morbid variability. During this period, about six minor exacerbations occur, each showing a tendency to regular increase and decrease within limits which are modified by the position of the minor period on the curve of the major period. Further, the five-yearly period is itself divisible, each year showing a season of prevalence of the disease with an intervening period of comparatively low incidence. The whole of the epidemic curve is linked up by the persistence/

persistence of endemic cases, which occur particularly in populous areas.

In dealing with the epidemiology of Epidemic Influenza the term "Epidemic Constitution" has been frequently used; terms implying the same idea date back to the earliest days of medicine. It seems that the formation of an epidemic constitution depends partly at least on the increasing percentage of susceptibles in a community and determines not only the number of cases likely to occur, but also the severity of the disease and the probable case mortality. It is very suggestive in Scarlet Fever that the minor epidemic period is five years and that the largest number of cases in an epidemic occurs in children in the second quinquennial age group. Scarlet Fever is uncommon in the first year of life, even in epidemic periods. If a child of that age has just escaped infection during an epidemic, the probability is that he will not, other things being equal, contract Scarlet Fever during the ordinary seasonal outbreaks. Thus he arrives at the age of six years when the next five-yearly exacerbation occurs. There must be, at each epidemic period, a very great proportion of such susceptible people available, according to the above hypothesis, leading, as it were, to a rapid as well as an ideal sub_culturing scheme which increases the invading powers of the organism as well as its virulence/

virulence.

When a certain proportion of the susceptible population has been infected, with the production of an active immunity, either with or without external evidence of the disease, the infective powers and the virulence of the organism diminish and the epidemic draws to an end. This is a most likely and important factor in the epidemiology of the periodicity of Scarlet Fever. But that there are other considerations is evident when we remember that, during the epidemic itself, the case mortality is lowest when the disease is most prevalent and that there is evidence, in comparing corresponding seasons of the year, of an inverse ratio between the number of cases occurring and the amount of rainfall.

With regard to the first of these, the causative organism may gradually undergo some change in its character; this may be the result of a continued renewal of an adverse environment (commencing active immunity) as the infecting agent is carried from person to person. Successive generations of the causative organisms probably undergo progressive crippling as the result of their ancestors' battle for existence. Thus, although the infective powers of the germs may yet remain undiminished, the virulence is gradually decreased. Continuance of an adverse environment, with/

with the additional fact that the likelihood of fresh soil lessens as the percentage of immune persons rises, may further modify the organism so that it now lives almost as a commensal. In this way its infectivity is lowered. On this theory, the virulence is decreased before the infective powers and would account for the period of highest case mortality failing to coincide with the period of greatest incidence in an epidemic. In actual fact, that order is observed.

With reference to the second point, the increase in rainfall may not be so mysterious in its effect on the prevalence of Scarlet Fever as at first appears. The common obvious things may be missed if we begin at once to probe for a learned scientific explanation. One thing that does happen in rainy weather is that susceptibles - mostly children - are less frequently in close contact with each other, having to remain indoors. But, of course, the laying of dust carried out by rain may also be important and there may be other obscure influences resulting from the barometric conditions which make rain possible. For example, a decrease of atmospheric pressure may cause an increased peripheral circulation, in which the mucous membranes probably share, thus being fore-armed with an excess of leucocytes when invasion by organisms occurs.

Predisposing/

Predisposing Causes:- Any factor, physiological or pathological, which puts a strain on the maintenance of health, is important in rendering a susceptible individual less resistant to Scarlet Fever. The most important may be grouped generally under three headings, viz, (1) Local (2) General (3) Environmental.

Local causes are principally those affecting the naso-pharynx and fauces and the chief is probably enlarged tonsils. Accompanying enlargement of the tonsils, adenoids are frequently found and not uncommonly the person so affected is a mouth-breather, thus fulfilling all the conditions necessary for the successful lodgment of organisms in the throat region. Catarrh of the nose and chronic congestion of the throat from such conditions as cough may also play some part in increasing the likelihood of infection.

Of general predisposing causes, a division may be made into temporary and chronic. Convalescence from another illness, excessive fatigue at the time of exposure to infection, anaemia, are all instances of the former, while congenital syphilis, tuberculosis and malnutrition are among the chronic group.

Environmental predisposing factors are self evident: Poverty, overcrowding, insanitary condition of the dwelling and clothing and uncleanliness of the body all tend towards lowered vitality and render infection more likely.

Infection:- The spread of Scarlet Fever may be either direct or indirect. It is often quite impossible to relate a case of the disease to some previous known case, but, bearing in mind the probability that many children almost certainly pass through very mild and undiagnosed attacks of Scarlatina, the writer is of the opinion that direct spread is much commoner than is generally stated. Infection is possible from the time the first symptom of the disease occurs; the duration of infectivity is very uncertain, there being no rapid laboratory method, such as can be utilised in the case of Diphtheria, of assessing the convalescent's freedom from infection. The chronic carrier must also be remembered, although his rôle is more properly described under indirect methods of spread.

Fomites plays a part in the spread of Scarlet Fever, but not uncommonly this particular method is stressed unduly. Clothes, toys, bedding, books have all been incriminated and in some cities and towns books from public libraries are destroyed, when these are discovered in an infected house. In this latter connection, Nesbit⁽³⁶⁾ has recently shown that although he carefully traced the redistribution of library books which had been in the possession of persons contracting Scarlet Fever during an epidemic, he could not find a single instance where the volumes in/
in/

in question could be said to be responsible for the spread of infection.

In his book, "Sources and Modes of Infection" Chapin of Michigan states that he does not now carry out disinfection when a case of Scarlet Fever is removed to Hospital and apparently there is no noticeable increase in the prevalence of the disease.

Common towels and handkerchiefs, cups and cutlery readily convey infection, as also do tongue depressors and appliances used in the treatment of scarlatinal throats.

It has been said in the past that schools play a considerable part in the dissemination of Scarlet Fever, but the consensus of opinion now is that they are relatively unimportant. I have personally made extensive and close investigations on this point during epidemics and so far I have been unable to satisfy myself that attendance at school is potentially dangerous during an outbreak of the disease.

Domestic animals and vermin have also had attention in connection with the spread of infection, but evidence of their culpability is far from convincing. Ker⁽³⁶⁾ states that the prevalence of Scarlet Fever synchronises to some extent with the prevalence of fleas. It was Hamer who first cited the apparent connection between the prevalence of fleas and the increase/

increase in the number of cases of Scarlatina, but Goodall⁽²⁷⁾ is inclined to think there is no close connection between them. He says that in London the period of increased incidence of Scarlet Fever shows no close correspondence to the period of maximum flea prevalence and he further points out that although the disease was very much in evidence in 1920 and 1921, those years showed the lowest recorded "flea-curves".

Infection has never been traced to water or to sewage, but the milk supply has been quite definitely associated with local and even more widely distributed outbreaks of Scarlet Fever. The Hendon epidemic is the classical instance. But it has to be remembered that milk is in close association with human beings during its production and distribution and may thus become inoculated, apart from any ulcerated condition of the udders and teats of the cows. Indeed, the sores themselves may be the result of infection from a human agency, thus, at the outset at least, being simultaneously infected with the milk and not having any primary causal relationship to the infected milk. W.G. Savage has put forward the view that ulcerated udders may merely act as carriers of the micro_organism, which is quite innocuous to the cow but capable of producing disease in human beings.

Auto_infection is possible too, as was mentioned in the introductory chapter. Scarlet Fever may develop within/

within a few days of the removal of tonsils and adenoids and also soon after extensive burning.

Age and Sex:- On the question of the age-period showing the greatest incidence, all the text-books appear to be agreed. Scarlet Fever is overwhelmingly a disease of young persons, the second quinquennial period furnishing the largest number of cases.

(27)
Goodall states that after the age-period of greatest incidence, the remaining five-yearly age-periods take their places of relative importance in the order of their succession. (36)
Ker says that only a small proportion of the total cases is made up of persons over (73)
15 years of age. Tidy is of the opinion that over (64)
80% of cases are under 10 years of age. Pope, in analysing the statistics of Chapin, in Providence, finds that the age of greatest incidence is 6 years. Further, he deduces from the figures that practically 75% of cases are under 10 years and nearly 90% of cases are under fifteen years.

In the 106 cases, in which the writer is to discuss the effects of serum therapy in Scarlet Fever, the following is an analysis of the age incidence:-

Age/

Age Distribution of Cases.

Age Period	0-1	1-5	5-10	10-15	15-25	25-35	35-45	Totals.
Number of Cases.	0	32	26	8	31	8	1	106
Percentage	0	30.2%	24.5%	7.6%	29.2%	7.6%	0.9%	100%

With regard to the importance of sex in statistics of the disease, opinion is divided. Ker gives it as his experience that sex has little influence on the incidence of the disease, but that females appear to be slightly more susceptible than males, particularly after the age of 10 years. Goodall states quite definitely that more females than males are attacked at all ages. Pope came to the conclusion, after a very detailed analytical study of records of 40 years' cases, that, up to the age of six years, males provided a slender majority of cases, but after the age of 7 years, there was a marked excess of females at all ages.

The following table shows the sex distribution of cases for each age group for 106 cases of Scarlet Fever.

Sex Distribution of Cases for each Age Group.

Age Period	0-1		1-5		5-10		10-15		15-25		25-35		35-45	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Number of Cases.	0	0	17	15	9	17	2	6	9	22	3	5	0	1

It will be seen at once that this series of cases bears unmistakable witness to Pope's assertion.

Diagnosis:- Why it has been chosen to discuss a few points in the clinical and serological diagnosis of Scarlet Fever in connection with this treatise is that the maximum possible benefit from specific therapy cannot possibly be attained until cases are sent to hospital earlier than obtains at present.

Day of Disease on admission in each Age and Sex Group.

Age Group	0 - 1		1 - 5		5 - 10		10 - 15		15 - 25		25 - 35		35 - 45	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1st Day	-	-	2	4	1	2	-	1	-	1	-	-	-	-
2nd Day	-	-	7	3	5	7	-	3	2	5	-	3	-	1
3rd Day	-	-	3	2	2	5	2	1	3	6	2	-	-	-
4th Day	-	-	3	2	-	3	-	-	3	6	1	1	-	-
5th Day	-	-	1	1	1	-	-	1	1	1	-	1	-	-
After 5th Day	-	-	1	3	-	-	-	-	-	3	-	-	-	-

It will be readily seen from the above tabular representation that practically half of the cases which will be under special discussion later, were admitted on or after the third day of disease.

On attempting to make a diagnosis of Scarlet Fever, undue prominence should neither be given to clinical findings nor to serological methods to the exclusion of the/



the other. All the advantages of both should be made use of and any symptom-complex which still leaves grave doubts as to the possibility of the disease being Scarlet Fever is almost certainly not due to that particular zymotic disease. Naturally, this only applies when dealing with early cases, for one not uncommonly sees children who may have had a mild attack three or four weeks previously and in whom little remains except some desquamation of the hands and feet. To apply the Dick Test in such a case and, getting a negative result, thereby diagnose Scarlet Fever is quite illogical, unless there is a definite record that at a very recent date (2 months or so previously) the child was Dick-positive. In this connection, much help could be given by Medical Officers of Health who are also School Medical Officers if every child were Dick-tested on entering school and at subsequent Routine Medical Inspections. For it is generally either the M.O.H. himself or one of his assistants with special knowledge of Infectious Diseases who is called in to consult on difficult cases. If it were known that a certain child was definitely Dick-negative, a negative diagnosis could readily be given in the majority of cases. Of course, the test can be applied when the patient is seen with reference to a diagnosis, but in such circumstances, time has to/

to be allowed before a reading can be made (probably 18 to 24 hours), thus losing valuable time before passive immunisation may be induced, as well as exposing other members of the family to a needlessly prolonged risk of infection.

The Schultz Charlton Reaction is more expeditious, as quite a reliable reading can be taken within six to eight hours and the results are trustworthy in the vast majority of instances. Even before the rash is more than a blush, the test may be applied and it is the writer's opinion that it is best, in early cases, to make two injections, one on the trunk where the rash is already evident and one on a limb, where the rash has not yet appeared. When the necessary time has elapsed, any ambiguity in interpreting one of the reactions will undoubtedly be moved in one or other direction by the findings in the second experimental area.

Where possible, both the Dick and Schultz Charlton tests should be applied in difficult cases with a rash and if both give no reaction, there is very strong presumptive evidence that the disease is not Scarlet Fever. In serious toxic cases with a poorly developed rash, the limited experience of the writer is that the Dick test is more often negative than positive, and this may be due to the patient being already overwhelmed/

overwhelmed with toxin and quite unable to react further to any added dose. An analogy is seen in the case of Acute Miliary Tuberculosis, where the intracutaneous tuberculin test is often negative.

In hospital, the repeated Dick Test is very useful, where a diagnosis is very doubtful. If a patient is definitely Dick-positive on admission and becomes Dick-negative during the course of the disease, with the proviso that no anti-serum has meantime been given, then a diagnosis of Scarlet Fever is perfectly justifiable. There is, however, a great advantage if definite information can be got from the Schultz-Charlton reaction, because it makes early treatment possible for patients who are really ill. On the whole, the test is a very reliable one; so much so, that the writer was accustomed to apply it as a routine test in cases with a definite rash, at the same time as giving the therapeutic dose of Anti-serum. After anti-serum, the rash is not sufficiently quickly altered in intensity, as a rule, to render the Schultz-Charlton test valueless. The relatively concentrated action of the serum used in the intracutaneous test produces changes far in advance of those instituted by the intramuscular therapeutic injection, so that, in cases where the patient is obviously ill, the simultaneous test and therapy occasion no loss of time. In this respect, I think its usefulness is even greater than the Dick test in suitable cases, for if serum/

serum be administered with the latter, the rapid diffusion of immune bodies will prevent any reaction at all.

When applying toxin or antitoxin tests or both in the diagnosis of Scarlet Fever, it must be kept in mind that neither is infallible. If, however, both point in one direction, the likelihood of error is small. If one only is used a certain proportion of cases will be found where no help is derived from the test and it is because of this that it is necessary to remember two points in particular. The first is that the reaction of the body to disease cannot be tabulated with precision. Immunity and susceptibility are not opposites with a great dividing space between them, but merge gradually into one another by a long chain of imperceptible gradations. This is simply another example of how nature works in gentle curves, or in other words, she has no water-tight compartments in her universe. The second point is that laboratory methods of diagnosis of Scarlet Fever are at present unable to replace the clinical interpretation of symptoms and signs.

It is not intended to discuss the Differential Diagnosis of Scarlet Fever, from the clinical point of view, but a short summary of one or two difficult cases may be of interest. I have only seen one case of/

of Scarlatina in a Negress. She is a nurse in one of our General Hospitals and a popular as well as capable member of the staff. She became ill, headache and sore throat being complained of. Her temperature was 102°F. I was asked to see her with a view to making a diagnosis, as this was very important from the point of view of the rest of the staff, as well as of the children in the ward where she had been on duty. On examination, the tongue was not typical and naturally the skin was not very helpful, although on standing well back from the patient, there was a warm tint about it, suggesting a rash hidden by pigment. The skin had the typical pungent feeling. The pulse was not unduly accelerated. The throat was very congested, both tonsils were a little enlarged and were covered with soft exudate. The soft palate showed quite definite punctation, although the colour of the puncta was modified by the increase of pigmentation of the mucosa. The cervical glands lying under the angles of the jaws were enlarged and tender. On stretching the skin at the flexures of the joints, purplish lines were seen and considered to be "flexure_staining". The chest was normal and the heart sounds closed and full; the cardiac rhythm was not toxic. A diagnosis of Scarlet Fever was made and the course of the disease confirmed this. Here is an instance where the Dick Test and the Schultz_Charlton Reaction were quite/

quite impotent to help. The appearance of the throat and mucous membranes, together with the burning sensation transmitted by the patient's skin and the presence of "flexure staining" were the main diagnostic features.

The second case is one which I saw recently in a General Hospital Ward. Prior to admission there, the patient - a child of 8 years - had been taken suddenly ill with headache and vomiting. There had been no sore throat. Convulsions had rapidly set in, followed by coma, and there had been and still was strabismus and slight rigidity of the neck. The abdominal, knee and plantar reflexes were normal. The breath smelt strongly of acetone and the urine contained acetone and diacetic acid. There was a uniform bright scarlatiniform rash with typical flexure staining. No paralysis other than the strabismus could be made out. Meantime, the patient had been treated with Chloral Hydrate and later, Morphia to control the convulsions and colon injections of glucose with gum had been given, along with intramuscular injections of insulin. Schultz-Charlton and Dick Reactions were not carried out. I should have mentioned that the tongue was heavily furred and there was a suggestion of enlargement of the tongue papillae. The throat was normal. A diagnosis of Scarlet Fever was not made, but the case was removed to the Isolation Hospital. Eventually the disease was definitely found/

found to be Polio-Encephalitis. The difficulties in this case were many. The administration of morphia and chloral hydrate causes scarlatiniform rashes in certain people. Continued vomiting gives acetonaemia, just as do Diabetes Mellitus and other diseases associated with acidosis. Coma is found commonly in children suffering from practically any acute disease. The strabismus and neck-rigidity suggested a condition having its origin in the central nervous system, but both may occur in gastro-intestinal conditions as well as acidosis from any cause, in pneumonia and any acute illness where meningism is a symptom. The main points against a diagnosis of Scarlet Fever were (1) The normal throat and buccal mucosae. (2) The extraordinary uniformity of the rash. (3) The absence of the burning sensation felt on touching the skin of Scarlet Fever patients. (4) The predominance of Central Nervous System symptoms and signs, especially squint.

The Schultz-Charlton and Dick Reactions would have been specially valuable here, but there were no facilities for carrying them out. In cases such as this, a previous record of the person's reaction to the Dick Test would be of supreme value, in so far that the definite knowledge of the patient's being Dick-negative would practically rule out Scarlet Fever as a possibility in many very difficult cases. One keeps/

keeps in mind, of course, that occasionally the dose of the organism is so massive as to render the immunity - all immunity is essentially relative to the dose and virulence of the infecting micro-organism - insufficient to deal successfully with the invader. There is the additional point too, that one sees cases from time to time at Centres for Prophylaxis of Infectious Diseases, in whom the Dick Test is variable in the reaction it produces in the same person at different times. But, taken as a whole, the knowledge of the result of a recent test in children, would be invaluable in doubtful cases.

Another case which was very interesting from the point of view of diagnosis, both for the patient's own welfare and that of other patients who might have been unduly exposed to infection, was one which was admitted to Hospital as Scarlet Fever and Laryngeal Diphtheria. The child looked extremely ill and was struggling for breath. The tongue was not typical of Scarlet Fever; the throat was clean; the buccal mucous membranes were congested; the conjunctivae were oedematous (Brownlee's Sign of Measles); there were symptoms of coryza and signs of bronchitis; a faint scarlatiniform rash was present on the upper part of the trunk; Koplik's spots were seen.

A diagnosis of Measles with prodromal scarlatiniform rash and severe laryngeal signs was accordingly made and/

and confirmed next morning by the appearance of a brilliant morbilliform eruption. During the patient's stay in Hospital, the Dick and Schick tests were carried out and were positive. These were done as a routine which was instituted so that (1) the re-arrangement of patients was facilitated in the event of a case of Scarlet Fever or Diphtheria occurring in the ward; (2) passive immunisation against either or both diseases could be carried out if necessary; (3) active immunisation against Scarlet Fever could be induced during the patient's stay in Hospital and the parents advised, if necessary, to bring the child to the Centre for Prophylaxis to have the necessary Anti-Diphtheria inoculations.

The last case I wish to mention in respect of diagnosis is a very recent one. A child was brought to the School Clinic for Minor Ailments, suffering from a Boil on the arm. He looked rather ill and the mother said that there had been vomiting the previous day and the child had complained of headache but had no sore throat. Examination showed that the tongue was heavily furred and the papillae were a little enlarged. The fauces were congested; the tonsils were clean. The soft palate showed definite punctation of a bright scarlet colour. There was a faint blush with very indefinite characteristics of a scarlatiniform rash on the sides of the neck and the upper part of the chest. The temperature was 100°F. and the pulse/

pulse rate 130 per minute. The point of importance is that the case might very easily have been missed, for conditions such as boils are rather wearing and the headache and vomiting, in the absence of sore throat, might quite pardonably have been attributed to the general malaise of a staphylococcic infection.

Second attacks of Scarlet Fever are not uncommon and naturally their occurrence lends support to the variations noted in the reactions to the Dick Test when applied to the same person at intervals. Goodall, in his text-book says that "It must be considered doubtful whether third or fourth attacks ever occur". I have, in the records of the Infectious Diseases Hospital in Wakefield, one case in which typical Scarlet Fever occurred three times in one individual. The second attack commenced about one week after recovery from the first and was followed in about two and a half months by a third attack. The correctness of each diagnosis is, I think, unquestionable. We can only presume that such a person simply fails to acquire a permanent immunity, the reaction to the disease being somewhat analogous to the average person's behaviour to pneumonia; namely, there is the production of the necessary temporary immunity, but when the stimulus of the invading micro-organism is removed, there tends to be a return, in the biochemical composition/

composition of the blood and tissue fluids, to the pre-existing normal.

In closing this chapter, I should like to mention how valuable I have found Rumpel-Leede's Sign, first taught me by Dr James of the City Fever Hospital, Edinburgh, in coming to a diagnosis of Scarlet Fever, when the case is not seen until the rash has completely disappeared.

OBSERVATIONS ON SCARLET FEVER AND
ITS SPECIFIC THERAPY.

IV. SELECTION OF DATA FOR ASSESSING THE VALUE OF
SPECIFIC THERAPY IN SCARLET FEVER.

(27)

Temperature:- Goodall states that the temperature usually reaches the normal at about the seventh to the tenth day. A critical fall is occasionally, but not commonly, seen. ⁽³⁶⁾ Ker records that the fastigium may last from one to four days, but in most instances not more than three and the normal is gained by a rapid lysis, lasting from three ⁽³⁸⁾ to five days. Savill notes that the temperature gradually subsides to normal in five or six days in mild cases. ⁽⁷³⁾ Tidy describes the temperature as reaching the normal in five or six days and mentions that a fall by crisis is unusual.

All of the above recorded opinions are unanimous that about a week is required for the normal temperature to be regained. This close correspondence signifies that the effect of any treatment on the temperature is a useful gauge of its efficacy in combating the toxaemia of Scarlet Fever.

(27)

Aspect of the Throat:- Goodall believes that/

that the appearance of the throat varies much, even in mild cases. Ker⁽³⁶⁾ describes in detail the various appearances of the throat encountered in the disease but does not state whether they are liable to great variation in cases which might be considered almost identical, in the early stages of Scarlatina.

In the writer's opinion, the variability of throat symptoms and signs is too great to be useful as a gauge of improvement in the general condition. Not uncommonly, throats which look extremely affected clear up very quickly, while, on the other hand, one or two crypts of the tonsils may continue infected for a considerable time, although the patient's general condition makes normal progress. In Toxic Scarlatina, the throat lesions are usually comparatively mild and their improvement is entirely dissociated from any satisfactory general reaction to the disease. On the other hand, in Septic Scarlatina, the condition of the throat is a reliable indication of the direction of progress of the disease.

Taken in wide survey, the aspect of the throat affords little guidance as to the course of the disease in ordinary cases.

(27)

Duration of Rash:- Goodall fixes the limits as from twenty-four hours to nine or ten days. Ker⁽³⁶⁾ gives the duration as seldom exceeding four days.

Savill/

(68)

Savill writes that the eruption has generally completely disappeared by the seventh or eighth day. Tidy says the rash usually lasts two to three days and is generally absent by the seventh or eighth day. Price records as follows:-

"The rash may be quite transitory or may last a week or even longer. Generally speaking, it is more pronounced in severe attacks, but sometimes attacks which are quite mild show rashes of considerable intensity and persistence."

There are such wide variations in the records of the duration of the rash in Scarlet Fever that the time of its disappearance appears to be of little help in assessing the progress of the patient. In this connection, I have seen many brilliant rashes disappear in just over twenty-four hours in patients not treated by Anti-Scarlatinal Serum, just as I have seen less pronounced rashes linger for about ten days.

Desquamation:- Goodall mentions that the commencement of desquamation may be delayed for some weeks. Ker lays it down that the process begins about the seventh day of the disease. Price notes that desquamation is a well known characteristic, but the degree to which it occurs is very variable.

The writer is of the opinion that the texture of the/

the patient's skin has a good deal to do with the time of commencement of desquamation. In young children, it starts very early as a rule, although the flakes are so delicate and powdery as to avoid ordinary notice. As a rule, there is nothing to be noted in the general condition of patients to account for speeding up or retarding the commencement of desquamation, nor is the early onset of desquamation in any way indicative that recovery from the disease will be hastened or that freedom from complications may be anticipated.

So far, it would appear that the effect of any treatment on the temperature is the most reliable guide as to the antitoxic properties of that therapy. This has led me to disregard the effects on the rash, throat, and desquamation, generally recorded in papers dealing with the specific therapy of Scarlet Fever.

The early toxæmia in Scarlet Fever is, unfortunately, only a comparatively minor consideration in endeavouring to evaluate the serum therapy of the disease. Septic complications are the dread of the clinician and their inhibition or amelioration by a serum of an "antitoxic" nature causes some division among the experts in the laboratory. Before summarising the records of text-book authorities and others as to the incidence of complications, it will probably be wise to consider:-

(1)/

- (1) The association of the Streptococcus Scarlatinae with septic complications of Scarlet Fever.
- (2) The complete rôle of the Streptococcus Scarlatinae in the disease.
- (3) Do local and general immunity exist in quantitative parallel?

(63)

(1) Pilot and Davis found that practically all apparently normal throats contain haemolytic streptococci in the crypts of the tonsils. But that does not mean that those organisms are serologically identical with the Streptococcus scarlatinae. Many workers have included experiments with antisera to such organisms in their investigation of the specificity of the Schultz Charlton Reaction and have found that such antisera do not give the blanching phenomenon.

(57)

O'Brien says: "With regard to septic complications, "there seems little doubt that the majority of the "organisms causing otitis, septic adenitis, etc., "belong to the Streptococcus scarlatinae group, for a "number of workers (Stevens and Dochez 1926; J. Smith "1926; etc.) have isolated strains from such complica- "tions, which agreed with the Dochez-Dick strains in "every test which was applied".

(19)

Dochez and Bliss found that a haemolytic streptococcus identical with the Streptococcus scarlatinae could be isolated from all/

all the complications - e.g. suppurating glands, otitis, nephritis etc. - in all cases of Scarlet Fever.

(58)

Okell states that there is little doubt that both the toxigenic and the pyogenic activities of the scarlet fever coccus are responsible for most of the clinical manifestations of the disease and that the injection of sterile toxin alone can produce a syndrome bearing the closest resemblance to scarlet fever.

(2) Most authorities are agreed that the *Streptococcus scarlatinae* can be isolated from the vast majority of cases of septic complications of the disease. If such is the case, then there may be a state of bacteraemia at some stage in the disease, followed by localisation in various organs and tissues which become the seat of complications. Okell (58) believes that the streptococcus plays a dual rôle in Scarlet Fever; it produces a toxin which diffuses through the body in the early stage of the disease; later, the micro-organism itself invades tissues like any other pyogenic organism. He believes the pyogenic function to be more or less separate immunologically from the toxaemia function. This does not necessarily mean that specific antitoxic therapy has no effect on septic complications of the disease, for (58) Okell himself states in the same contribution to the literature/

literature on the subject that "It is not clear to us if the preventive property of the "antitoxin" is purely an antitoxic effect". Proceeding, he mentions that if there is the presence of an antibody other than antitoxin, the preparation of a serum rich in such antibody might be valuable in treating human beings in the pyogenic stages of the disease. Those pronouncements deal with animal experimental work, where-
 by injection of antitoxin, five hours before the intravenous administration of 5 c.cm. of young broth culture of the scarlet fever streptococcus, prevented the death of the experimental animal. The difficulty in interpreting the real significance of such experimental work in its application to the therapy of the naturally acquired disease, - Scarlet Fever - would seem to be that the induction of a primary "septic-
 aemia" is not really analogous to the pyogenic phase of a condition which commences as a toxaemia. The *Streptococcus scarlatinae* may and probably does require to be preceded by the effect of its toxins, manufactured at the local seat of infection, before it is capable of attacking in its pyogenic capacity.

(58)
 Okell subscribes to this theory when he says "The aggressive action of the toxin seems to be an important factor in the invasive power of the streptococcus."

(3) Probably immunity of the body generally to the toxins of the *Streptococcus scarlatinae* in the later stages of the disease, implies some degree of local immunity of all the tissues. The essentially different functions of the organs and tissues of the body render some more likely to certain diseases, while others are apparently unaffected. Variations in tissue susceptibility are probably partly due to physico-chemical differences among themselves, but may they not also be due to actual quantitative differences in the supply of immune bodies reaching them? It is significant that most of the septic complications of Scarlet fever affect mucous surfaces and secretory organs. Such tissues depend almost entirely on the diffusion of lymph for their nutrition and as antitoxic substances are contained in the globulins of the blood serum, these may not diffuse readily, thus causing a persistently low standard of immunity in tissues nourished in this way. Another factor which may operate in encouraging the involvement of certain tissues in the pyogenic activities of the streptococcus may be the "fixation" of toxins by them, thereby rendering toxin-antitoxin neutralisation difficult or impossible and as a result, they are infinitely more vulnerable when general invasion by the micro-organism occurs.

The/

The affinity between certain tissues and particular toxins is well known as is also the selective tissue and organ invasion by micro-organisms. A parallel affinity probably exists with reference to antitoxin, not necessarily being exhibited by the same structures as the above. If these are facts, it is at once seen how irregularly distributed the toxins and antitoxins concerned in any disease may be. This may actually have some bearing on the incidence of complications in disease. The whole subject of local and general immunity is very involved and there are no very useful records of experimental work on it, but it seems to be beyond doubt that the specialisation of function necessary in the various tissues and organs of the human body, render them peculiarly vulnerable in varying degrees to the effects of certain toxins and the invasion of certain organisms, without necessarily being able to avail themselves correspondingly of the antitoxins circulating in the system generally.

NOTES ON THE COMPLICATIONS OF SCARLET FEVER:-

Albuminuria:- In the early stages of any acute infectious disease, albuminuria is common and does not imply any injury to the renal tissue. Goodall states that actual nephritis occurs as a complication about the end of the third week, but may be much earlier (first week) or very late (twelfth week). The occurrence of nephritis has little to do with the severity of the disease, unless it occurs very early, when the type of case affected is the severe anginous variety. In 3,888 cases observed during the years 1904-07, Goodall found that albuminuria occurred in 8% of cases of Scarlet Fever. He distinguishes late albuminuria from actual kidney involvement, but finds it difficult to draw any definite line between them. The artificial distinction is probably based on degree of involvement of the kidney rather than the real pathological significance of the occurrence of albumin. Ker states that patients between the ages of 5 years and 7 years are most liable to nephritis and he gives the percentage of total cases affected with either albuminuria or nephritis as below 10%. Savill states that 7.9% of cases are affected with albuminuria and an addition of 4% with true nephritis. Tidy considers the percentage incidence of kidney involvement to be only 5% and mentions/

mentions that this complication is commoner in children.

(36)

Adenitis:- Ker records that about 13% of cases develop adenitis, which, of course, does not include the early enlargement of glands during the acute throat symptoms. Goodall and Tidy note the occurrence of this complication commonly in conjunction with Nephritis.

(27)

Arthritis:- Goodall, in giving a record of 3026 cases of Scarlet Fever in the South-Eastern Hospital, analysed by Hodges, states that this complication occurred in 3.8% of cases. He mentions that the most frequent age period is from 8 years to 25 years and that the condition seldom lasts longer than a week. Ker gives the percentage incidence as 4% and the time of occurrence as between the 6th day and 12th day. He is also of the opinion that arthritis seldom lasts more than a week. Savill considers that this complication is seen in 6.7% of cases of Scarlet Fever. Tidy gives the period of onset as the end of the first week of the disease and believes the condition to be very frequent in adults, but uncommon in children.

In connection with arthritis, the writer has been interested to note in nearly all of the cases developing this complication, that, during the eruptive period, the rash was very blotchy on the limbs/

limbs with special localisation round joints. Indeed, in cases untreated by serum, an anticipatory diagnosis has frequently been made. No doubt others interested in infectious diseases have similarly noted this apparent connection between the character and distribution of the rash on the limbs and the incidence of joint complications.

Otitis:- Layton gives the percentage incidence (26) in a large series of cases as 8.61%. Gibson states that 9% of Scarlet Fever patients developed Otitis. (76) Logan Turner deals with the findings of Gardiner, Consulting Otologist to the City Fever Hospital, Edinburgh, stating that Gardiner finds that from 6% to 10% of Scarlet Fever patients suffer from purulent Otitis Media, which occurs most frequently in the first and second weeks of illness. About 50% of the cases are associated with adenoids and mucopurulent rhinitis. In 300 cases of otorrhoea in Scarlet Fever, Gardiner found that 7% developed a mastoid complication and of these, ten required exposure of (68) the lateral sinus at the time of operation. Savill quotes Caiger's figure of 15% as the case-incidence rate of Otorrhoea and Otitis Media in Scarlet Fever. (73) Tidy says that ear complications are rare after the (27) age of 15 years. Goodall believes there is no comparatively fixed period when the ear complications of/

of the disease may make their appearance and gives the percentage of cases exhibiting Otitis Media as 11% ⁽³⁶⁾ Ker records 10% as representing the prevalence of the complication and finds that it usually makes its appearance within three weeks of the onset of Scarlet Fever. It may last for several months, but as a rule the discharge ceases in a week or a fortnight. An interesting record of 1757 cases of Scarlet Fever, giving the percentage incidence of Otitis Media for the sexes separately is contained in the Medical Officer, ⁽⁵²⁾ where it is shown that the occurrence in males (12%) is slightly higher than in females (10%). ⁽⁴⁰⁾ Lämél minutely investigated a series of cases and found that 12.9% had had Otitis Media during the course of the disease.

Rhinitis: - ⁽³⁶⁾ Ker finds 8% of cases complicated by Rhinitis, including septic cases, where the condition exists from the commencement of the illness and probably should not therefore be counted as a true complication. He states that it is most frequently observed in young children.

Heart Affections: - Dilatation and hypertrophy of the heart may occur as the result of Scarlatinal Nephritis. Endocarditis or pericarditis may accompany scarlatinal arthritis, there being a tendency for the aortic valve to be affected, rather than the mitral/

(36)
 mitral. Ker writes that endocarditis is by no means common and only occurred in 0.58% of 22,096 cases treated in the M.A.B. Hospitals. He believes that even this figure would be too high for the incidence of this complication in the Edinburgh City Fever Hospital. According to the same writer, pericarditis is still more rare and generally occurs in septic cases only. He mentions an interesting point in connection with the not uncommon variability of temperature during convalescence, when he notes that slight endocarditis may account for some otherwise unexplained temperatures. Goodall⁽²⁷⁾ agrees as to the rarity of heart complications in Scarlet Fever. Tidy⁽⁷³⁾ also comments on the extreme rarity of endocarditis and states that the malignant variety, as well as purulent pericarditis, only occurs in Septic Scarlet Fever.

The rarer complications are not given in percentages in the text books consulted and need only be mentioned in passing. Opinions appear to differ as to the frequency with which Bronchitis and Broncho-pneumonia occur. Goodall⁽²⁷⁾ states that Bronchitis is not uncommon in children and Broncho-pneumonia may supervene. Price⁽⁶⁵⁾ lays it down that neither Bronchitis nor Broncho-Pneumonia is common, but that Aspiration Broncho-Pneumonia may occur in septic cases. Tidy⁽⁷³⁾ believes/

believes that Bronchitis frequently complicates the disease. ⁽³⁶⁾ Ker notes that Broncho-Pneumonia may play some part in causing death in septic cases and rarely is it seen during the desquamative period in ordinary cases. His experience is that this complication is usually trivial, comparing it to the type of lung complication found in Measles and Whooping Cough.

Oedema of the lungs may be seen during the course of acute nephritis. In this connection, it is interesting to remember that pilocarpine was at one time used very considerably in inducing increased action of the skin in cases of acute nephritis with a greatly diminished secretion of urine. Pyaemic infarction of the lung sometimes occurs in the rare condition of Lateral Sinus Pyaemia. Lobar Pneumonia is extremely rare and of correspondingly extreme gravity.

All forms of paralysis as well as peripheral neuritis have been noted as complications of Scarlet Fever. Other nervous and psychical phenomena occur, among them being Chorea, Tetany and Maniac-Depressive Insanity. With reference to Chorea, the writer has several times noted the development of Chorea in young Scarlatinal patients who have some considerable time previously suffered from this toxic nervous disability, as ascertained by reference to their school medical cards.

Diphtheria/

Diphtheria is a not uncommon complication of Scarlet Fever, apart from the cases which at the outset are found to be a combination of the two diseases. ⁽³⁶⁾ Ker writes, in this latter connection, that as many as from 10% to 15% of Scarlet Fever patients have been found in different years, in the Edinburgh City Fever Hospital, to give positive results when swabs have been examined, on admission, for the presence of Diphtheria Bacilli. When developing in the convalescent stage, its incidence is probably closely bound up with the "carrier" question. Suppurative tonsillitis or secondary sore throat is not at all uncommon in children, probably about 3.0% being so affected, although Goodall ⁽²⁷⁾ says it is rare. It may be very severe and accompanied by rhinitis and even suppurative adenitis. Retropharyngeal abscess may co-exist. The mouths of convalescent children appear to be liable to ulceration of the mucosa, causing considerable general upset from difficulty in eating.

⁽³⁶⁾ I am encouraged by Ker's submission of the not infrequent occurrence of Jaundice as a complication of Scarlet Fever. Quite a few writers do not mention this condition at all and most others simply include it in the list of very rare events in the course of the disease. In the introductory chapter of this thesis, the question of "ward epidemics" was mentioned and, /

and, although I cannot account for it in any really satisfactory manner, I have had, on two occasions, "ward epidemics" of jaundice in connection with Scarlet Fever. The degree of pigmentation has always been comparatively slight but quite definite.

Percentage of Total Complications:- Few of the authorities on Scarlet Fever give the incidence of total complications of the disease in the form of a percentage, but fairly accurate estimates can, of course, be obtained by adding together the figures quoted for individual complications. According to this method, it is found that Ker's total complications (not complicated cases) would be just over 40%; Goodall, Price, Savill and Tidy are found to be in comparatively close agreement with this figure.

(16)
Cushing states that, previous to the introduction of antitoxin treatment, 45% of cases were complicated.

(26)
Gibson found only 26% of complications in his cases, but the number dealt with was comparatively small, so that no useful purpose is served by considering this figure. During an epidemic of the disease, which is apparently one of uniformly greater severity in Warsaw than in our cities, Chodzko reported that 50% of cases were complicated. Probably the average text-book figure of 40% is a reliable one.

Septic Cases:- The occurrence of this type of Scarlet Fever would, at first sight, appear to negative the/

the opinions of those authorities who lay it down that the toxic action of the *Streptococcus scarlatinae* is necessary to prepare the way for the later pyogenic invasion. But "septic" does not imply a condition of septicaemia, but simply an exaggeration of the local septic process in the throat and associated structures. The ordinary toxic symptoms and signs of Scarlatina are present, but with their abatement, there is no parallel improvement in the throat condition. Septic Scarlet Fever is seen in its most devastating form in children and especially in those about the age of five or six years. The case mortality is very high, and those who recover do so after a very protracted convalescence. In the older editions of his work on Infectious Diseases, Ker was of the opinion that Septic Scarlet Fever appeared to owe its clinical signs to a secondary infection with pyogenic organisms and that death, so frequent in this class of case, was the result of Septicaemia rather than of infection with scarlatinal germs. Now that a haemolytic streptococcus has, beyond all reasonable doubt, been identified as the causative organism of Scarlet Fever, it is no longer necessary to postulate secondary pyogenic invasion.

(27)

Toxic Cases:- Goodall's experience is that few sufferers from Toxic Scarlet Fever recover. This form/

form of the disease is always fatal in children and the duration seldom exceeds two days. ⁽³⁶⁾ Ker describes various types and is of the opinion that this form of Scarlet Fever practically never constitutes more than 1% of cases. He is in agreement with all other authorities that the condition is a very fatal one.

Length of Stay in Hospital:- As early as 1911, Dr Lauder of Southampton considered 28 days to be a sufficient minimum period of detention in hospital for Scarlet Fever patients and in 1914 he reported that the average length of stay per patient was from 32 to 36 days. Moore of Huddersfield appears to have had extraordinarily good fortune as the result of reducing the minimum period to 28 days, for he attained the highly commendable, if somewhat incredible, average duration of stay per patient of 29 days. ⁽⁵³⁾ In a special article on Scarlet Fever and Diphtheria in Aberdeenshire, the figure of 37.7 days is quoted, the minimum period being again 28 days.

Return Cases:- The elapse of a period of not more than 28 days is the one generally accepted in tabulating "return" cases, which are considered by some authorities to constitute some 3% or 4% of all Scarlatinal cases. Personally, I have never found more than 1.5% in which definite evidence of infection/

infection from a previously discharged case could be established. In this connection, two interesting episodes occurred quite recently. A maid was required in the Fever Hospital and one of the applicants, who was unsuccessful, was the sister of a patient admitted with Scarlet Fever seven days later. This is not, of course, an instance of what would have been a "return" case, but it is an example of co-incidence, for, if the above applicant had been successful in obtaining employment at the Hospital and had paid a visit to her home before her sister's admission with Scarlet Fever, it would have been difficult to convince the parents that the infection had not, in fact, been conveyed directly from the institution to their home. The second case is even more striking: A girl was discharged at 10 a.m. after an attack of Scarlet Fever and her sister was admitted with the same disease in the afternoon. Instances of this kind could be multiplied almost indefinitely and probably comprise a not inconsiderable proportion of "return" cases.

The length of the period of isolation in Scarlet Fever and the percentage incidence of "return cases" do not vary in inverse ratio. Indeed, many observers are of the opinion that the shortening of the minimum detention in Hospital to 28 days has had the effect of/

of lowering the percentage of "return" cases. But, nevertheless, one cannot help feeling a little uncomfortable when a "return case" is admitted, for, although to the initiated, there is really no reflection on the persons concerned in the discharge of the infecting case, yet the general public form strong opinions on the subject. There seems to be little doubt that the persistence of catarrh of mucous membranes is the most important factor in such infections and in winter particularly, patients, who are apparently incapable of conveying infection at the time of discharge, do harbour the *Streptococcus scarlatinae*, whose virulence may be suddenly increased by a recurrence of catarrh after discharge.

Cameron carried out investigations on behalf of the M.A.B. and found that about 4% of discharged Scarlet Fever patients were still infectious and the percentage was much higher in those affected with enlarged tonsils and adenoids. Stevens and Dochez examined a large number of throats of Scarlet Fever patients who had been in hospital for one month and they found the *Streptococcus scarlatinae* in 47.3%. The majority of cases examined had inflamed tonsils.

The presence of residual desquamation in discharged cases has been considered by some authorities as a contributory cause of "return" cases, but there appears/

appears to be little ground for continuing to regard this matter seriously. Moore of Huddersfield has pointed out that, instead of there having been an increase in the number of "return" cases following the discharge of incompletely desquamated scarlatinal patients, the number has actually decreased.

If the matters discussed in this chapter are materially bound up with the efficiency of any therapy in the disease, as the writer most assuredly believes they are and if the Antitoxic Serum Therapy of Scarlet Fever is specific, then there should be, - other details such as dosage, day of disease on administration of serum, potency and properties of the serum being carefully considered, - undeniable evidence that real benefit accrues in the disease in all its varied manifestations and implications. It is now the writer's intention to analyse minutely the effect of Antitoxic Serum Therapy on 106 definitely diagnosed cases of Scarlet Fever and compare them with the foregoing and with the findings of various workers.

OBSERVATIONS ON SCARLET FEVER AND
ITS SPECIFIC THERAPY.

V. THE ANTITOXIC SERUM TREATMENT OF SCARLET FEVER:-
PRELIMINARY.

Before commencing the analytical study of this form of therapy, certain preliminary details are worthy of some consideration, namely:-

- (1) The uniformity in potency of the serum used.
- (2) Dosage. Should all cases be treated with serum?
- (3) Method of administration:
 - (a) In normal patients.
 - (b) In sensitised patients.
- (4) Day of disease on which the therapy is instituted.
- (5) Serum rashes and Anaphylaxis.
- (6) The dangers of sensitisation. A means of recognising serum-treated patients.

(1) Potency:- The preparation of an anti-serum for Scarlet Fever has been carried out in different ways by different workers. Dochez⁽⁶⁶⁾ may be considered the pioneer in the production of a specific antitoxic serum, which he carried out by the actual inoculation of the *Streptococcus scarlatinae* into agar media, which had previously been introduced aseptically into the cellular tissues of a horse's neck/

neck. Drs George and Gladys Dick used increasing doses of sterile filtrate obtained from the *Streptococcus scarlatinae*. Both of those sera were entirely antitoxic in character. In 1925, Messrs Parke Davis & Company attempted to produce and claimed to have produced an antibacterial and antitoxic serum. Other reputable firms and notably Messrs Burroughs Wellcome and Company quickly took up the study of this new therapy and set about preparing specific antiserum. Whether any serum prepared from the bacterial antigen of the *Streptococcus scarlatinae* is really antibacterial is a matter for grave doubt. But as the initial symptoms of Scarlet Fever are those of toxæmia, it is the antitoxic content of a given serum which is important in early treatment.

At first, Scarlet Fever Antitoxin was unconcentrated and this probably accounted for the large number of cases of serum rash recorded by early observers. Previous experience with concentration methods for Diphtheria Antitoxin soon pointed the way to a suitable technique for similar elimination of the major protein fraction in the new antitoxin. Pick and Atkinson had shown that antitoxins were present in the globulin fraction of an immune serum. Later, Gibson and Banzhaf showed that it was the pseudoglobulins with which the antitoxin was closely associated and they described a method of fractioning blood/

blood serum to obtain increased antitoxic properties in a smaller volume. Banzhaf further modified the technique, so that an antitoxic serum containing from four to six times the original quantity of antitoxin in a given volume was obtained. Such a serum only contained about half the quantity of protein found in the same volume of unconcentrated serum.

So far, the procedure in the preparation of Scarlet Fever Antitoxin presents no great difficulties, but when the question of standardisation is approached, there are barriers which have not yet been surmounted. (66)

Robb of Belfast says "The fact that the ordinary laboratory animals cannot be made use of to measure the antitoxic value of the serum is a great handicap". He goes on to say that because human beings have to be used in testing and because even with this test there is such a great margin of error in estimating potency, he is afraid that serum of low antitoxic value may find its way on to the market. In this connection, (58) Okell points out that probably comparatively few people, especially in the older age groups, can be taken as being virgin soil so far as scarlet fever infection is concerned.

Two principal methods have generally been utilised in estimating the potency of Scarlet Fever Antitoxin

(a) The Schultz Charlton Test (b) Neutralisation of a known toxin.

In/

In the case of the Schultz Charlton test, it is estimated that even where definite and apparently comparable results are obtained, the error is much too great to allow any reliance to be placed on it in estimating the antitoxic content of curative serum. In addition, the Schultz Charlton test is not positive in 100% of cases. This may be due, as Smith says in an article in the Journal of Hygiene, to the division of the Scarlet Fever group of Streptococci into several sub-groups, as is found in carrying out agglutination tests. ⁽⁶⁰⁾ Park has also pointed out that there may be groups of Scarlet Fever Streptococci which produce toxins, not identical but having an antigenic overlap.

(b) Neutralisation of a known toxin:-

Drs McCoy and Dyer of Washington prepared an antiserum of high antitoxic content in 1926 and this is issued as a provisional standard serum, pending the finding of some really satisfactory method of evaluating anti-⁽⁷⁸⁾toxin. Prior to this, Wadsworth, Kirkbride and Wheeler suggested an antitoxin unit, namely the amount of antitoxic serum which will neutralise 100 skin-test doses of toxin. This is analogous to the unit for other antitoxins, substituting skin-test doses in human beings for minimum lethal doses in the standard guinea-pig. This unit is quite unsatisfactory, because of the great variability of the reaction obtained in susceptible individuals on injecting a skin-test dose of/

of toxin. The latter itself is only an empirical quantity, being 0.1 c.cm. of a 1-1,000 dilution of Dick toxin. Even when the same individual is used for repeated experiment, it is found that the minute doses of toxin produce, in time, refractory phenomena. In the same article, the three workers mentioned above state that white goats may be used very satisfactorily for skin tests, but Parish and Okell do not agree that any reliance may be laid on the results in those animals.

The potency of Scarlet Fever Antitoxin is therefore to be regarded as quite empirical and reliance has to be placed on its therapeutic effects in the disease itself as a gauge of its antitoxic content. This is highly unsatisfactory but inevitable at present. For this reason, it is important to procure the serum from firms of high standing, in order to ensure a more or less constant level of therapeutic value. My own observations lead me to prefer Messrs Burroughs, Wellcome and Company's serum, because of the much less evident disagreeable sequelae of the therapy using their preparation. I do not know whether this firm succeeds in reducing the protein content to a lower level than do Messrs Parke, Davis & Company but my experience, in using antitoxins prepared by the last mentioned firm, both for Diphtheria and Scarlet Fever, convinces me that serum reactions are much/

much more common than when the English firm's preparations are employed.

In dealing with a new batch of Scarlet Fever Antitoxin, I always test it against the remnant of a previous batch, comparing the Schultz-Charlton reactions carefully. I know that this method is not at all scientific, but I am bound to admit that the apparent constancy of antitoxin content is quite remarkable. The difference in the percentages of serum reactions produced by the sera of the two firms mentioned does not seem to me to be accounted for by any difference in therapeutic worth.

(2) Dosage:- Before the advent of Antitoxic Serum prepared by actively immunising the horse against Scarlet Fever, Reiss and Jungman recommended the intravenous injection of 50 cc. to 100 cc. of pooled convalescent serum. Zingher advocated even larger doses, up to 200 cc., intramuscularly.

(61) Park observes that fresh normal blood injected intravenously in doses of 120 cc. to 240 cc. and repeated, if necessary, in three or four days has shown very beneficial effects in some desperately ill cases.

The original Dochez Serum was unconcentrated and in sending a supply to Robb of Belfast, a dose of (66) 30 cc. to 40 cc. was recommended. This antitoxin was later produced in a concentrated form and the dose/

dose now advocated was 20 cc. Still later, the dose was reduced to 10 cc. Peters⁽⁶²⁾ and Allison used from 10 cc. to 40 cc. of the concentrated antitoxin, according to the severity and duration of the disease. Banks⁽³⁾ used a uniform dose of 10 cc. during an epidemic in a Public School, but every case was treated intravenously, instead of by the usual intramuscular method. Later, he⁽²⁾ modified the dose, but not the method of administration, giving children from 5 cc. to 10 cc. of the Parke Davis Serum, and adults from 10 cc. to 20 cc. McGarrity⁽⁵⁰⁾ recommends doses of 10 cc. to 20 cc. of concentrated antitoxin or 40 cc. of the unconcentrated type. Craig⁽¹⁵⁾ treated Scarlatina Simplex with 10 cc. of specific antitoxin; toxic cases were given 20 cc. and septic cases had a mixed serum therapy, consisting of 10 cc. of Scarlet Fever Antitoxic Serum and 50 cc. to 100 cc. of Polyvalent Antistreptococcic Serum. Harries⁽³³⁾ considered 12 cc. of the usual concentrated antitoxin an adequate dose. Where he had employed the earlier unconcentrated variety, he gave 25 cc. Cushing⁽¹⁶⁾ records the clinical course of the disease in 500 patients treated by intramuscular injection of a uniform dose of 10 cc.

⁽²⁷⁾ Goodall says that the exact dose of Scarlet Fever Antitoxin is far from being settled, but that up to the present, doses of from 10 cc. in moderately severe cases up to 50 cc. in severe, have been successfully employed/

(36)
employed. Ker mentions the same ratio in dosage and states that a second or third dose should rarely be necessary, if the first dose is an adequate one.

(65)
Price defines the limits of dosage very narrowly, recommending the early administration of 10 cc. to 15 cc.

Messrs Burroughs, Wellcome & Company suggest 10 cc. in mild cases and from 20 cc. to 50 cc. in severe forms of the disease.

In my earlier acquaintance with the specific therapy of Scarlet Fever, I used fairly large doses, up to 30 cc. or 40 cc., but I have formed the opinion that there is nothing to be gained by giving the ordinary case more than 10 cc. and rarely is it necessary in any case to increase the dose above 20 cc. in severe attacks of Scarlatina. But, as has already been mentioned in an earlier chapter of this treatise, there is often the greatest difficulty in prognosing in Scarlet Fever. Cases are seen which appear identical in all their initial clinical manifestations, yet one reacts to antitoxin in a very satisfactory way while another appears little improved, even after an interval of seventy-two hours. The theory of unidentical toxins is a fascinating one in such instances, but I have seen a number of cases of this type - and I include one in the series under review - where/

where a second dose of antitoxin from the same batch produced quite a dramatic change for the better.

In my opinion it is unnecessary, as a rule, to make any great modification in the dose of antitoxin for children as compared with adults. If the body weight is less, the intensity of the toxæmia seems to warrant a greater antitoxin content per kilogramme. Doses of less than 10 cc., given intramuscularly, seem quite inadequate. One of the cases included for discussion was apparently a very mild one and was given 5 cc. Scarlet Fever Antitoxin, only to require an additional 10 cc. next day, because there was no observable improvement in the patient's condition.

I am inclined to agree with Craig, that certain septic cases are much benefited by a combined therapy of Scarlet Fever Antitoxin and Polyvalent Antistreptococcic Serum. Indeed, where the throat symptoms and signs have predominated out of all proportion to the general toxæmia after 48 hours or so, I have repeated the polyvalent serum with very encouraging amelioration of the septic process.

The co-existence of Diphtheria and Scarlet Fever is probably less of a rarity than is sometimes stated and where the clinical picture has left some doubt as to the presence of diphtheria, I have not hesitated to give Diphtheria Antitoxin along with Scarlet Fever Antiserum. The reliability of the bacteriological diagnosis/

diagnosis of Diphtheria when combined with Scarlet Fever leaves something to be desired. On not a few occasions I have given Diphtheria Antitoxin in suspicious cases, only to receive a negative laboratory report from both the direct swab and the examination of cultures. In a large percentage of these, however, I have had the accuracy of the clinical diagnosis strongly supported by what I believe to be a very important sign of the disease, namely the slowing of the pulse to 60 or even 50, exhibited between the seventh and tenth days of disease. This bradycardia may be due to an actual stimulation of the vagus nerve by the diphtheria toxin or it may be a relative vagal preponderance due to the intoxication of the sympathetic innervation of the heart.

The inclusion of polyvalent antistreptococcic serum and Diphtheria antitoxin in the treatment of patients does not vitiate the conclusions to be drawn from the specific therapy of the disease itself. The co-existence - it might well be called accidental co-existence - of the pathological results of some other organism or organisms cannot possibly be affected by any therapy which is specific for one particular invader. If Scarlet Fever Antitoxin is to be given an even chance of proving its worth, conditions which are not due to the *Streptococcus scarlatinae* must be eradicated by intelligent therapy.

The/

The mildness of many cases of Scarlet Fever has caused the question to be asked:- Should Scarlet Fever Antitoxin be used in all cases? Dr J.D. Rolleston,⁽⁶⁷⁾ addressing the Nottingham Medico-Chirurgical Society on 4th January 1928, gave it as his opinion that the antitoxin treatment of Scarlet Fever was of great value, but need not be employed except in cases of some severity.⁽⁵¹⁾ McLachlan and Hunter mention in their tabulated study of the effects of specific therapy in Scarlet Fever that "chiefly for reasons of economy, it has been restricted to the severe and complicated cases." This seems to imply that those two observers considered the routine serum treatment of Scarlet Fever desirable. O'Brien⁽⁵⁷⁾ subscribes to the view that all cases should receive antitoxin when he says "The large amount of evidence available has convinced practically all observers that Scarlet Fever Antitoxin is a specific curative serum, and that, given early in the disease, its beneficent action approaches that of the specific antitoxin used in diphtheria." Dr O'Brien further points out that it is the antitoxin content of the serum which is important and that there is no evidence of any useful therapeutic purpose having been served by sera reputed to be antibacterial. Banks of Leicester is a strong advocate for the universal adoption of specific therapy in all cases of Scarlet Fever.⁽³⁸⁾ Kirkhope says/

says that in cases in which serum is administered early - as it should be - and the disease runs a mild course, it cannot be determined whether the illness was originally of a mild type or whether the serum modified its severity. This comment is quite scientific, but it is equally true that many mild cases develop complications if not treated with antitoxin, so that a uniform absence of septic sequelae in early serum-treated mild cases would argue in favour of the administration of Scarlet Fever Antitoxin to all patients suffering from the disease. Flusser has treated all Scarlet Fever patients with antitoxin since 1926 and he says that if the administration of the therapy is sufficiently early and is adequate, every case reacts satisfactorily to this form of treatment. " (10) Bröcker states that the real value of serum in Scarlet Fever is in treating the early toxic stage of the disease. Scott used Scarlatinal Antitoxin for the most severe cases of the disease only. (70) Meyerdirks (55) concluded from his observation of specific therapy that antitoxic serum should be given in every case of Scarlet Fever in the febrile stage. Harries (53) records the clinical course of 1071 cases treated with Scarlet Fever Antitoxin in 1926 and gives it as his formed opinion that convalescence in Scarlet Fever is definitely shorter when specific therapy/

therapy is employed. Attempts have been made to tabulate clinically the type of case which should be treated with Antitoxin, and Lenthe⁽⁴³⁾ mentions that temperatures exceeding 102°F. in adults and reaching 101.4°F. in children are indications for the administration of serum. In the same treatise, this observer notes that the resultant feeling of well-being was a marked feature, as expressed by the patients treated. Lenthe⁽⁴³⁾ does not find that every case reacts objectively in an entirely satisfactory manner. Husler⁽³⁴⁾ used Scarlet Fever Antitoxin on 34 cases of moderate severity and is emphatic in stating that the serum had a remarkable effect on the toxæmia of the disease. He does not consider that mild attacks need be treated with Antitoxin. Benson and Maciver⁽⁶⁾ state that septic cases did not appear to benefit from specific antitoxin. Banks and Mackenzie⁽⁴⁾ give a report on 404 cases treated, intravenously for the most part, and are eulogistic in their praise of this special method of employing the antitoxin. They describe the beneficial results as being quite dramatic. Toomey and Dolch⁽⁷⁵⁾ are inclined to the opinion that when given intramuscularly there is very little real benefit to be gained from the antitoxin, although the period of toxicity appears to be slightly reduced in duration. In more encouraging language, Craig⁽¹⁵⁾ records/

records that twice as many multiple complications occurred in untreated, as compared with treated cases. His series of cases included ten Septic and two Toxic, all of which recovered. As mentioned previously, Craig included polyvalent anti-streptococcic serum in the treatment of Septic Scarlet Fever. Friedemann⁽²⁵⁾ and Deicher at first reserved Antitoxin treatment for severe cases, but later observations convinced them that all definite cases of Scarlet Fever should be given the benefit of serum, for, although the initial signs and symptoms might suggest a mild attack, such cases might become quite serious later, if untreated. Yoannovitch⁽⁷⁹⁾ supports the routine treatment of all cases of Scarlet Fever by means of Antitoxin when he says that in nearly all the cases so treated there was a resulting decrease of the temperature and a notable improvement in the patients' general condition. Zoeller,⁽⁸³⁾ on the other hand, enlarges on the dangers of serum sickness and the undesirability of sensitisation to horse serum of patients in whom the disease is mild.

From the foregoing, it may be said quite justly that the majority of the workers quoted are definitely in favour of the universal administration of Scarlet Fever Antitoxin in all definite cases of the disease. If I could, by my own observations, convince myself that/

that a case which begins mildly will remain true to its colours, I think I should agree that specific therapy should be withheld in such, but I am repeatedly reminded by hard facts that prognosis in Scarlet Fever is one of the most difficult things in Medicine; indeed, to give anything approaching a definite prognostic opinion involves taking a "long chance". Entirely on scientific grounds, in spite of seeming inconsistencies in the results of this form of treatment, a definite position in favour of universal specific therapy must be taken up, for if, as has been generally agreed by eminent scientists, the toxin of the *Streptococcus scarlatinae* is a specific toxin and is responsible for the toxic stage of the disease, nothing but benefit for the patient can accrue from the neutralisation of that toxin by its specific antitoxin.

(3) Method of Administration:-

For ordinary cases of Scarlet Fever, especially in children, there appears to be little to be gained by using any other than the intramuscular route in giving Antitoxin. Intravenous injection in young subjects is a difficult procedure and however expert the operator, restlessness of the patient may be difficult to control. The strain on the child is much greater in employing intravenous therapy and apprehension/

apprehension is increased. By this method, antitoxin must be given more slowly than when intramuscular injection is used and there is a much greater likelihood of severe serum reaction. But Banks ^(3 & 4) is definitely of the opinion that the intravenous administration is the method par excellence in all cases and it must be admitted that his results are striking.

In using serum intramuscularly, I have always employed the rapid "stab" method which is largely used by Syphilologists in administering mercurial preparations and I have repeatedly succeeded in having finished the operation without the patient being aware that anything had taken place. Goodall ⁽²⁷⁾ dislikes this route, because of the risk of abscess formation. I have yet to see an abscess from giving antitoxin into the gluteal muscles and I attribute my apparent good fortune to two ordinary precautions. First, the serum must be given into the actual muscles and not into the thick gluteal pads of fat; and second, gentle massage of the superficial structures on the deep ones by means of a firm pad causes rapid diffusion of the antitoxin as well as expediting its absorption.

The subcutaneous method, preferred by Goodall, must be a little tedious, and it is difficult to understand why the great tension of the very superficial tissues into which he chooses to introduce the serum is not more likely to lead to abscess formation, /

formation, because of the very slow absorption, than is any temporary and rapidly diminished disturbance in the deep and well supported muscular strata.

(36)
Ker takes a very sane view in recommending the intramuscular route as the one of choice except in toxic cases, when the intravenous administration should be practised. (75)
Toomey and Dolch describe the much accelerated action of the serum when given intravenously.

Various workers describe their own particular methods of dealing with cases already sensitised to horse serum. One which I have found to be admirably suitable is to give 0.1 cc. subcutaneously first and then 1.0 cc. intramuscularly, repeated at hourly intervals for two injections. At the end of three hours, I gave the remainder of the dose of antitoxin and there has never been any untoward result. It is interesting that I have on record about a dozen cases where, because of the inaccuracy of the previous history of the patients, it was unknown to me that Diphtheria Antitoxin had been required in the past. All of these were treated with Scarlet Fever Antitoxin, without desensitisation and in only one case were there any anaphylactic phenomena observable. The case which did react certainly caused considerable anxiety but quickly responded to the usual adrenalin treatment.

All the series of cases collected for this treatise have been given antitoxin by the intramuscular method.

(4) Day of Disease on which Serum Therapy is instituted:-

The early symptoms and signs of Scarlet Fever are those of a toxæmia, which must necessarily increase in intensity until the antitoxins of the tissue-fluids and the blood are sufficiently mobilised to deal effectively with the condition. This active immunity may be greatly assisted in the early phase of its production by inducing a co-existent passive immunity. It is therefore reasonable to presume that the earlier the administration of specific antiserum, the greater is the help afforded in overcoming the general intoxication.

The greatest drawback to the really efficient antitoxin treatment of Scarlet Fever is the fact that the average day of disease on admission to Hospital is the third day, as is seen from the table below.

TABLE./

Average Day of Disease on Admission.

Age Group.	Sex.	Average Day.
1 - 5 yrs.	M	3
	F	4
5 - 10 "	M	2.5
	F	2.25
10 - 15 "	M	3.0
	F	2.5
15 - 25 "	M	3.25
	F	3.5
25 - 35 "	M	3.25
	F	3.0
35 - 45 "	M	-
	F	2.0
Average for all patients		3.0

Some authorities consider that the clinical course of the disease is directly related, so far as the incidence of complications is concerned, to the promptness of the administration of Antitoxin. Such a statement must be qualified by adding that after the first five days of illness, the results of antitoxin treatment are so negligible that the time of giving becomes unimportant. By the fifth day, many patients give a negative reaction to the Dick Test, /

Test, from which it may be deduced that they now have a sufficiency of antitoxin in their blood and tissues fluids and are unlikely to benefit from further additions to their store of antibodies. In this connection, Peters and Allison found, in Dick-Testing ⁽⁶²⁾ 131 Scarlet Fever patients on the third day of disease, that 67 were already negative, i.e. 51%. Their work suggests that the first two days of illness constitute the most important period in the administration of specific antitoxin, if favourable results are to be anticipated. This view is strongly supported by ⁽⁵¹⁾ McLachlan and Hunter, who found that in 13 cases treated on the first day of disease, only 1 was complicated. Of those treated on the second day of disease, nearly 15% showed complications; thereafter, the percentage of complicated cases was approximately 20% for cases where it had not been possible to give serum until the 3rd or 4th day of disease.

On the other hand, because a case of Scarlet Fever is not seen, with a view to specific therapy, until the 3rd or 4th day of disease, there is no reason for withholding the therapy and almost certainly some benefit is derived from it. ⁽⁵⁰⁾ McGarrity notes that particularly in toxic cases, he has noticed a great change for the better after intramuscular injections on the third day of illness.

The/

The prevention of complications cannot be said to be the immediate effect of Antitoxin Therapy, which is primarily concerned with the toxic manifestations of the disease. The effect on the temperature may be regarded as a gauge of the efficacy of the treatment and it is definitely found that the rate of subsidence of the patient's temperature is, broadly speaking, in direct ratio to the day of administration of Scarlet Fever Antiserum. ⁽⁶⁶⁾ Robb of Belfast goes so far as to say that, given early, antitoxin had completely aborted cases of the disease. ⁽⁸¹⁾ Zikowsky records a very favourable impression gained during the use of Scarlet Fever Antitoxin, stating that in over half the number of cases treated, the temperature was normal or nearly so in less than twenty-four hours. ⁽⁷⁾ Bipoli concluded from his observations that when given within three days of onset, the most constant effect was a markedly beneficial one, especially in severe and toxic forms of the disease. ⁽¹⁷⁾ Drs George and Gladys Dick note that in early treated cases, the temperature falls and there is general improvement within twenty-four hours. They further mention that only in one of sixty-four cases of Scarlet Fever, where antitoxin was given on the first day of disease, did any complication arise. In the same series of cases, five developed ear complications, out of a total of 59 treated on the second day/

(16)

day of disease. Cushing upholds the definite relation of the time of giving antitoxin to the observed effects, saying that if given early, there is a marked fall in the temperature and a definite reduction in the pulse rate in 12-36 hours. ⁽²⁴⁾ Flusser, although he found that cases receiving treatment late in the course of disease were not benefited, states quite definitely that no single case failed to react satisfactorily if adequate early treatment was given; even severe attacks showed a fall of temperature and a lessening of the toxicity.

(6)

Benson and Maciver show that a much larger percentage of patients have a rapid reduction in temperature if treated on the first or second day of illness than is noted in those who have had serum given on the third day. ⁽²⁵⁾ Friedemann and Deicher appear to incline to the belief that as many as 60% of patients, treated so late as the fifth day of disease, derive definite benefit from the therapy, with regard to temperature. It is difficult to give an opinion on the value of such an observation, since a very large proportion of Scarlet Fever cases have approximately normal temperatures by the evening of the fifth day.

Many other workers have given valuable analyses of the results of Specific Therapy in Scarlet Fever and have concluded that the treatment should be commenced early, but a number of them do not detail any statistical synopsis of their findings, arranged according to the day of administering serum. The following tables/

tables show the writer's findings with reference to differences in the course of disease, as a result of specific treatment, instituted on various days of disease.

(1) Day of Disease, on which Scarlet Fever Antitoxin was given. The numbers signify cases, and the table is arranged for each Age and Sex Group:-

Age Group.	Sex.	Day of Disease.			
		1st	2nd	3rd	Later than 3rd
1 - 5	M	2	6	4	5
	F	3	2	3	6
5 - 10	M	1	5	2	1
	F	2	5	7	3
10 - 15	M	-	-	2	-
	F	1	3	-	2
15 - 25	M	-	1	4	4
	F	1	4	7	10
25 - 35	M	-	-	2	1
	F	-	3	-	3
35 - 45	M	-	-	-	-
	F	-	1	-	-

This tabular representation shows that only 10 cases out of 106 cases were treated with antitoxin on the first day of the disease, but 40 cases actually had specific therapy no later than the second day. In passing, it may be noted again that the number of female cases exceeds that of males in all the age groups above 1-5 years.

- (2) Periods and Average Periods elapsing between the administration of Scarlet Fever Antitoxin (for (a) Total Cases (b) Total Males (c) Total Females) and the return of the temperature to normal, when the antitoxin was given on the first day of disease.

Cases.		Period elapsing.						Average Period elapsing.
Description	No.	1 Day	2 Days	3 Days	4 Days	5 Days	6 + Days	
Total Cases	10	2	4	3	-	1	-	2.4 Days
Total Males	3	1	2	-	-	-	-	1.7 Days
Total Females	7	1	2	3	-	1	-	2.7 Days

It is seen that 9 cases out of ten (i.e. 90%) had a normal temperature by the evening of the fourth day. This must be considered to be due to the treatment, for though various observers have said that they have/

have yet to see a series of antitoxin-treated cases which could not be matched by results in untreated cases, it is usually agreed by text-book authorities and all who have an intimate knowledge of Scarlet Fever that from five to seven days are commonly required for the subsidence of the temperature.

- (3) Periods and Average Periods elapsing between the administration of Scarlet Fever Antitoxin (for (a) Total Cases (b) Total Males (c) Total Females) and the return of the temperature to normal, when the antitoxin was given on the second day of disease.

Cases.		Period elapsing.						Average Period elapsing.
Description	No.	1 Day	2 Days	3 Days	4 Days	5 Days	6 + Days	
Total Cases	30	4	10	10	4	-	2	2.8 Days
Total Males	12	2	6	4	0	-	-	2.2 Days
Total Females	18	2	4	6	4	-	2	3.2 Days

When antitoxin was given on the second day of disease, 24 cases out of 30 cases (i.e. 80%) had normal temperatures by the end of the fifth day, a result which is certainly unusual in untreated cases of Scarlet Fever. What is more significant is that whereas/

whereas 90% of those treated on the first day of disease had normal temperatures by the evening of the fourth day, only 47% of cases receiving antitoxin on the second day succeeded in establishing normal temperatures by the end of the same time-limit.

- (4) Periods and Average Periods elapsing between the administration of Scarlet Fever Antitoxin (for (a) Total Cases (b) Total Males (c) Total Females) and the return of the temperature to normal when the antitoxin was given on the third day of disease.

Cases.		Period elapsing.						Average Period elapsing.
Description	No.	1 Day	2 Days	3 Days	4 Days	5 Days	6 + Days	
Total Cases	31	8	14	3	3	1	2	2.5 Days
Total Males	14	4	5	1	1	1	2	2.9 Days
Total Females	17	4	9	2	2	-	-	2.1 Days

In this series, 22 cases out of 31 cases (i.e. 71%) had normal temperatures by the end of the fifth day. There is thus a percentage decrease when compared with cases treated on the second day of disease (i.e. 80%). The difficulty in influencing the fall of temperature by means of serum given on the third day/

day of disease is made even more evident by the further rapid diminution in the percentage of cases having normal temperatures at the end of the fourth day of disease. As is seen, only 8 cases (27%) reacted sufficiently to make this possible. So far, the tables go to show that each day of delay in diagnosing Scarlet Fever which is to be treated specifically, reduces the likelihood of the temperature being normal by the end of the fourth day by 50%; in other words, cases treated on the second day of disease give approximately only half the number of normal temperatures exhibited by cases treated on the first day of disease when these are compared at the end of 96 hours' illness; and similarly, third day cases only show half the number of normal temperatures compared with second day ones. The actual percentages in the above groups are 90%, 47%, and 27% respectively.

On examining the temperature charts of cases in the 106 under special consideration in this treatise, I fail to discover that any benefit accrues, so far as influence on pyrexia is concerned, when antitoxin is given later than 72 hours after the onset of Scarlet Fever. A table of such cases is here appended but it gives no information which could be interpreted as different from the course of the toxæmia of Scarlatina in untreated cases.

Periods/

- (5) Periods and Average Periods elapsing between the administration of Scarlet Fever Antitoxin (for (a) Total Cases (b) Total Males (c) Total Females) and the return of the temperature to normal, when the antitoxin was given later than the third day of disease.

Cases.		Period elapsing.						Average Period elapsing.
Description	No.	1 Day	2 Days	3 Days	4 Days	5 Days	6 + Days	
Total Cases	35	14	7	5	3	3	3	2.8 Days
Total Males	11	7	1	1	-	2	-	2.0 Days
Total Females	24	7	6	4	3	1	3	3.0 Days

It may be noted that, with one exception, the average period elapsing, as detailed in the above tables, is considerably longer in the case of females than males.

(5) Serum Rashes and Anaphylaxis:-

The two conditions have little in common, except that they both arise from the introduction of foreign protein into the system by a parenteral route. No sensitising dose is required to cause the production of a serum rash; while, in the case of true anaphylaxis, the/

the patient must have become sensitised to the particular protein. But occasionally after the first injection of serum, a patient may develop alarming symptoms, closely resembling those of anaphylaxis and these may be followed by death. Children are usually the victims and the class of case exhibiting such unfortunate sequelae generally belongs to the "lymphatic" type. It has been estimated that death as a direct result of a primary injection of serum may be expected to take place in 1 out of 70,000 cases treated. Apparently, the dose has little to do with the onset of fatal symptoms; for example, Kerley found that although death did not actually supervene, extraordinarily urgent symptoms of collapse occurred after a subcutaneous injection of four minims of serum.

It is impossible to recognise, beforehand, the cases which will react either generally or externally to the injection of serum. Several authorities have recommended the intracutaneous injection of a small quantity of the serum as a test of sensitiveness to serum, but there is now very convincing evidence that a positive skin reaction may be obtained (i.e. the appearance of an urticarial wheal at the seat of intracutaneous injection) in persons who exhibit no general serum rash when given the therapeutic dose. The contrary is also true.

With regard to anaphylaxis, it is unwise to take
a/

a risk in treating any patient who has already had serum therapy at some period previously, unless the interval elapsing between two injections is less than ten days. It appears quite a simple rule, to remember to desensitise such patients, but in actual practice, while the greatest vigilance is exercised with reference to new cases coming into hospital, unnecessary risks are occasionally run during the convalescence of patients in wards where mixed infection has been accidentally introduced. For instance, the inclusion of a case of combined Diphtheria and Scarlet Fever in a Diphtheria Ward may occur. It becomes necessary to give a temporary passive immunity to Scarlet Fever to Dick-positive patients and for this purpose, 5 cc. of Scarlet Fever Antitoxin may be used per patient. Patients whose residence in hospital is less than ten days do not require desensitisation, but all the remainder must be so treated, if risks are not to be run. The amount of serum used as a desensitising dose is important, as even very small injections of the foreign protein to which a patient is already sensitised may cause anaphylactic shock instead of preventing it. Some persons are exquisitely hypersensitive to the parenteral administration of foreign proteins. Fortunately, the number of cases reacting severely to second injections of horse serum, after an interval/

interval of two weeks or longer, is very small and while it is the clinician's duty to avoid risks, it is also necessary for him to avoid alarm, if something untoward does occur at some time. It is a poor philosophy to neglect the relief of thousands because the therapy was, in spite of reasonable precautions, followed by an unfortunate result in one or two cases. Care beyond ordinary limits is only necessary in patients with a history of Hay Fever, Asthma, Urticarial eruptions and allied recognisable phenomena of hypersensitiveness to foreign proteins. Such persons should only be treated intravenously with the greatest reluctance and where urgency is extreme.

It is impossible to discover any moderate agreement among observers as to the incidence of serum rashes in the specific treatment of Scarlet Fever. This may be because of differences in the protein content of various sera. It is certainly partly because of great differences in the sensitiveness of different groups of individuals. I should like to reiterate here that in treating Diphtheria and Scarlet Fever with antitoxin, I have found the percentage of serum rashes to be consistently much lower when Messrs Burroughs Wellcome and Company's Serum was used than when employing preparations by Messrs Parke, Davis and Company.

I propose to give a résumé of the experiences of various observers with reference to serum rashes and anaphylaxis and finally to quote my own findings in respect of 106 cases of Scarlet Fever. Robb used whole serum (unconcentrated) on 14 cases in 1925, with only 21% (3 cases) serum reactions. Kirkhope⁽⁶⁶⁾ treated 101 contacts by injecting 2.0 cc. of Scarlet Fever Antitoxin intramuscularly and 20% of these exhibited serum phenomena. MacFarlane⁽⁴⁹⁾ gives details of the treatment of more than 800 cases of indubitable Scarlet Fever in the City Hospital, Birmingham, and states that 28.6% suffered from serum reactions, most of which were slight. In about one-quarter of the reacting cases, there was intense rash and about one-ninth of those affected had severe multiple symptoms. Craig⁽¹⁵⁾ describes the results of treatment in 512 cases of Scarlet Fever; in his series 41% had reactions to the serum, but he notes that there were no alarming symptoms. Benson and Maciver⁽⁶⁾ found symptoms and signs of serum sickness in 34% of cases treated. Lenthe⁽⁴³⁾ was fortunate enough to discover only 2 cases of serum reaction in 44 cases injected. Harries⁽³³⁾ had 17 cases (20%) out of a total of 84 patients. Bröcker⁽¹⁰⁾ records the details of treatment in 50 cases of Scarlet Fever by means of Specific Antitoxin at the Municipal Hospital, Aachen, and his experience was that only 6% (3 cases) had signs attributable to the serum proteins. In his earlier experiences/

experiences with Serum Therapy, using unconcentrated
 Antitoxin, ⁽³²⁾ Harries mentions that practically every
 case developed serum sickness. ⁽¹⁶⁾ Cushing's cases in-
 cluded 13% showing hypersensitive symptoms. ⁽²⁹⁾ Gordon
 and his co-workers have made an interesting comparison
 between Polyvalent Antistreptococcic Serum and Scarlet
 Fever Antitoxin with regard to the incidence of serum
 reactions. The percentages of cases reacting were
 33% and 31% respectively. This lends support to the
 views of various authorities, including Park, that
 the immune bodies which constitute the antitoxic and
 antibacterial content of sera play little or probably
 no part in promoting reactions to horse serum.

⁽⁴⁵⁾ Lunin analyses the results of antitoxin treatment in
 100 children under 12 years in the Rauchfuss Children's
 Hospital and states that 31 cases developed serum rash.
 He distinguishes three types of eruption; the urticarial,
 the morbilliform and also a multiform erythema. There
 seems to be little purpose served by typing serum
 rashes and it is the writer's opinion that if watched
 closely, eruptions will be found to change their
 general appearance within a few hours in a large
 majority of cases. It must be very rare for a serum
 rash not to exhibit urticarial wheals either as an
 evanescent or comparatively lasting characteristic at
 some period of its existence.

⁽⁴⁾ Banks, who, as already stated, is a strong advocate
 of/

of intravenous therapy, found that when patients were treated in this way, 60% had immediate reactions, as evidenced by rigors, pyrexia and rapid pulse. The symptoms generally passed off in about half an hour, but there was one death in 404 cases treated. A death as the direct result of therapy militates against a certain treatment finding public favour and few cases of Scarlet Fever at the present time have initial toxic symptoms sufficiently urgent to warrant universal intravenous treatment of the disease. But Banks mentions that only 2.8% of the cases showed any evidence of serum rash after the subsidence of the early disagreeable symptoms. Toomey⁽⁷⁵⁾ and Dolch treated 283 cases in one of the Cleveland Hospitals with resulting serum reactions in 109 (38.5%).

My series of 106 cases gave a percentage incidence of serum rash of 9.4% (10 cases). It is of interest that only 7.5% of the male patients developed this sequela, as against 10.6% of females. An observation was made above with reference to the time elapsing between the administration of antitoxin and the return of the temperature to normal, it being noted in that connection that males reacted, on the whole, more favourably than females.

(6) The dangers of sensitisation. A means of recognising serum-treated patients. Once a patient has had an injection of a therapeutic or immunising serum prepared by actively immunising an animal, there is set up in that person a "sensitised" state to that particular serum. It is important to note that the presence of immune bodies does not in any way modify the hypersensitiveness induced, the reaction being excited by the normal protein fraction in the serum. Neither can any future modification of the dosage prevent sensitisation, unless the whole of the protein can be removed from the therapeutic agent. It seems that such a triumph of the laboratory, even if possible eventually, will be long delayed, since the immunity conferred by an antitoxic serum is due to "substances" closely associated with the pseudo-globulin fraction of the protein content. The actual amount of serum, administered parenterally, required to sensitise a person to the contained protein is infinitesimal. Rosenau and his co-workers found that an experimental guinea pig could be sensitised to horse serum by the injection of 0.000001 cc.

There are no outward signs of hypersensitiveness after injection of a serum, and it is not until a second dose has been given after an interval of, say, two or three/

three weeks, that it becomes evident in a percentage of cases that a previous injection of an identical protein has taken place. The occurrence of serious anaphylactic phenomena is rare, but that is no reason why everything possible should not be done in an attempt to obviate urgent serum sequelae altogether.

In Fever Hospital Practice, it is by no means easy to get accurate histories of the patients admitted. Children constitute a large proportion of the hospital population and they cannot be expected to have any detailed knowledge of previous illnesses. Moreover, parents are frequently so distressed by the acuteness of their child's illness and by the necessity for removal to hospital that only scant attention is given to queries which seem for the moment of very secondary importance. A very useful purpose would be served, if some international method could be devised, whereby cases previously treated with serum could be unmistakably recognised. There is an alternative, which has already been on trial for some time and about which, opinions differ very materially. This comprises the utilisation of different animals for the preparation of immunising and curative sera. For example, Messrs Parke, Davis and Co. have made use of goats in connection with active immunisation against Diphtheria. But even in such an arrangement, unless there be universal agreement as to the animal to be used in each/

each specific instance, there can only be eventual confusion, with a result no less undesirable than the difficulties at present experienced in using preparations of horse serum.

I have given this problem very considerable thought and I have concluded that the following scheme is practicable and might be useful. International agreement with regard to distinctive skin colours as evidence of previous treatment of a particular disease seems quite feasible. Such is not absolutely essential, as the factor of prime importance is the recognition of previous serum treatment, but there would be some value in an agreed colour scheme instead of one constant colour, in so far that definite information of second and third attacks of the same disease would thus be afforded. Having concurred in the desirability of "skin recognition of previous serum-treated diseases", it would only be necessary to include in each package of antitoxin a wafer, resembling an ophthalmic "lamella", enclosed after sterilisation in a parchment envelope and having on it a small quantity of some indelible harmless dye. After preparing the patient's skin, the wafer would be applied to the site of injection and the antitoxin needle would enter the skin after traversing the dyed surface, carrying with it a small quantity of the pigment into the superficial tissues/

tissues and in this way ensuring a permanent stain. It might be necessary to stipulate certain areas as those to be used for the administration of antitoxin, such as (1) The Gluteal Regions (2) Either Thigh (3) Either Flank (4) Either Deltoid (5) Either Cubital Fossa (6) The Lumbar Spinous Area (7) The Base of the Skull (8) The Anterior Fontanelle.

Clinicians could survey those areas very rapidly and students would learn to consider an "antitoxin mark" a routine observation in the examination of a patient, just as they learn at present to examine for evidence of vaccination in the differential diagnosis of Varicella.

Precautions against anaphylaxis would in nowise affect the immediate reactions seen from time to time after an initial intravenous injection of antitoxin, which method appears to be to me unreasonable as a routine practice in the treatment of a disease whose antitoxic therapy is not, as a rule, a matter of extreme urgency.

OBSERVATIONS ON SCARLET FEVER AND
ITS SPECIFIC THERAPY.

VI. THE ANTITOXIC SERUM TREATMENT OF SCARLET FEVER.

DISCUSSION:-

The headings proposed in the introductory chapter of this treatise were:-

- (1) Effect of Scarlet Fever Antitoxin on the Toxicity of the disease.
- (2) Effect of Scarlet Fever Antitoxin on the Incidence of Complications.
- (3) Effect of Scarlet Fever Antitoxin on the Length of Stay in Hospital.
- (4) Effect of Scarlet Fever Antitoxin on the Percentage of Return Cases.
- (5) The Prophylactic Use of Scarlet Fever Antitoxin.

(1) The effect on the Toxicity of Scarlet Fever has already received detailed attention in connection with the arguments advanced for the earliest possible specific treatment of the disease. It has already been seen that the majority of workers are agreed that early administration has a definitely beneficial effect on the toxaemia, though there are differences in the conceptions of what constitutes hastened decline of the toxic phase and at what time limit/

limit antitoxin may be said to be of relatively little importance in the treatment of the initial stages of Scarlatina. The Dicks, ⁽¹⁷⁾ for example, consider the effect on the rash to be the best indication of the benefit derived from early injection of antitoxin. Others have laid emphasis on the subjective state of the patient - the feeling of well-being and the relief of symptoms - and it must be allowed that practically all my patients capable of analytic thought have pronounced themselves as being much better, about twenty-four hours after antitoxin treatment. But the subjective improvement almost certainly runs in parallel with the diminution in temperature and I see no reason to accept a patient's statement as evidence, rather than the mechanical record of a clinical thermometer. The writer's opinion, as has been previously stated, is that the temperature chart is the best guide to the antitoxic effect of serum. It is true, as Robb ⁽⁶⁶⁾ points out, that the administration of a non-specific serum may cause quite a dramatic fall in temperature; but in such a case the temperature does not remain at the low level reached as a result of the protein injection. It rapidly regains its former register, whereas after adequate early specific therapy, although the fall may not be in any way critical, the new level is maintained, or succeeded by a still more favourable reading.

(2) The consideration of the effects of Scarlet Fever Antitoxin on the incidence of complications bristles with difficulties. Three distinct opinions may be said to require discussion. The first is that there is undoubted benefit from the specific therapy. The second contends a direct negative to the foregoing assertion. Lastly, an intermediate position is taken up by many workers with an intimate and vast experience; their observations have been that the beneficial results following early treatment are distinctly convincing, but that the administration of serum after the second or third day of disease appears to have little influence on the incidence of complications.

To prevent undue involvement, it will be most convenient to deal with the several points of view in relation to (a) Total Complications (b) Individual Complications.

(a) Total Complications:- There is comparatively close agreement in the text-books that 40% of cases, untreated by serum, may be expected to develop complications. The figure is naturally subject to considerable qualification, depending on the characteristics of any given epidemic, the previous physiological condition of the persons affected and all the other factors discussed/

discussed in an earlier chapter. The main point at issue here is, that if the antitoxin is specific and if complications are definitely the handiwork of the *Streptococcus scarlatinae*, one of two things must follow; viz.- (I) The Incidence of Complications should be markedly diminished (II) A scientific explanation of the failure of antitoxin to reduce the complication-rate appreciably is required.

Dealing with the findings of workers who confidently assert the beneficial action of Scarlet Fever Antitoxin in the prevention of complications, the following records are notable. Peters ⁽⁶²⁾ and Allison treated 114 of the worst cases of 860 admissions to hospital and they found that the incidence of septic complications was low. No classification of the cases is made with regard to the day of disease when the antitoxin was given, but they state that even when administered so late as the fifth day, there was definite benefit derived from its use in septic cases. ⁽⁵⁸⁾ Okell states that experience has been uniformly in favor of the view that, if it is given sufficiently early, antitoxin tends to prevent the septic complications of Scarlet Fever. He also notes that once pyogenic complications have become established, serum treatment does not have any modifying effect on them. It may be well to say at once that the actual treatment of/

of pyogenic manifestations of the late stages of the disease will not be considered in this treatise.

Although some authorities - and among them Okell himself - incline to the belief that Scarlet Fever Antitoxin may possess antibacterial, as well as antitoxic, qualities, there seems to be little doubt that the invasion of the tissues by the actual micro-organisms follows and is indeed made possible by the antecedent crippling effects of the diffusible toxin.

(51)

McLachlan and Hunter had only 27% complicated cases in 230 patients suffering from severe attacks of the disease. I have already mentioned that marked initial signs and symptoms do not necessarily imply a complicated or even protracted convalescence.

(49)

Mair MacFarlane was fortunate enough to have only 19.2% of complicated cases when antitoxin had been given. Banks has no doubt whatever that antitoxin is of paramount importance in preventing the pyogenic invasions of the *Streptococcus scarlatinae*. As already mentioned elsewhere, he treated all his cases intravenously. In the *Medical Officer*, 1927. V 38, p.147, a review of the antitoxic treatment of all cases of Scarlet Fever admitted to the Borough Fever Hospital, Wolverhampton is given and very favourable results are reported. It is stated that "Apart from its effects in cutting short the disease, this serum has been of particular therapeutic value in the treatment of severe/

severe cases of Scarlet Fever". Complications were inhibited in such cases. In his Annual Report, Burton⁽¹¹⁾ definitely opines that serum prevents complications. Dr Thomas Archibald⁽¹⁾ found that in nearly 1400 cases treated, complications rarely occurred.

Scott⁽⁷⁰⁾ treated with serum only those patients whose initial clinical manifestations were severe and yet only 30% developed any complication. Toomey⁽⁷⁴⁾ agrees that septic sequelae are less evident in treated than in untreated cases. Birkhaug⁽⁸⁾ early formed the conclusion that, given in adequate dosage, Scarlet Fever Antitoxin brings about a rapid recovery without septic complications. Gordon⁽²⁸⁾ appears to have been particularly unfortunate in the clinical course of untreated severe cases of Scarlet Fever, for he states that none of these escaped complication, whereas 35% of treated severe cases were uncomplicated. The difficulty of matching cases has already been referred to. Some patients react tremendously in the matter of heat regulation to any infection; which in turn gives a very high pulse rate and an abnormal peripheral dilatation of capillaries, seen as a brilliant rash. Yet they may prove by the sequence of events during convalescence that they were not seriously ill during the acute stage. This naturally applies to both treated and untreated cases, but whether or not it applies equally in a limited number of cases is difficult/

difficult to answer. No reference is made to the ages of the patients in the two groups, but presumably they corresponded closely. In ordinary cases of Scarlet Fever, ⁽²⁸⁾ Gordon records that 66% were uncomplicated when treated with serum.

⁽⁶⁹⁾ Schottmüller found very definite evidence of the decrease of septic complications on the institution of specific therapy in Scarlet Fever. ⁽⁵⁶⁾ Nankivell notes that no serum-treated case in his recorded series suffered from any severe complication, but some of the untreated cases had serious complications and many had minor septic sequelae. He makes an interesting observation that two of the controls nearly died during the septic stage, but after treatment with antitoxin they made complete and quite remarkable recoveries.

⁽³⁹⁾ Kolmer is insistent on the value of serum in the treatment of the disease and the prevention of complications.

⁽⁴⁴⁾ Lindsay, Rice and Sellinger are convinced that the administration of antitoxin reduces the incidence of complications. ⁽³³⁾ Harries says that more cases can be discharged by the thirtieth day of disease and complications are markedly reduced in number, when antiserum is used in the treatment of the toxic phase.

⁽³²⁾ In an earlier communication, the same observer notes that "Septic complications in their early stage are "lessened. A decrease is noted in Rhinitis and early "Adenitis,/"

"Adenitis, which may be due to the decrease in the
 "congestion of the mucous membranes. In regard to the
 "septic conditions, the author agrees with the opinion
 "of the Dicks that by removing toxæmia, not only is
 "the true extent of septic involvement made evident,
 "but the patient is better enabled to tackle it."

(16)
 Cushing found that, whereas previous to the institution
 of antitoxin treatment, 45% of cases of Scarlet Fever
 were complicated, only 25% of serum treated cases
 developed a septic phase. (23)
 Eley asserts that the number
 of complications is definitely reduced as a result of
 specific therapy. (7)
 Bipoli experimented in the Isolation
 Hospital, Pudna and formed the opinion that complica-
 tions were, in a measure, prevented, but not influenced
 after they had become established.

The findings of the foregoing careful observers
 would seem to permit of no doubt of the value of
 Scarlet Fever Antitoxin in preventing complications.
 But the case has still to be stated for the directly
 opposite point of view. (20)
 Doolittle says "I myself have
 yet to see the data of a series treated with intra-
 muscular injections of Scarlet Fever Antitoxin which
 I could not, without much discredit, match with a
 series of my own untreated cases". (25)
 Friedeman and
 Deicher are emphatic that, while the toxic stage of
 scarlatina reacted favourably to antitoxin, the late
 septic/

septic complications were neither prevented nor influenced after they had manifested themselves. Husler⁽³⁴⁾ states that he failed to find any beneficial effect of serum on the incidence of complications. Baxter⁽⁵⁾ is slightly more indulgent in his pronouncements on the effects of specific therapy, for he allows that, while the numbers of complicated cases in treated and untreated cases showed close correspondence, the septic processes were mitigated by serum. von Borman⁽⁷⁷⁾ records that his experience with Scarlet Fever Antitoxin was that the incidence of complications was not influenced by the treatment. Buschmann⁽¹²⁾ praises the effects on the toxic type of Scarlatina in the early stages, but he found no reliable evidence of lessened incidence of complications. Lautier⁽⁴¹⁾ and Dreyfus,⁽⁸²⁾ Meyer⁽⁵⁴⁾ all agree that the percentage occurrence of septic sequelae is not lowered by antitoxin treatment of the toxic phase. Gottsche⁽³⁰⁾ takes the same view as Baxter; that the seriousness of complications is distinctly lessened, but their incidence is quite uninfluenced. Lenthe⁽⁴³⁾ does not conclude from his observations in the Bremen Municipal Hospital that any benefit accrues, so far as the lessened frequency of septic phases of the disease is concerned, from the use of specific treatment. A special committee, of which Lunin was president, reported on the treatment of/

of 714 cases of Scarlet Fever in five Children's Hospitals in Leningrad in 1926. Their considered opinion was that antitoxin had no effect on Septic Scarlet Fever or on the incidence or course of septic complications of the ordinary forms of the disease.

(75)
Toomey and Dolch are quite uncomplimentary to the treatment, in its relation both to the toxic phenomena of scarlatina and the septic processes resulting from the bacterial invasion of the tissues. In connection with the latter, they note that there were actually more complicated cases per cent in the treated than in the untreated control series.

So far, the extreme views have been presented and it is difficult to reconcile them. Certainly the reports referred to are not lacking in conviction and it requires more than a passing thought to discover some reasons why both may be perfectly correct findings and yet diametrically opposed to each other.

The third class of record to be dealt with, as setting forth the influence of antitoxin on the incidence of septic manifestations in Scarlet Fever, is one in which the observers choose a middle path. They are agreed that the early administration of antitoxin lessens the percentage occurrence of complications, but that, given later in the toxic phase, no such useful purpose is served by the therapy. Goodall makes
(27)
the/

the general statement that, the earlier the serum is given, the less likely are complications to occur.

The Dicks⁽¹⁷⁾ note that in a series of cases treated with antitoxin on the first day of disease, only 1 out of a total of 64 was complicated. The same workers treated 59 cases on the second day of disease, with a very great relative increase in the percentage incidence of septic sequelae. The complete prevention of Scarlatinal nephritis is noted as having followed specific therapy. Chodzko⁽¹⁴⁾ puts forward a strong argument for the power of antitoxin to diminish the number of complications, if given early. He records that his experience in Warsaw was that all cases, injected on the first or second days of disease, made an uneventful recovery. Where serum had been administered on the third day of illness, 25% of cases showed complications. Those treated later than the third day ran a much less favourable clinical course, there being 40% of the patients exhibiting septic sequelae. Craig⁽¹⁵⁾ is definitely of the opinion that the percentage of complicated cases shows an additional increase for each day of delay in treating the disease specifically. Benson⁽⁶⁾ and Maciver note a considerable diminution of complicated cases if serum is given during the first three days of disease. They conclude that, if given later than the third day, complications are/

are not noticeably inhibited. (66) Robb records that in 100 cases of Scarlet Fever receiving early treatment with antitoxin only 3 per cent were complicated.

Of the three cases, one developed arthritis and two had mild otorrhoea. The patient who had arthritis had had Rheumatic Fever two years previously. O'Brien⁽⁵⁷⁾ makes a general statement that there is considerable evidence to suggest that the early administration of antitoxin decreases the liability to complications.

The findings in my own series of cases agree with those recorded by workers who failed to find that any favourable influence was exerted by antitoxin on the incidence of complications. The real test of whether specific antiserum prevents complications is undoubtedly the comparison of the percentage incidence of these in groups of cases treated on different days of disease. It is reasonable to expect that cases treated on the first day of illness should show fewer complications per cent than cases treated on the second day. Similarly second day treatment should ensure greater freedom from septic manifestations than third day treatment. Yet I have failed to demonstrate any inhibitory influence, for, although the percentages in the table include Serum Rashes, of which about 10% occurred, the close correspondence in the percentage numbers on the various days quoted, leaves little argument in favour of antitoxin being useful in promoting an uneventful convalescence.

Numbers and percentage numbers of Complicated Cases occurring in
(a) Total Males, (b) Total Females, (c) Total Cases, when Scarlet
Fever Antitoxin was given on (1) 1st Day of Disease (2) 2nd Day
of Disease, (3) 3rd Day of Disease (4) After 3rd Day of Disease.

Day of Disease on which Scarlet Fever Antitoxin was given	Description of Cases.	Total Males	Total Females	Total Cases.
1st Day	Number of Cases	3	7	10
	Number of Complicated Cases	1	3	4
	Percentage No. of Complicated Cases.	33.3%	42.9%	40%
2nd Day	Number of Cases	12	18	30
	Number of Complicated Cases	5	7	12
	Percentage No. of Complicated Cases	41.6%	38.8%	40%
3rd Day	Number of Cases	14	17	31
	Number of Complicated Cases	5	5	10
	Percentage No. of Complicated Cases	35.7%	29.4%	32.3%
After 3rd Day	Number of Cases	11	24	35
	Number of Complicated Cases	5	9	14
	Percentage No. of Complicated Cases	45.5%	37.5%	40%

(b) Coming now to the question of the effect on Scarlet Fever Antitoxin on the incidence of individual complications, it will be convenient to discuss each of the common sequelae under a separate heading. Observations by various workers will be grouped according to their implications, in the order adopted with regard to the study of total complications. It may be imagined, at first sight, that no useful purpose can be served by dealing with the late manifestations under clinical headings, since it has already been shown that opinions are divided on the question of the effect of specific therapy on the occurrence of complications generally. But such is not necessarily the case, for modifications may result from specific therapy to inhibit or reduce the number of certain complications, although others may be completely unaffected. For example, as will be detailed during the study, some observers note that nephritis was entirely absent from the clinical course of serum-treated cases. Nephritis is one of the most dreaded of the sequelae of Scarlet Fever and if it can be altogether eradicated from the Scarlet Fever Wards by the use of Antitoxin, a very useful purpose will have been served in instituting specific therapy of the disease.

Late/

Late Albuminuria and Nephritis:- In Scarlet Fever, the incidence in untreated cases is about 8% on the average, but there is great variation. Some epidemics show the percentage of these sequelae to be as low as 2% or even less; other outbreaks have a very high nephritis complication-rate. Further, it varies considerably in different countries, according to whether Scarlet Fever is a mild or serious disease there. For example, Lämél⁽⁴⁰⁾ notes that in a series of cases in the Infectious Diseases Hospital at Berndorf, 30.6% had late albuminuria and 19.3% actually had haematuria. On the other hand, Gibson⁽²⁶⁾ had no case of kidney involvement in cases untreated by antitoxin.

Using antitoxin intravenously, in contra-distinction to the other workers to be quoted, Banks⁽⁴⁾ and Mackenzie show that no case of nephritis occurred in the 404 cases treated. Harries⁽³²⁾ was similarly fortunate in his experiences with Scarlet Fever Antitoxin in one series, although he had two cases of this complication in another series of 1071 cases. Nankwell⁽⁵⁶⁾ reports his findings in the treatment of thirty severe cases of the disease; there were no cases of damage to the kidney tissues. Gordon⁽²⁸⁾ was favourably impressed by the action of antitoxin in lowering the incidence of nephritis and states that the number of cases occurring was reduced by one half. He notes, however, that the percentage occurrence of late albuminuria did not appear to be influenced.

The opinions of the above workers are sufficient to demonstrate that quite a strong case may be stated for the beneficial effect of antitoxin in inhibiting or at least reducing the incidence of kidney mischief in Scarlet Fever.

Selections will now be made from the records of workers whose formed opinion it is that no diminution of the percentage occurrence of nephritis results from the specific therapy of scarlatina. Cushing⁽¹⁶⁾ reports, after a careful survey of 500 treated cases, that no benefit, so far as the protection of the kidneys is concerned, resulted from antitoxin. A like statement is made by Toomey and Dolch.⁽⁷⁵⁾ The special Committee in Moscow, referred to earlier, could find no reason to believe that nephritis was less common in treated than in untreated cases. Göttsche⁽³¹⁾ studied 622 cases closely in the Municipal Hospital, Bremen, but he could not discover any real reduction in the number of cases of nephritis among Scarlet Fever patients, although he concedes that the cases occurring were probably less severe. Meyer⁽⁵⁴⁾ records the findings of a special Congress on Scarlet Fever, held at Königsberg; the Congress agreed that nephritis, as one of the complications of Scarlet Fever, was not prevented by the administration of antitoxin. Buschmann⁽¹²⁾ sees no reason to believe that the cases he treated enjoyed any special immunity from kidney complications. von Borman⁽⁷⁷⁾ came to/

to a similar conclusion. Husler, Friedemann and Deicher,⁽³⁴⁾ and Doolittle⁽²⁰⁾ all agree that from their careful respective studies of the results of Scarlet Fever Antitoxin in the treatment of Scarlet Fever, they are unable to produce data to show that an enhanced protection was afforded to the renal glomeruli by the use of specific serum.⁽²⁵⁾

The most detailed reports are given by several observers with regard to the relation between the percentage incidence of nephritis and the day of disease on which antitoxin was administered. The following general conclusions are noteworthy. Birkhaug⁽⁸⁾ states that when antitoxin was given in adequate dosage during the first four days of disease, convalescence was uneventful. Benson and Maciver⁽⁶⁾ note that if serum is given after the third day of disease, the incidence of nephritis is not favourably influenced. Craig⁽¹⁵⁾ details the clinical course of 512 cases, practically all of which were treated during the first three days of disease and in his series there was only one case of nephritis. Chodzko⁽¹⁴⁾ shows that, taken in complete survey, kidney complications were reduced to less than half their previous case-rate by antitoxin, but he further asserts that the frequency of occurrence varied according to the day of disease on which serum was administered. Robb⁽⁶⁶⁾ reviews a hundred cases treated very/

very early in the course of the disease; there was no case of late nephritis. McLachlan and Hunter⁽⁵¹⁾ give an interesting analytical study with reference to complications, including Nephritis. They found that no case of real nephritis (they distinguish albuminuria from nephritis) occurred in any case treated on or before the fourth day of disease. No case of either of the two kidney conditions occurred if antitoxin was given on the first day of illness; three cases of albuminuria were found among 72 cases of Scarlet Fever treated on the second day; two out of 43 cases treated on the third day and four of the 49 cases having antitoxin on the fourth day developed albuminuria. Three cases of nephritis and one of albuminuria were noted among 53 patients undergoing serum treatment on the fifth day of disease.

In my own series of 106 cases, there was only one case of nephritis (i.e. 0.94%). It developed in one of the 40 male patients treated. All of the 66 females escaped kidney disorder. The complication occurred in a patient treated after the third day of disease. I therefore feel disposed to argue, that although the total complications occurring in Scarlet Fever show little modification in number as a result of antitoxin treatment, there is a definite limitation of the incidence of nephritis and that probably if all cases could have serum treatment by the second or third day of/

of disease, this complication would become very rare indeed.

Adenitis:- In Scarlet Fever cases untreated by antitoxin, from 10% to 15% develop adenitis. The figures quoted take no account of the early enlargement of cervical glands, particularly the tonsillar, which is commonly seen in the early stage of the disease. (3) Banks describes the complication as having occurred in seven out of nine cases of the semi-septic type, which may be regarded as complicated from the beginning of the clinical syndrome. But even in Scarlatina simplex, the incidence of adenitis is very variable and as was mentioned in another chapter, there tends to be small concentrated outbreaks of the condition from time to time in hospital wards. (51) McLachlin and Hunter record less than 5% as the case-incidence of late enlargement of cervical glands. This complication is not a serious one, only a very minor proportion of cases requiring any surgical treatment. (26) Gibson is either unusually fortunate or he considers adenitis of extremely little importance for he does not mention it among the complications arising in his cases. (40) Lamel analyses in detail the clinical characteristics and complications of 62 cases and states that over 30% developed adenitis. It should be noted that the Case Mortality was 8% which implies that Scarlet Fever is a serious disease in Berndorf/

Berndorf.

Some observers appear to include all enlargements of cervical glands, independent of the time of occurrence, i.e. whether initial or subsequent to the acute stage, as a complication. This is probably entirely wrong, for it is impossible to conceive that no reaction occurs in healthy cervical glands during the local attack of the *Streptococcus scarlatinae* on the tissues of the fauces.

Gordon⁽²⁸⁾ states a convincing case for the usefulness of Scarlet Fever Antitoxin in minimising the incidence of Adenitis. He found that this sequela occurred in only one-third of the number of cases hitherto affected and he notes that the duration of the inflammatory process was reduced. Schottmüller⁽⁶⁹⁾ singles out adenitis particularly as being very noticeably reduced in its incidence, although, even in treated cases, 22% were thus complicated. Harries⁽³³⁾ investigated the clinical course of 100 treated cases and found only three instances of adenitis. Banks⁽⁴⁾ and Mackenzie note that the percentage incidence of enlargement of glands was very low (1.5% : 6 cases) in 404 patients who had anti-toxin administered intravenously.

Evidence pointing to failure of specific therapy to influence the development of glandular enlargement may now be reviewed briefly. Bröcker⁽¹⁰⁾ says that the occurrence of adenitis seems to be little modified by/

by serum; at the same time he quotes figures which give the benefit to serum-treated cases. But the percentage incidence is certainly comparatively great, 38% being the complication-rate in this particular instance.

Friedemann⁽²⁵⁾ and Deicher could find no diminution in the occurrence of adenitis as a result of giving anti-toxin. Husler⁽³⁴⁾, Baxter⁽⁵⁾, von Borman⁽⁷⁷⁾, Buschmann⁽¹²⁾, Lautier⁽⁴¹⁾ and Dreyfus, all observe that in their carefully critical investigations of cases treated serologically, there was no definite evidence to show that adenitis was less common in patients receiving antitoxin than in those treated by expectant methods. Gordon⁽²⁹⁾, Bernbaum and Sheffield record that in their experimental work with Scarlet Fever Antitoxin, Convalescent Serum and Polyvalent Antistreptococcic Serum, they found that 18.2% of patients receiving specific therapy developed adenitis as against 10.2% treated with a polyvalent serum. Cushing⁽¹⁶⁾ reports an almost negligible reduction in the incidence of this particular sequela; he found that before the introduction of antitoxin, about 15% of cases had adenitis as a complication; treated cases gave a complication-rate of 12% for adenitis.

As the theme develops, it becomes more and more apparent that little agreement is reached by competent observers with reference to any beneficial effects exhibited by antitoxin so far as the incidence of adenitis/

adenitis in cases of Scarlet Fever is concerned. There are yet to be considered, the opinions of those circum-spect observers who are unwilling to range themselves either in support of an unqualified affirmative or of a complete negative. ⁽⁶⁶⁾ Robb writes that only one case (7%) of slight enlargement of the cervical glands occurred in 14 cases of the disease receiving early antitoxin treatment. But there were three cases of mild adenitis among 7 cases receiving their serum on the third day of disease. Such an incidence, (43%) would be very large in untreated cases. Reviewing 100 cases in the same article, ⁽⁶⁶⁾ Robb states that all were treated very early in the course of the disease and there was no case of glandular enlargement. ⁽¹⁴⁾ Chodzko agrees that cervical adenitis is much less evident if cases receive antitoxin very early. ⁽⁸⁾ Birkhaug had no evidence of adenitis in the series reported, when antitoxin had been given on or before the fourth day of disease. ⁽⁵¹⁾ McLachlan and Hunter compile a table showing the incidence of various complications, according to the day on which Scarlet Fever Antitoxin was administered. Investigation by them showed that no case treated on the first day of disease developed adenitis. Two cases out of a total of 72 having antitoxin on the second day developed the complication. Of the third day series, numbering 43, only 1 had glandular/

glandular enlargement. So far, their evidence seems to suggest that injection of antitoxin on the first day of disease obviates adenitis and that the incidence of this complication is approximately the same for cases treated on the second and third days of illness.

But the argument breaks down at this point, for in 102 patients undergoing specific therapy on the fourth and fifth days of disease, there was not a single instance of infection of the cervical glands.

My series of 106 cases of Scarlet Fever treated with antitoxin includes 11 instances of adenitis (10.4%). Three cases occurred in 40 males and eight in 66 females. Those developing in male patients had the following distribution, :- one case in the 1-5 years age-group; two cases in the 5-10 years age-group. Adenitis in the female patients were distributed more widely, so far as age groups are concerned, :- two cases developed in the 1-5 years age-group; a similar number was found among patients between five and ten years; the 10-15 years age-group afforded one case; three cases occurred in the 15-25 years age-group.

As regards the relation between the percentage incidence of the complication and the day of disease on which antitoxin was administered, my experience does not strengthen the argument that the earlier the treatment by means of Scarlet Fever Antitoxin, the less likely is adenitis to be found complicating Scarlet Fever./

Fever. Out of a total of 10 patients treated on the first day of disease, three developed infection of the cervical glands. A like number, out of 30 patients treated on the second day of disease were affected. Thirty-one cases were treated on the third day of disease and of their number, three developed adenitis. The complication was also seen in two cases out of a total of 35 patients receiving their antitoxin after the third day of disease.

I am not convinced that adenitis is in any way minimised by the antitoxin treatment of Scarlet Fever and I see no reason to believe that, even if its incidence varies in different epidemics and different countries, the question of co-incidence can entirely be ruled out of the favourable reports given by some observers.

Arthritis:- Pain in various joints is a not uncommon occurrence during the course of Scarlet Fever. Some 4% to 6% of patients suffer from this complication, which generally appears about the end of the first week of illness or in the earlier part of the second week. It is important to remember that joint pains are sometimes very marked as a manifestation of serum sickness. It is not suggested that patients suffering from serum rash and joint pains would be diagnosed as suffering from Scarlatinal Arthritis, but eruptions caused by the/

the injection of antitoxin are not always true to text-book limits of duration. No other skin condition, unless it be Urticaria itself, is so volatile and deceptive as serum rash. A brilliant rash may be noted by a nurse during the early morning, but when it is hoped to show it to the Sister or Medical Officer, no abnormality of the skin can be found. In this connection, the writer remembers a case where the Sister of a ward was very anxious to show him a perfect morbilliform serum rash, which she has noted about two hours previously. Not a blemish could be found on the patient's skin. Some confusion followed, but definite proof that no mistake had been made as to the identity of the patient was soon forthcoming. The point has been laboured perhaps, but only to show that great care is necessary not to include serum sequelae among true cases of arthritis. The difficulty is increased by the fact that approximately the same period elapses after giving serum, before the joints become painful, as is required for the development of arthritis after the onset of Scarlet Fever. Occasionally, joint pains without any evidence of rash are noted as a result of administering antitoxin.

⁽⁴⁾
Banks and Mackenzie quote no case of Arthritis among the complications which occurred in 404 cases of Scarlet Fever treated intravenously. Harries⁽³³⁾ had 2 cases/

cases in 100 patients treated intramuscularly, which is the method to be inferred throughout, unless otherwise stated. Gordon⁽²⁸⁾ says that serum treatment greatly reduced the incidence of arthritis, only about one-third of the number of cases occurring, as compared with the normal percentage.⁽⁵¹⁾ McLachlan and Hunter record that the complication was completely inhibited in 230 cases undergoing specific therapy.⁽¹⁸⁾ Cushing notes that only 2% of 500 serum-treated patients complained of joint pains from Scarlatinal Arthritis. Brocker⁽¹⁰⁾ had no case of arthritis in his series.

Toomey⁽⁷⁵⁾ expresses the opinion that antitoxin does not lessen the number of cases of arthritis occurring. Similarly, there was no noticeable reduction in the percentage incidence of joint complications in the investigation of 714 cases of Scarlet Fever treated specifically in five Children's Hospitals in Leningrad. Gordon⁽²⁹⁾ and his co-workers found that in treating 1021 cases, the percentage occurrence of arthritis was 7.4%. This was less than the figure for cases treated with convalescent serum (11%) but considerably greater than the incidence in patients having polyvalent anti-streptococcic serum (4.7%).⁽⁷⁷⁾ von Borman could find no disparity, with a bias favourable to antitoxin-treated cases, between the percentages of joint complications in treated and untreated patients.

Craig/

(15)

Craig notes that only slightly over 1% of his cases developed the complication, the actual number being seven in 512 patients treated with antitoxin.

(14)

Chodzko believes that the percentage incidence of the complication depends on the day of giving antitoxin. He had no case of arthritis in patients treated on the first day of disease. Thereafter the number increased for each day of delay in instituting specific therapy, until, when antitoxin was injected on or after the fourth day, no appreciable reduction in the percentage occurrence of arthritis was noted. The Dicks⁽¹⁷⁾ support this opinion in their record of cases. Robb⁽⁶⁶⁾ had only one case of Arthritis, occurring in a patient who had had Rheumatic Fever two years previously, among 100 cases receiving very early specific therapy.

Only two cases in my series of 106 treated with antitoxin, developed Scarlatinal Arthritis. No case occurred in patients having serum on the first or second day of disease. Of the 31 patients to whom antitoxin was administered on the third day, one had arthritis. The other case was one in 35 patients injected with serum after the third day of disease. Both occurred in females.

The possibility of including joint disorders due to serum was mentioned above, but it must also be allowed that instances of real Scarlatinal Arthritis may be missed because of the co-existence of a serum rash. There seems to be no valid reason why a serum sequela/

sequela consisting chiefly of a skin eruption should not appear simultaneously with real Scarlatinal Arthritis. Because of the great difficulty in distinguishing whether joint pains are in fact really arthritic, consequent on the toxæmia of Scarlet Fever or whether they form part of a reaction to serum therapy, it is not easy to assess the value of anti-toxin in preventing joint complications. It is also true that the percentage incidence of this complication is variable, comparative freedom from it being enjoyed for perhaps some weeks in Hospital Practice, only to be followed by a closely grouped series of cases. I am inclined to believe that no entirely satisfactory case has yet been stated to show a consistently beneficial effect exerted by Scarlet Fever Antitoxin so far as the incidence of arthritis is concerned. If I must take up a definite position, I should agree that very early treatment probably tends to minimise the number of cases occurring, but treatment with serum after the second day of disease is impotent in inhibiting joint involvement. Benefit from early treatment is quite a rational thesis, since arthritis is not a septic complication due to the invasion of the tissues of the joints by the *Streptococcus scarlatinae*, but entirely due to the toxæmia of the disease, the toxin being in comparatively great concentration because of the/

the liberal distribution of blood vessels around the articulations of the body.

Otitis Media:- The percentage incidence of Otitis is from about 8% to 12% and it becomes evident, as a rule, during the latter portion of the third week of disease. Mention has already been made of the fact that valuable information might be forthcoming, with regard to the previous health of patients developing septic complications in Scarlet Fever, if it were possible to have the closest co-operation between Infectious Diseases Hospitals and the School Medical Service. My own observations lead me to conclude that a large percentage of patients who develop otitis, already have abnormalities of the throat and nasopharynx.

(7)

Bipoli analyses a series of cases treated specifically in the Isolation Hospital, Pudna and records that there was a decrease in the number of instances of otitis media. " (10) Bröcker obtained very encouraging results during his investigation at Aachen, for he notes that antitoxin treatment reduced the incidence of ear complications to one-third of the usual percentage in untreated cases. But even with this diminution, this particular septic sequela was still found in 8% of cases. In 500 cases, Cushing (16) also had a complication/

complication rate of 8% for otitis, but he mentions that prior to the introduction of antitoxin treatment, the usual figure for cases exhibiting ear infections was 14%⁽¹⁶⁾ Cushing makes a further very interesting observation, namely, that whereas about 18% of the cases of otitis media, occurring during the course of Scarlet Fever, used to develop mastoiditis necessitating mastoidectomy, the use of specific anti-serum had reduced the percentage by more than half; in fact, to 8%. Other workers infer this, in some instances, when they remark that not only are the complications reduced in number, but also in severity.⁽¹⁾ Archibald affords unstinted praise to the value of antitoxin in preventing otitis, among other complications. He also believes that serum benefits the actual established complication, for he says "Their progress was in all instances arrested and in many, definitely improved at an early period. The effect on rhinitis and otorrhoea would appear to suggest an antibacterial action on the part of the serum, as well as an antitoxic one".

⁽²⁸⁾ Gordon found very definite reduction in the number of cases of otitis occurring. The percentage incidence was roughly only half as great in serum-treated patients.⁽³³⁾ Harries had only 2 cases of discharging ears in 100 cases treated.⁽⁴⁾ Banks and Meckenzie can apparently well afford to brave the criticism of those whose opinion it is that universal intravenous injection/

injection of serum in Scarlet Fever is unnecessarily drastic, for again their record shows that no case, out of 404 treated, developed otitis media.

It seems almost a pity to have to temper the zealous enthusiasm of the above protagonists by introducing arguments for the negative, but the fact that the balance has still to be held suggests that many modifying factors are at work. In the future it may be necessary to look much wider than the laboratory and the disease and their inter-relation; the vast importance of a knowledge of the previous physiology and pathology of Scarlet Fever patients will, almost undoubtedly, be increasingly realised.

(34)
Husler is definitely of the opinion that the percentage number of cases of otitis was not any less as a result of the introduction of specific therapy.

(77)
von Borman was equally unable to demonstrate, in his series of 102 cases, that any inhibition of otitis media followed the use of antitoxin. Buschmann (12) argues in the same strain as the two foregoing observers.

In an article on the proceedings of the Congress on Scarlet Fever at Königsberg, Meyer (54) states that the unanimous opinion expressed by the members was that septic sequelae (which necessarily includes otitis media) were not at all reduced in relative incidence by the administration of Scarlet Fever Antitoxin during/

during the early stage of the disease. Gordon ⁽²⁸⁾ has already been quoted as finding that polyvalent anti-streptococcic serum had a more beneficial effect on the incidence of complications than had Scarlet Fever Antitoxin. Once again he records the same conclusion with regard to ear involvement in the septic stage. In his series of 1021 patients, he found that 11.5% of serum-treated cases developed otitis media. Patients treated with polyvalent anti-streptococcic serum were much more satisfactory, only 6.6% having purulent discharge from the middle ear. ⁽⁴⁵⁾ Lunin carried out careful clinical observations at the Rauchfuss Children's Hospital, but he failed to discover that ear complications were less common in treated, than in untreated, cases.

Qualified findings:- ⁽⁶⁶⁾ Robb states that only 2 cases of mild otorrhoea occurred in a series of 100 patients. All his cases were treated very early. The Dicks ⁽¹⁷⁾ found that the fundamental requirement in the prevention of septic complications was the early administration of the antitoxin. Of 64 cases treated on the first day of disease, only 1 case developed otitis media; this was actually the only complication found in the whole series. Cases treated on the second day of disease had a much less favourable clinical course; of their number (59), five developed middle ear infection and one of those affected developed mastoiditis. ⁽¹⁵⁾ Craig also notes that there/

there was a smaller percentage of cases of otitis media in Scarlet Fever patients receiving antitoxin on the first and second days of disease than in those treated at a later period. ⁽⁶⁾ Benson and Maciver found that if antitoxin were given after the third day of disease, the incidence was comparable to that in untreated cases. ⁽⁸⁾ Birkhaug says that he had no case of otitis in cases of Scarlet Fever receiving adequate antitoxin treatment on or before the fourth day of disease.

My experience is that otitis media is infinitely more common in children under five years than in any other age-group. To state a percentage occurrence for a large series of cases is sometimes misleading. The best method is to give the number of cases for each age group as well as for the total cases treated on the various days of disease. In the series of 106 cases treated at King's Cross Hospital, Dundee, there were 4 instances of suppurative otitis media. All occurred in the 1-5 years age-group which comprised 32 cases of Scarlet Fever. There was thus a percentage incidence of 12.5% for the age-group, although only 3.8% for the total cases under review. One patient was a male and the other three were females. No case of otitis media was found among the patients receiving antitoxin on the first day of disease; 1 occurred in the series treated on the second day; 1 also among third-day cases. The other two instances were in patients/

patients not undergoing specific therapy until after the third day of disease. No case of mastoiditis occurred in the series.

The age-group 1-5 years, in which the complication developed, comprised 17 males and 15 females. Seven males were treated with serum on the second day of disease without the occurrence of any case of otitis, whereas in the females, numbering only two, treated on the same day, one case of otorrhoea developed. The only case of purulent discharge from the ears in male patients was one where antitoxin was administered on the third day. In this age-group, eleven patients (5 males and 6 females) had antitoxin after the third day of illness, yet no case of otitis occurred in the male portion, whereas two cases were found among the six females.

Admittedly, the numbers are too small to allow of any definite conclusion, but from observations previous to and consequent on the period when the cases under discussion were selected, I am unwilling to agree that there is any real decrease in the incidence of otorrhoea as a result of serum therapy. The early admission to hospital, permitting of expert nursing in the toxic phase, may have as much to do with limiting the number of discharging ears as has the administration of Scarlet Fever Antitoxin. I think that attention ought to/

to be concentrated on the age-group or age-groups in which otitis most commonly occurs in attempting to assess the virtues of antitoxin in preventing this complication. There must be considerable variability in the ages of patients per cent of hospital populations, resulting in widely divergent records of the complication-rate in Scarlet Fever. Statistical surveys of experimental work anent a new therapy should certainly take account of the individual age-groups most concerned, when dealing with the several complications, rather than emphasising the variation per cent of total cases treated.

Rhinitis:- Sepsis of the nasal mucosa and accessory sinuses occurs in about 8% of Scarlet Fever patients. It is a late complication and is chiefly seen in children under ten years, but the age distribution is not at all limited, As in otitis, the type of patient most likely to develop rhinorrhoea is the one having pre-existing throat or nasal abnormalities. The whole of the statistics with reference to rhinitis may be made or marred by the competence of the nursing staff. The condition certainly spreads at a great rate unless the strictest vigilance is observed.

Banks⁽⁴⁾ and Mackenzie were not completely successful in ousting this complication by means of the intravenous/

intravenous injection of antitoxin, but they present a very creditable record, having had three instances of rhinitis in over four hundred cases of Scarlet Fever.

(33)

Harries quotes no case of nasal sepsis in 100 cases;

a really remarkable record, if the majority of the

(56)

patients were children. Nankivell came to the con-

clusion, after careful observation of thirty cases of

severe Scarlet Fever, that rhinitis was very much

(28)

reduced in frequency by antitoxin. Gordon had only

5 cases of rhinitis in 317 patients treated. He notes,

in addition, that the condition cleared up more

quickly in serum-treated patients than in others.

(1)

Archibald makes an observation with regard to rhinitis

similar to the one quoted in the discussion on otitis

media. He therefore agrees with Gordon's opinion,

that antitoxin hastens the disappearance of purulent

(16)

nasal discharge. Cushing was extremely favourably

impressed with the action of antitoxin in inhibiting

(10)

rhinitis. Bröcker reports that no case of rhinitis

occurred during the course of disease in 50 patients

treated specifically.

The findings of the above workers are by no means the unanimous verdict of all careful observers.

(29)

Gordon and his co-workers had actually more cases of

rhinitis in treated than in untreated cases of Scarlet

(31)

Fever. Gottsche sees no reason to believe that any

real benefit, so far as the incidence of rhinitis is

concerned, /

concerned, results from specific therapy. von Borman⁽⁷⁷⁾ says that his experience was that the percentage incidence of rhinitis was about the same for treated and untreated cases. McLachlan⁽⁵¹⁾ and Hunter had one case of rhinitis in 13 patients treated with antitoxin on the first day of disease; 4 instances in 72 patients treated on the second day; 3 in 43 third day cases; a similar number in 49 undergoing antitoxic therapy on the 4th day. There is no possible ground for asserting that their statistics show that any beneficial inhibitory influence on the incidence of rhinitis is exerted by Scarlet Fever Antitoxin.

But, just as in discussing the other complications, it is necessary to consider the findings of those workers who qualify their findings by relating them to the day of disease when antitoxin was administered and concluding that early treatment means a lowered percentage of complicated cases. Chodzko⁽¹⁴⁾ found that no case of rhinitis occurred in patients having antitoxin on the first day of disease. Thereafter, the numbers showed progressive increase, until, when the patients were not subjected to specific treatment until after the fourth day of disease, there was no noticeable decrease in the occurrence of rhinitis. Robb⁽⁶⁶⁾ states a strong case for the early institution of antitoxin treatment in cases of Scarlet Fever. In his detailed/

detailed record of 100 cases treated early, it is noted that no case of rhinitis occurred.

I can find no evidence in my series of cases to suggest that antitoxin plays any useful part in suppressing rhinitis in the late stage of Scarlet Fever. The community served by the hospital, where the cases were collected, was a working-class one, veering towards pauperism. Rickets and Congenital Syphilis were, in my opinion, more than usually evident and they may account for the relatively large percentage incidence of Rhinitis. Certainly I am unable to incriminate the hospital staff in any way, for in one ward which was particularly affected by the complication at one period (it had been receiving patients for several days from a very undesirable quarter in the city) was supervised by one of the most competent and energetic Hospital Sisters I have ever known.

Of 32 patients in the Age-group 1-5 years, 22% had rhinitis. Patients in the next age-group numbered 26 and of these 23% had the complication. A considerable fall in the incidence is noted in the age-group 10-15 years, although a percentage of 12.5% cannot be regarded as a satisfactory indication of benefit derived from antitoxin. In the 15-25 age-group, there were 31 patients and rhinitis only occurred in 3.2%. The complication is not common in this age-group in ordinary records of the disease and the low figure recorded/

recorded is of no value at all. The sexes were affected about equally throughout.

With regard to the relative incidence in cases treated on various days of disease, it will be seen from the analytical tables given at the end of the thesis, that 10% of cases treated on the first day of disease had rhinitis; 23% of second day cases were affected; only 9.7% developed rhinitis, when antitoxin had been administered on the third day and 11.4% of those undergoing specific therapy later than the third day.

It was mentioned when discussing Otitis that prolonged concentration by competent observers on the age-groups most affected was required. The statement may be reiterated here. The decrease of the gross percentage of complications is of far less importance than (a) the definitely beneficial effect in the age-groups seriously affected and (b) the demonstration that any particular therapy is enhanced in its action, in proportion to the day of disease on which it is administered.

Cardiac Complications:- These are very rare in actual practice. When they do occur, they are usually seen in conjunction with arthritis, but that does not signify that they are a sequel to the joint complication, but rather a further manifestation of the toxicity/

toxicity of the disease which makes arthritis possible. It is not proposed to deal with affections of the individual coats of the heart separately. The total incidence of any cardiac involvement will be sufficient to demonstrate whether or not antitoxic therapy is distinctly beneficial in this connection. Ordinarily, from 1 case in 200 to 1 in 500 may be expected to develop signs of the local effects of Scarlet Fever Toxin on the heart. No account will be taken of the temporary cardiac abnormalities which occur in the early phase of the disease. In two of his records, (32 & 33) Harries makes a special note that no case of cardiac complication occurred in the case treated with anti-toxin, whereas untreated cases showed the usual incidence of carditis. (4) Banks and Mackenzie report that all of their 404 patients, treated intravenously, (29) escaped cardiac mischief. Gordon, Bernbaum and Sheffield found that 3.5% of 285 serious cases of Scarlet Fever had carditis, although specific therapy had been used; the percentage was roughly comparable to that in 120 severe cases treated by the injection of convalescent serum. (51) McLachlan and Hunter note one case of cardiac irregularity among 230 patients treated and that particular patient had not received antitoxin until the fifth day of disease. Cardiac irregularity is a disappointing classification in a statistical survey. In dealing with children, nothing is/

is more common in the cardiac action than irregularity - apart from sinus arrhythmia - and the only one of grave import, in my opinion, is the presence of extra systoles. Robb details no case of impairment of the heart's action in 100 cases of Scarlet Fever having early antitoxin treatment. ⁽⁶⁶⁾ Craig ⁽¹⁵⁾ found that cardiac complications were completely inhibited in 512 cases treated with serum.

The writer's series of cases shows an unfortunately high incidence of sequelae affecting the heart. Out of 106 cases of Scarlet Fever, one had Endocarditis and another Myocarditis. The case of Endocarditis occurred in a patient treated on the third day of disease and the case developing myocarditic signs was treated after the third day of illness. The former was a male patient in the 5-10 years age-group; the latter a female in the 1-5 years age group. The Scarlet Fever patient exhibiting myocarditis was suffering from the septic form of the disease. Heart signs developed on the seventh day of illness. The patient developing endocarditis, did so on the nineteenth day and was an ordinary case of Scarlatina Simplex on admission.

The writer is of the opinion that antitoxin is impotent to inhibit cardiac complications. It is true that no involvement of the heart occurred in patients receiving specific therapy on the first two days of illness, but an incidence of 2 cases out of a total of/

of 106 patients treated, is above the average incidence when expectant methods of therapy are utilised.

Other Complications:- Little, if any value, can be placed on the percentage incidence of rare complications, comparing treated with untreated cases. The only complications coming under this heading, in the writer's series of cases, were:- 2 cases of Peritonsillar Abscess and 1 case of Conjunctivitis. One of the patients developing Peritonsillar Abscess was a female in the 10-15 years age-group. She had had antitoxin on the first day of disease. Cervical adenitis became evident on the fourteenth day of illness and seven days later the classical signs of quinsy made their appearance. The second instance of the complication was in a male patient in the 15-25 years age-group. He had undergone specific therapy on the fourth day of disease and had no other septic sequela during the course of the illness; there was enlargement of the lymph glands draining the affected peritonsillar region.

The case of Conjunctivitis occurred in a male patient in the 10-15 years age-group and the condition was particularly refractory to treatment, thereby necessitating an extension of stay in hospital of three weeks. There is a possibility in cases of this kind that involvement of the eyes may be determined by/

by refractive error. In ophthalmological practice, the writer finds almost without exception that where stye or blepharitis or conjunctivitis or keratitis selects one eye for its inflammatory activities, that eye is defective in its refraction. If both eyes have refractive errors and only one is the seat of a pathological process, the affected eye has invariably the greater refractive error. This observation is probably not beside the point and it strengthens the argument that the previous health of patients should be known in detail, in order to assess accurately the part played by a specific disease in causing complications and the degree to which various organs and tissues are already predisposed to complications by reason of inherent defects.

Septic and Toxic Cases:- These may be dealt with here, for they are, in fact, complicated cases for the time of onset. It is to be expected, theoretically, that toxic cases will benefit very materially from antitoxic serum, whereas septic cases will be less obviously influenced. Both types are relatively uncommon, but nevertheless contribute considerably to the number of deaths from Scarlet Fever, the case-mortality being high and particularly so in the toxic variety. Of five deaths in Scarlatina, Harries states that two were due to the septic form of the disease and one/

one to the toxic variety.

"⁽⁶⁹⁾
Schottmüller records that of six hypertoxic and apparently hopeless cases of the disease, three re-
covered as a result of antitoxin treatment. Zikowsky⁽⁸⁰⁾
states that in 60 cases of severe Scarlatina, largely made up of septic and toxic cases, the case-mortality was reduced to the very satisfactory figure of 5% by adequate serum therapy. In another treatise, the same
⁽⁸¹⁾
observer notes that in four septic cases included in a series of 73 cases, antitoxin had no observable effect and all proceeded to a fatal termination.

⁽⁴¹⁾
Lautier and Dreyfus say that marked benefit was derived from serum in the treatment of toxic cases, improvement rapidly following the administration.

⁽¹²⁾
Buschmann similarly praises the action of antitoxic therapy in toxic forms of the disease.

⁽⁵⁾
Baxter found that the results of specific antitoxin treatment of septic cases gave disappointing results.

⁽⁷⁾
Bipoli concludes from his observations that, when given within three days of onset, antitoxin has a particularly beneficial effect on the hypertoxic forms of Scarlet Fever. He also records that septic cases, if treated early, undoubtedly benefit. Craig's series⁽¹⁵⁾
of 512 treated cases included ten septic and two toxic cases, all of which recovered. All were treated early in the course of the illness.

(57)

O'Brien says that septic cases are not, in his opinion, favourably influenced by antitoxin. Benson⁽⁶⁾ and Maciver remark that their critical observation of cases did not lead them to conclude that septic cases reacted favourably to antitoxin.

There is absolute agreement that toxic cases of Scarlet Fever derive marked benefit from specific therapy. The writer's series of cases does not include any toxic cases, but the fact is immaterial, for controversy on the effects of Scarlet Fever Antitoxin on such appears to be non-existent.

The same cannot be said with regard to septic cases. Some observers are satisfied that these are favourably influenced by antitoxin and others are either uncertain that mitigation of the septic process follows the administration of serum or are quite uncomplimentary to the treatment as it applies to Scarlatina Maligna.

Three cases of the septic variety of Scarlet Fever are included in the writer's series. One was a female, aged 3 years, admitted on the 10th day of disease and given antitoxin on the same day. The temperature did not regain the normal until the nineteenth day. The patient made a very slow convalescence and was not fit for discharge until the 108th day of disease. A very persistent and wearing Otitis Media was the cause of such a prolonged sojourn in hospital.

The/

The second case was that of a boy of four and a half years, admitted on the fifth day of disease and treated on the same day. The temperature only became normal on the 17th day and convalescence was very tedious. General debility necessitated his stay in hospital for a considerable period and a very late rhinitis (61st day) then appeared, resulting in the postponement of discharge until the ninety-second day of disease.

The other septic case was a girl of four years, who was admitted on the fourth day of disease and whose temperature subsided after eight days. The length of stay in hospital was 51 days in this instance.

I can find no evidence from the clinical course of the septic cases referred to above, or from observations of a number of other septic cases treated with antitoxin, that any definite curative influence is exerted by Scarlet Fever Antitoxin on this particular variety of scarlatina.

Deaths:- The case mortality is very variable, but probably the limits are roughly from 1% to 4% in untreated cases. If specific therapy is really effective, antitoxin-treated cases in this country should show a very low percentage death-rate. It has been demonstrated fairly conclusively in the foregoing portion of this chapter that the initial toxæmia of Scarlet Fever is very definitely reduced and particularly/

particularly are toxic cases benefited. Deaths occurring should therefore be found to be chiefly from Septic Cases, Septic Complications, or cases treated late in the disease.

No deaths occurred in the writer's cases.

(1)
Archibald says that although all the cases treated were of the severe type, the case-mortality was only a fraction of 1%, whereas the usual case-mortality in untreated cases was 1.6%. Nankivell had no deaths in 30 severe cases, while an equal number of untreated cases included two patients who nearly died from serious complications and whose lives were apparently saved by the late administration of antitoxin. Baxter had two deaths in 100 cases treated. He qualifies this comparatively high case-mortality by detailing the causes of death. One was a Septic case and the other fatality was probably determined by a co-existent Gastro-Enteritis and Broncho-Pneumonia. (5)
(43)
Lenthe records one death in 44 cases; the victim of the disease was not treated with serum until the ninth day of illness. (45)
Lunin experienced a moderately high case-mortality in his series of cases treated in the Rauffuss Children's Hospital. Six children out of a total of a hundred died. But all of the deaths except one were due to Septic complications; the sixth was due to Broncho-Pneumonia following Measles.

(75)
Toomey not only finds that serum treated cases had/

had a higher percentage incidence of complications than untreated cases, but also that four deaths in 283 patients treated, were directly attributable to anti-toxin. All four died of anaphylactic shock. Such findings are not reassuring.

(81)

Zikowsky states that he had four fatal cases in 73 severe attacks. All the deaths occurred in septic cases. The Dicks had no fatalities among patients who had had antitoxin before the sixth day after the disappearance of the eruption. Craig records only one death in 512 patients and he notes that there was tuberculous peritonitis present.

(17)

(15)

The above extracts from the literature substantiate the thesis postulated with regard to the type of case, which, in spite of antitoxin treatment, may progress to a fatal termination.

Now to hark back to the beginning of this section of the treatise and to deal with the two alternatives stated there. The first of these was:- "The Incidence of Complications should be markedly diminished as a result of specific therapy". Critical analysis of the findings of other observers, combined with deductions from the statistical record of the writer's own cases allow certain conclusions to be formed. (1) That the incidence of nephritis is definitely lessened by anti-toxin treatment of the toxæmia of Scarlet Fever.

Given/

Given early, it renders the possibility of this complication very remote. (2) Adenitis, Otitis, Rhinitis and comparable septic sequelae generally, are not favourably influenced by serum treatment of the toxic phase of Scarlatina. (3) Cardiac complications are as common when serum has been administered as when non-specific methods are employed. (4) Arthritis is probably minimised in its percentage occurrence by very early serum treatment.

Having taken up an indeterminate position in this aspect of the antitoxin treatment of Scarlet Fever, the second alternative requires to be faced:-

"A scientific explanation of the failure of antitoxin to reduce the complication-rate appreciably is required".

The theory of unidentical toxins readily presents itself as a possible solution to the anomalies in the findings of different observers. If a number of sub-groups of *Streptococcus scarlatinae* exists, producing unidentical but closely related toxins, it is possible that only a percentage of cases of Scarlet Fever cases treated by means of serum are, in fact, specifically treated. Such would explain with a fair measure of satisfaction the praiseworthy effects of antitoxin recorded by many observers, without invalidating the disappointing results obtained by others. But the consistently good results on the toxaemia of Scarlet Fever could hardly be attributed to a serum which was other/

other than specifically antitoxic.

The empirical standardisation of antitoxin must be kept in mind, but it is probably less important than appears on the surface. No commercial firm of repute can afford to give anything less than its best to experimental medicine and almost certainly no such laboratory falls short of the true realisation of its responsibility in the matter. Even if a definite standardisation were possible, as it is in Diphtheria, there is no means of standardising the disease in the same way. The number of Streptococci scarlatinae cannot be gauged within thousands of millions; neither can the rate of the production of toxins in vivo be measured, for each individual attacked reacts at a different rate in the matter of phagocytosing bacteria, neutralising their toxins, eliminating toxins, fixing toxins and actively preventing or passively allowing the inroad of pathogenic micro-organisms. Some scientists are almost too exact; a sprinkling of philosophy might, on occasion, modify their outlook. For instance, having carefully standardised Diphtheria Antitoxin and decided the most serviceable scale of contents of ampoules of the remedy, hardly any two experts are agreed as to actual dosage in the disease itself. This is entirely because Diphtheria cannot be standardised and its special treatment must remain a qualified empirical/

empirical one as regards the amount of antitoxin used, the qualification being that the unit, in terms of Minimum Lethal Doses of Diphtheria Toxin for a guinea-pig of 250 grammes, is known and moderately constant.

The early fixation of toxin by certain tissues offers scope for deductions, with reference to the inability of antitoxin to prevent septic complications. Earlier in this work, quotations were made from eminent authorities who are of the opinion that the destructive action of the toxin of the causative organism makes the later bacterial invasion possible. This hypothesis is interesting and is, in the writer's opinion, a comparatively satisfactory explanation of the relative escape of joints and kidneys in antitoxin-treated cases. Fixation of toxin is probably integrally bound up with the rate of tissue fluid exchange. Because of their function, the kidneys must permit of rapid interchange of fluids as well as actively excreting harmful substances. The continuous bathing of the renal tissues - and particularly the glomeruli - with fluid of a rising antitoxic titre, cannot fail to give the maximum "unfixing" result. Similarly, the joints are richly supplied with blood and the secretion of synovial fluid, along with extensive lymph drainage, must hasten fluid interchange around articulations. This, in turn, speeds up the local increase in concentration of antitoxin, thus enhancing the protection of the structures concerned.

Structures/

Structures which are prone to septic infection in Scarlet Fever are such as have a relatively slow exchange of fluids, in the sense that their nutrition is by means of very gentle diffusion. Toxins are much more readily diffusible than antitoxins and accordingly, a moderately concentrated and prolonged toxic action precedes the neutralisation process. The result is probably an intimate distribution of toxin, which so cripples the involved tissues that recovery is very slow; too slow to have been substantially established before the micro-organisms themselves attack.

EFFECT OF SCARLET FEVER ANTITOXIN ON THE LENGTH OF STAY
IN HOSPITAL.

The normal period of detention in Hospital for uncomplicated cases is 28 days. But the average length of stay is much greater than this, because the septic processes which are mainly responsible for lengthening convalescence are usually slow in clearing up.

It may be assumed almost at once that, since complications regarded "en bloc" are not materially reduced in incidence or shortened in duration, anti-toxin can have little effect on the average length of stay. There is naturally as little concurrence of opinion/

opinion in this aspect of the therapy as has already been noted when discussing the complications of Scarlet Fever.

(15)

Craig records a considerable reduction in the average detention in hospital as a direct result of antitoxin treatment. Baxter⁽⁵⁾ states that, of 100 patients treated, only two had to remain in hospital beyond a period of six weeks. Gordon⁽²⁸⁾ concludes that serum treatment lessened the average stay in hospital by at least a week; in fact, he says from seven to ten days. Nankivell⁽⁵⁶⁾ observed a similar reduction of hospital detention in his series of cases. Harries⁽³³⁾ says that from his observations, more patients could be discharged by the thirtieth day of disease, when antitoxin had been used in treating Scarlet Fever.

(3)

Banks discharged sixteen patients, who had been treated intravenously, after about a fortnight's residence in Hospital. All had been treated within the first four days of disease. The patients in this series were all boys between 12 years and 18 years of age. Speaking at the Annual Meeting of the Fever Hospital Medical Service Group of the Society of Medical Officers of Health in 1929, the same observer⁽²⁾ said that in 300 cases, extending over a period of seven months, the average stay in hospital had been sixteen days. Continuing, he said that adults did so well that they were discharged, as a rule, after eight/

eight or nine days.

(66)

Robb notes that discharge from hospital had been possible earlier, since the introduction of antitoxin treatment. In the later period of his experimental clinical work with antitoxin, he had released a number of patients after a period of isolation varying from seventeen to twenty-four days from the date of onset of the disease. The statement has a qualification, that all such releases were cases which had undergone specific therapy very early in the disease.

The question of the effect of Scarlet Fever Antitoxin on the Length of Stay in Hospital, of cases of Scarlet Fever, resolves itself into (1) The effect of antitoxin in the prevention of complications.

(2) Can a definite prognosis be given? (3) Do cases treated early have a shorter average stay than cases treated late in the disease?

The first of these has already been dealt with in full on another page and it was definitely concluded that, with the exception of nephritis and probably arthritis, the early treatment of patients with antitoxin was no adequate safeguard against complications. Banks appears to take an unreasonable risk in discharging patients so early as the sixteenth day, for a large proportion of septic complications do not make their appearance by that time. A few quotations from my/

my series of cases may be instructive in this respect. A female patient in the 1-5 years age-group, treated with antitoxin on the first day of disease, developed Adenitis on the 24th day and Rhinitis on the 37th day. Another female patient in the 10-15 years age-group, treated on the first day of disease, commenced symptoms of peritonsillar abscess on the 21st day of disease. Numerous examples of late septic complications could be quoted from the records of patients treated on the second and third days of disease.

The second point: Can a definite prognosis be given, when antitoxin has been employed in the treatment of Scarlet Fever? My own cases convince me that it is foolish to attempt to try to select patients who will make an uneventful recovery. I have to admit that it may be entirely different when cases are treated intravenously, but as I believe few clinicians would feel justified in applying this drastic method of therapy to ordinary cases of Scarlet Fever, the excellent results obtained by Banks can hardly be taken to represent the general findings in the matter. My own observations leave me satisfied that there is no royal road to uneventful convalescence through the agency of intramuscular injections of Scarlet Fever Antitoxin.

Coming to the third point: Do cases treated early have a shorter average stay in hospital than cases treated late in the disease? In my series, the average detention/

detention in Hospital for cases treated on the first day of disease was 41 days; for cases treated on the second day, 34 days; third day cases remained 31.5 days on an average and 33 days represents the period for cases treated later than the third day. The average length of stay in Hospital for all cases treated was 34 days. The average Day of Disease on discharge was the 37th. It may be noted that clean cases were discharged on the 28th day of disease and not after 28 days' Stay in Hospital.

I am unable to discover that antitoxin exerted any favourable influence on the length of stay in Hospital. The figures quoted for my cases correspond very closely with those given for untreated cases in Aberdeenshire, as reported in the Medical Officer, 1926, V.36, p.213. The average duration of Stay in Hospital is stated as 37.7 days, when the minimum detention was 28 days (not until the 28th day of disease as was my custom).

THE EFFECT OF SCARLET FEVER ANTITOXIN ON THE
PERCENTAGE OF "RETURN" CASES.

If a case of Scarlet Fever is admitted to Hospital and the patient found to have been in association with a patient discharged from Hospital after an attack of the/
the/

the disease, it is called a "return" case, provided that not more than the arbitrary period of 28 days has elapsed since the release from Hospital of the "infecting" case. The type of patient chiefly responsible for "return" cases is the one who has suffered from one of the septic complications of the disease, notably rhinitis. The percentage of "return" cases varies, depending partly, at least, on the assiduity with which investigations of the possible source of infection are carried out. Co-incidence has also to be kept in mind, as was mentioned in an earlier chapter.

Various investigators have given widely divergent percentages for "return" cases of scarlatina. From just over 1% to nearly 5% are found in the literature.

(51)

McLachlan and Hunter give a report on the condition of patients after discharge from hospital and this tends to show that although there are no obvious complications at the time of discharge from hospital, it does not necessarily follow that the patients have ceased to be infected with the *Streptococcus scarlatinae*. Of 230 patients treated in Hospital, McLachlan and Hunter state that 63 were complicated. The usual standard was required for discharge, yet when home visits were made, 37 were found to have septic sequelae. Of these, 16 cases were due to recurrence of complications after leaving Hospital, while 21 cases developed complications for the first time at home. A large percentage/

percentage of the total complications found, was due to rhinitis.

The above is a strong argument against the limitation of "return" cases as a direct result of serum therapy. It is also very suggestive of the existence of numerous carriers of the *Streptococcus scarlatinae* among patients discharged as "clean" cases. The tonsils, the adenoid tissue in the naso-pharynx, the nasal spaces and their adjacent sinuses offer excellent protection for the micro-organisms and it must be very difficult indeed to be certain that the invader has not only been forced to recede but has also been completely ousted from the tissues of the host. Until some relatively rapid bacteriological test can be applied to convalescents, as is now applicable in Diphtheria, there must continue to be a risk consequent on the release from Hospital of every convalescent patient. Some workers have found nearly 50% of throats harbouring the *Streptococcus scarlatinae* at the end of thirty days from the onset of disease; this implies that probably several months are required before all discharged patients are completely free from infection.

It has already been noted that the incidence of septic complications is not reduced by antitoxin and it follows that the number of "return" cases is unlikely to be limited by the use of specific therapy. If an anti-bacterial serum were available, there would almost/

almost certainly be a very different opinion formed, but at present no such serum has been satisfactorily demonstrated in the therapeutics of Scarlet Fever.

(49)
Mair MacFarlane had only 1.7% of "return" cases, although he discharged patients very early - adults had an average stay in hospital of eight or nine days - , but the result does not necessarily imply a beneficial influence on the incidence of "return" cases.

Apparently, MacFarlane intends to convey this favourable impression. All the cases were clean on discharge, because the period for the onset of septic processes had not then arrived. If and when sepsis did manifest itself, there would tend to be more rapid recovery than occurs in hospital, where it is the massive infection in wards that undoubtedly contributes largely to the lingering of septic processes. If each patient with a septic sequela could be completely isolated, I feel sure the complication would disappear much more rapidly than is the case in the average Scarlet Fever Ward. Incidentally, rhinitis is not really common in adults and it is pre-eminently the cause of "return" cases.

(66)
Robb prefers a period of 42 days as the time-limit for calculating the percentage of "return" cases. Even then, the figure he quotes is only 2.7%. This seems to point in the direction of discounting the time elapsing between the discharge of a patient and the/

the admission of a "return" case. And such an argument is perfectly logical, for it is the definite relation which is of primary importance and which must remain so until Hospital Staffs are able to give a clean bill of health, based on laboratory findings, to persons leaving Fever Hospitals after an attack of Scarlatina.

My series of 106 cases includes only one "return" case (0.94%), which was admitted 15 days after the discharge of the "infecting" case, but this low apparent incidence does not convince me that antitoxin was necessarily responsible for such a satisfactory percentage. Very careful enquiry by medical practitioners might have modified the percentage considerably. Moreover, the type of home to which a patient is discharged is certainly important. If a discharged patient is the only child in a household, very ordinary precautions will obviate further cases, for the adults are probably already immune and child relatives will be discouraged from visiting for the time-being. Similarly, because in the submerged tenth of the population, the percentage of immunes is very high among children, there is little chance of "return" cases occurring. The state of overcrowding and insanitary conditions generally would very probably cause all the susceptibles to be infected at the time of the development of the disease in the first instance.

On/

On the other hand, the well-to-do working-class and the middle-class homes with families of two or three children are likely to provide more "return" cases. The young inmates have been sheltered during their early years and probably, as a result, have not acquired an immunity to the disease. They readily become infected if the discharged sister or brother should still harbour virulent *Streptococci scarlatinae*.

THE PROPHYLACTIC USE OF SCARLET FEVER ANTITOXIN.

Cross-infections are the dread of those in clinical charge of Hospitals for Infectious Diseases. Yet they are not uncommon, in spite of the utmost vigilance and therefore any measure which is likely to minimise their incidence is welcomed whole-heartedly. Whatever may be said for or against the antitoxic therapy of the disease itself, one thing, I think, is conclusively proved and that is, the great value of Scarlet Fever Antitoxin as a prophylactic.

Everyone is agreed that the best prophylactic against Scarlet Fever is the development of an active immunity. This is possible either as a result of sub-infective doses of the *Streptococcus scarlatinae* unknown to the individual or by the injection of increasing doses of Scarlet Fever toxin. But the acquisition/

acquisition of an active immunity is a useless proposition when it is desired to protect patients who have already been exposed to the disease and who are positive Dick-reactors. The only method then available is to provide patients with a temporary security against the development of the disease.

It is very advantageous to test all admissions - other than Scarlet Fever patients, of course - for susceptibility to Scarlatina and to have the result of the test charted. If a case of Scarlet Fever is then found at any time in the ward, there is no loss of time in taking steps to prevent the spread of the disease. All Fever Hospitals do not have a sufficiency of Side-Wards to permit of dividing susceptible contacts into small groups, but much can be done, even in the absence of ideal facilities. There is usually a considerable percentage of Dick-negative patients in a ward, if several age-groups are represented. Advantage should be taken of this by alternating "negative" and "positive" patients' beds during the rearrangement which becomes necessary. I have usually endeavoured to obtain an even more liberal spacing, in dealing with the susceptible contacts who had been in immediate proximity to the case of Scarlet Fever; two "negatives" to one "positive", if the Dick-Reactions of the patients permitted.

Immediately/

Immediately after the removal of the case from the ward, all susceptibles should be given at least 5.0 cc. of Scarlet Fever Antitoxin. If their Dick-Reactions are noted as being markedly positive, a dose of 10.0 cc. is probably required. I have, unfortunately had occasion to use Scarlet Fever Antitoxin prophylactically on a considerable number of occasions in Hospital practice and I have been entirely satisfied with its action.

In my earlier application of the preventive qualities of antitoxin, I was a little disappointed, but it was the dosage which was at fault. At that time, 2.5 cc. were given and I am bound to confess that such a dose is, for the most part, useless. But since giving 5.0 cc. to 10.0 cc., according to the age of the patient and the degree of the Dick Reaction, I have had no second case in any ward which became "infected". The sense of security is a great relief and especially so where patients' relatives have to be interviewed. There is also the additional cause for satisfaction that patients about to be discharged may be released as if no untoward incident had occurred. At least fourteen days immunity is ensured by prophylactic doses of antitoxin. I have Dick-tested quite a number of passively immunised patients at the end of three weeks and found them still "negative".

(35)

Dr Joe's observations lend weight to my own.

He/

He states that the ordinary dose of 2.5 cc. to 5.0 cc. of antitoxin, used prophylactically, is not always sufficient. Continuing, he lays it down that if a Dick-positive reaction of under 20 millimetres is obtained, 5.0 cc. should be given. If the reaction exceeds that in extent, then 10.0 cc. are indicated. His final comment is that 5.0 cc. is only given with safety, if carefully decided on after examining the Dick Reaction in patients. If no such control is carried out, Dr Joe considers that the routine dose should be 10.0 cc.

(37)

Kirkhope gives a detailed analytical study on the prophylactic use of antitoxin. He, first of all, tried 2.0 cc. doses of unconcentrated serum intramuscularly as a prophylactic in fourteen contacts. One of the persons so treated, developed Scarlet Fever the following day. Similarly treating a second series of 101 contacts, he found that 10 developed Scarlet Fever. At this point he makes an interesting observation as to the time elapsing between the inoculation and the development of the disease. In one case it was so long as twelve days. It has to be understood that the actual patients with which contacts were associated, were being treated at home.

His next contacts were only three in number and each was given 5.0 cc. of unconcentrated Scarlet Fever Antitoxin. Two of the three escaped Scarlet Fever, while/

while the other developed the disease on the same day as the serum was given. Such a result does not necessarily mean that 5.0 cc. of antitoxin were useless, but simply that the prophylaxis was applied too late in the incubation period.

Thirty-four more contacts were given 10.0 cc. unconcentrated antitoxin and of their number, three developed Scarlet Fever.

Experimenting now with concentrated antitoxin,
(37)
Kirkhope carried out prophylactic passive immunity in 140 children, who were contacts of cases of Scarlet Fever. Doses varying from 2.5 cc. to 5.0 cc. were given and the only child who developed Scarlet Fever was one receiving 3.0 cc. of serum. Incidentally, the attack of Scarlatina did not develop until fourteen days after inoculation. This appears to demonstrate that the duration of passive immunity is probably more dependent on the dose of antitoxin than is the actual immediate protection afforded. Such a conclusion is a perfectly reasonable one, for destruction of the "foreign" immune bodies is a gradual process and the initial supply must have a fairly definite relationship to the period required for their complete removal from the system.

(37)
Kirkhope's experimental work gives strong support to the hypothesis that 5.0 cc. is a suitable average dose/

dose of antitoxin in the case of a child-contact of
(50)
Scarlet Fever. McGarrity recommends the same limits
of dosage in prophylaxis as does Dr Joe of the Metro-
politan Asylums Board Hospital Service, namely, from
5.0 cc. to 10.0 cc.

In the case of very young children, say, under
six months, the disease is so rare that prophylaxis
by means of injecting antitoxin seems hardly justifiable.
The apparent "natural" or "inherited" immunity to
certain infectious diseases is an interesting one and
has taxed the ingenuity of many eminent epidemiologists.
Cases are on record where the infants of scarlet fever
patients have escaped infection and yet an "inherited"
immunity could not be offered as an explanation in such
a case. One explanation which I have not found offered
by any authority I have consulted is, that the escape
from infection may be due to a simple failure to react,
on the part of the immature organism. When it is re-
membered that a disease is the specific reaction of
the organism to the invasion of micro-organisms or
other causative factor, the failure of the infant to
produce a specific response is feasible. It is well
known that certain parts of the nervous system, for
instance, are very immature at birth and there is no
reason why other organs and tissues should not be
graded in their development. Those structures, whose
highly specialised development at birth is essential
to life, will naturally be completely capable of full
function/

function when extra-uterine life begins. Others, whose development is not so urgent, or the inhibition of whose complete function is actually beneficial, will proceed to maturity at a later period. Immature structures and tissues will probably be incapable of reacting specifically to disease. The occurrence of Whooping Cough in early infancy and the relative rarity of Measles may depend on such factors as are mentioned above. The trachea is certainly highly developed in the early months of life and its rapid and thorough response to adverse local conditions is of vital importance to the child.

The above remarks may be entirely unscientific, but I am inclined to think that the immunity in early infancy, followed as it often is by later susceptibility, is of a different character from the immunity of later life and is probably a simple failure to react specifically to the causative agents of certain diseases.

In the above connection, it is of interest that the blood of very young children has not acquired the group characteristics which are to be constant in the later period of life. It is really undifferentiated. This strongly suggests that a comparable state may exist in some of the infantile tissues, thus rendering recognisable specific reactions to certain invaders quite impossible.

OBSERVATIONS ON SCARLET FEVER AND
ITS SPECIFIC THERAPY.

VII. SUMMARY AND CONCLUSIONS.

SUMMARY - INTRODUCTORY.

The diagnosis of Scarlet Fever may be very easy or very difficult. The help made possible as a result of laboratory research should not be ignored, although, as a rule, cases which are clinically indefinite are the ones in which serological methods of diagnosis render little assistance.

Experimental therapy with specific antisera should demonstrate clearly that such treatment is uniformly valuable, before the administration of Scarlet Fever Antitoxin becomes a routine measure in Hospitals for Infectious Diseases.

Streptococci have been consistently found associated with the throat lesions in Scarlet Fever since 1885, but the struggle for the establishment of a definite causative relationship between streptococci and Scarlatina continues even up to the present. Many authorities have now concluded that it has been shown, beyond reasonable doubt, that the disease is the clinical syndrome of a specific reaction of the body to a special streptococcus, which is toxigenically constant/

constant and which has been designated *Streptococcus scarlatinae*.

Controls are essential in exact scientific work. In this respect, researches dealing with susceptibility to Scarlet Fever can be perfectly controlled, the same person being used for both test and control. But in the investigation of specific therapy, deductions from observations are seriously handicapped, because separate individuals must be made use of as "clinical controls". Before such a method can be at all reliable, the previous physiological and pathological condition of both "treated" and "control" cases must be known. Close co-operation between School Medical Departments and Infectious Diseases Hospitals would do much to enhance the scientific accuracy of clinical therapeutics in Experimental Medicine. The difficulty in prognosing in Scarlet Fever must also be kept in mind in controlling specific therapy, the initial symptoms and signs not uncommonly giving an impression which requires considerable modification as the disease runs its course. In addition, the complement of patients per ward has some bearing on the percentage of complicated cases in "treated", as well as "untreated" Scarlet Fever and what I have termed "Ward Epidemics" of various sequelae, due to relative overcrowding, play a part in determining the course of the disease in individual cases.

If/

If Scarlet Fever is a clinical entity due to the *Streptococcus scarlatinae* and if the therapeutic serum used is specific for the disease, the results of therapy should compare very favourably with the text-book records of the disease, whatever the antecedent history of the patients may be. The serum is probably only antitoxic, although some workers believe it to be antibacterial too. If it is simply an antidote to the toxic manifestations, it is unreasonable to expect it to prevent or mitigate septic complications, unless these are made possible by the previous crippling of the tissues by toxins fixed in them. The dependence on the aggressive action of its toxins has been postulated as a requirement before the *Streptococcus scarlatinae* can itself invade the organs and tissues of the body.

Arguing against the desirability of employing Scarlet Fever Antitoxin, the expedient must be weighed against the ultimate. Passive immunity may prevent the development of an adequate active immunity and thus increase the percentage of second attacks. Or, the type of disease may become modified as a result of the increased antagonism experienced by the causative micro-organism.

The ideal method of ensuring the disappearance of Scarlet Fever is the universal adoption of methods bestowing an active immunity. The best treatment for any/

any disease is prevention.

The spread of Scarlet Fever is probably much more commonly due to carriers than is at present recognised and the importance of carriers must eventually take its rightful place in the epidemiology of the disease, now that the identity of the cause is regarded as established. Difficulties in the rapid identification of the organism in the laboratory still require solution, but, it is to be hoped, are not unsurmountable. Recrudescence of septic complications after discharge has also been shown conclusively to contribute materially to the spread of infection, not necessarily confined to a period justifying the new case being categorised as a "return" case. Missed cases are certainly of moment as links in the chain during an epidemic. Fomites, cutlery, milk, are all capable of spreading Scarlet Fever. Desquamated scales have been incriminated, but evidence of the spread of infection by this means can only be justified when the possibility of the existence of any focus of sepsis in the desquamating patient has been ruled out.

HISTORICAL:-

It is more than two and a half centuries since Sydenham differentiated Scarlet Fever from Measles, but two hundred years elapsed before bacteriological method made it possible to demonstrate the presence/

presence of haemolytic streptococci in the throats of patients suffering from early Scarlet Fever. Some time later, attempts were made to prepare an antitoxic serum; Marmorek⁽⁶⁶⁾ actually treated cases with such a preparation and several other notable workers took up the study.

The laboratory pendulum has swung "for" and "against" the streptococcal origin of Scarlet Fever ever since the discovery of the consistent presence of a streptococcus haemolyticus in the throats of persons affected; an oscillation of great amplitude in one direction being followed, as soon as experimental evidence would permit, by an equally pronounced deviation in the opposite direction. Not only have extreme views been put forward, but intermediate positions have also been taken up; some recording that the finding of the streptococcus was not the whole story; some putting forward symbiotic theories; some regarding the *Streptococcus scarlatinae* as being implicated in the toxic phase of the disease but not in the septic sequelae and so on. The elusiveness of the comparatively recently discovered ultra-microscopic viruses has only intensified the search by other workers to discover a particular one responsible for Scarlet Fever.

Each sect of laboratory research workers has had a following, the duration of the impression made depending on the degree of repute attained either previous/

previous to or during the experimental investigations. Long and painstaking reviews of the bacteriological literature were undertaken and the evidence interpreted critically, in order to establish or refute a particular thesis.

It was in 1917, that the epoch-making experiments of Schultz and Charlton were carried out, when they demonstrated that the blood of convalescent Scarlet Fever patients contained an antitoxin which specifically counteracted the toxic effects of Scarlet Fever on the skin. They also showed that many persons, who, apparently had not suffered from Scarlet Fever at any time, had this same specific antibody in their blood. Comparatively little interest was manifested in this wonderful work at the time of publishing a report of it.

During the next few years, a great deal of work was done by Dochez and his co-workers to establish the toxigenic specificity of the various groups of haemolytic streptococci. Gordon investigated the agglutination characteristics of streptococci from the throats of Scarlet Fever patients and decided that 80% of them were identical in this respect. Park strongly opposed this view, backing up his arguments by careful laboratory researches. In 1923, the well-known experimental work of Drs. George and Gladys Dick was carried out, and in the following year, the same workers established the/

the Dick Reaction as an accurate scientific test for susceptibility to Scarlet Fever.

Since then, there has been a renaissance in the laboratory interest respecting Scarlet Fever. A tremendous amount of experimental work has been carried out and correlated. The true value of the serological diagnostic tests of Schultz and Charlton has been recognised and pioneers in Experimental Therapy, notable among whom are Zingher, Dochez and Behring have done much to establish the specific antitoxic treatment of the disease. Favourable records of the use of Scarlet Fever Antitoxin necessarily raised the question of its production on a commercial scale and firms such as Messrs Parke, Davis and Company and Messrs Burroughs Wellcome and Company entered wholeheartedly into the immunological struggle against the *Streptococcus scarlatinae*.

The overcoming of the toxic effects of the invasion of the human organism by the *Streptococcus* is not the whole story of any form of serum therapy in Scarlet Fever. The septic complications are the dread of those in clinical charge of the cases, and the difficulties requiring solution, before these can be effectively dealt with, have not been overlooked. Some reputable observers have formed the opinion that the *Streptococcus scarlatinae* can be isolated from all cases of the septic sequelae; others are less dogmatic.

(58)

Okell, supporting the view that the complications are due to the bacterial invasion of the tissues by the causative organism, lays it down that the Streptococcus plays a dual rôle, the toxic and pyogenic activities being separate phases of the invasion. He rules that the toxic effects on the tissues are necessary fore-runners of the actual bacterial attack.

The history of the clinical elucidation of the various atypical forms of Scarlet Fever is interesting. So long ago as 1838, Eiselt⁽²²⁾ described Scarlet Fever without a rash and a little later Taupin⁽⁷²⁾ described two similar cases, where the rash could not have been missed, because the observer had been keenly observant and exceptional circumstances made it possible to follow the course of the disease from the very moment of invasion. Scarlet Fever without pyrexia is described in the British Medical Journal of 1896 and probably a proportion of cases of Erythema Scarlatini-forme seen in Dermatological Clinics belong to this form of the disease.

All possible modifications of Scarlet Fever have been noted in the historical clinical records; the variations and effective disguises tax the acumen of trained diagnosticians and are almost certain pitfalls for the beginner. The Streptococcus scarlatinae, half secluded in the mass of streptococci generally, appears unwilling to proclaim its identity and is all the time side-tracking/

side-tracking scientific experiment by wanton sallies from the beaten track. It is easy to understand that the protean character of Scarlet Fever and the great difficulties in the way of the ultimate positive establishment of the causative organism make serum therapy difficult to evaluate. If severe initial symptoms were always followed by the clinical manifestations of a severe attack of the disease, results of treatment could be detailed with mathematical precision.

Progressive sanitation, increased hospital accommodation, disinfection of houses and clothing and all the other measures introduced by virtue of various Acts of Parliament, have not lessened the incidence of Scarlet Fever. Active Immunisation would minimise the number of cases, but until such becomes a routine procedure, the treatment of Scarlatina by the introduction of immune serum is worthy of the fullest investigation.

Aetiology and Diagnosis:- The strictly literal interpretation of the classification of diseases into "epidemic", "endemic" and "sporadic" has gradually become more difficult to defend, as increasing knowledge has afforded scientific workers a more comprehensive view of the workings of natural processes. Epidemic curves are themselves made up of smaller curves, /

curves, which in turn are undulated; endemic and sporadic cases link up and complete the graphic representation of the major and minor periods of incidence of a particular disease.

The "Epidemic Constitution" theory is an apt one in relation to Scarlet Fever. A large percentage number of susceptible persons permits of rapid spread and ideal conditions for enhancing the virulence of the invader. The fact that the case mortality is lowest when the disease is most prevalent may be due to an inherited attenuation of virulence by the micro-organisms, as the direct result of their ancestors' struggle for existence in the face of circumstances which are constantly becoming more antagonistic, as each new host commences to develop an active immunity.

Scarlet Fever is less prevalent in rainy weather; this might possibly be due to an increased peripheral blood-supply resulting from lowered barometric pressure. If such does actually occur, the supply of polymorphonuclear leucocytes will be increased in the mucous membranes and adenoid tissues of the throat.

Conditions predisposing to Scarlet Fever are (1) Local (2) General (3) Environmental; the second of which may be of a temporary or chronic nature.

The spread of Scarlet Fever is probably quite often a direct one, but until it is possible to make use of the laboratory in determining the freedom of convalescents/

convalescents from infection, convincing evidence will be difficult to obtain. Chronic immune carriers are also worthy of note. Clothes, toys, books, bedding and many other classes of common articles have all subscribed their quota to the spread of the disease, although it seems likely that now that Scarlet Fever is less mysterious than hitherto in its bacteriology, the human carrier question will require more emphasis and the fomitic transmission will dwindle in importance. In this respect, it is instructive to note that Chapin of Michigan does not carry out disinfection after removal of cases of Scarlet Fever.

Domestic animals, vermin, milk, have all received attention in connection with the spread of infection. Of these, milk alone has been definitely incriminated, but it is important to remember the close and prolonged association of human beings with this product during the various dairy processes.

Auto-infection after the removal of enlarged tonsils and adenoids and after extensive burning, is quite definite.

The age and sex distribution of Scarlet Fever requires little comment, except that the writer's cases agree with the findings of Pope⁽⁶⁴⁾ in that, after the first quinquennial age period, the disease is vastly more common in females than in males.

In/

In the diagnosis of Scarlet Fever, clinical and laboratory methods are complementary, not antagonistic. The former must remain, for the moment, the more important in difficult cases, where the results of intradermal tests are often of very little help. The repeated Dick Reaction is an important exception to the above statement, unless in very toxic cases, where a failure to react in the early stage of the disease - comparable to the negative tuberculin test in Acute Miliary Tuberculosis - may be noted. The Schultz Charlton test may be applied at the same time as the administration of a therapeutic dose of Scarlet Fever Antitoxin and the result is quite reliable. This saves time in instituting remedial measures in patients who are obviously ill. In the interpretation of the results of intradermal tests, it has to be remembered that all immunities are relative and that persons with definite records of negative reactions may be overcome by massive doses of the infecting micro-organism and its toxin.

Several difficult clinical cases have been detailed in the text, one of them exhibiting a prodromal scarlatiniform rash of Measles.

In dealing with Infectious Diseases among School Children, great help could be afforded in diagnosis if each child were Dick and Schick tested on being examined as an Entrant at Routine School Medical Inspection.
Better/

Better still, if active immunisation against Diphtheria and Scarlet Fever could be carried out in the Child Welfare Centres, those diseases would rapidly cease to be a drain on Hospital accommodation and public resources.

Second, and even third, attacks of Scarlet Fever may be more common than is generally admitted. These are probably the result of an inherent inability, on the part of the individual, to develop a permanent active immunity (c.f. Pneumonia).

SELECTION OF DATA FOR EVALUATING SPECIFIC THERAPY:-

Of the toxic symptoms, the temperature is the only one which is sufficiently consistent in its duration and character to show definite modification as the direct result of specific therapy. Various observers have recorded the effect of antitoxin on the throat, the duration of the rash, the commencement and character of desquamation; but the writer is of the opinion that the normal limits of variation in these are too great to allow of any deduction which could be considered rational.

The effect of specific therapy on the complications of Scarlet Fever is of paramount importance, as these account for all the cases of chronic ill-health following/

following the disease and for the vast majority of protracted periods of convalescence. It is to be remembered that the anti-serum is anti-toxic and not antibacterial, but that the aggressive action of the toxins of the *Streptococcus scarlatinae* is probably a necessary precursor of the invasion of the tissues by the micro-organisms themselves. ⁽⁵⁸⁾ Okell is definitely of this opinion. The fact that some careful observers have failed to demonstrate any favourable effect on the incidence of complications, does not necessarily mean that antitoxin does not help materially in reducing complications if it can gain the injured tissue or organ early enough and in sufficient concentration. Fixation of toxins by certain tissues is given as one reason for the localisation of pyogenic activities during the late stages of Scarlet Fever, but the difference in diffusibility of toxins and antitoxins may be fundamentally important and this in turn may be accentuated or made less apparent, according to the manner in which individual tissues are nourished. In other words, the rate of tissue-fluid exchange may be vitally important in determining the antitoxin content of individual tissues. Since antibodies are closely identified with pseudo-globulins, they are necessarily less rapidly diffusible than toxins.

The complications of Scarlet Fever have been detailed, giving the average percentage incidence of each/

each in cases of the disease untreated by antitoxin. A note is made of the very blotchy character of the rash on the limbs, often observed in patients who develop arthritis. Mild degrees of jaundice are not uncommon in Scarlet Fever and, in the writer's experience, this complication has usually occurred in small outbreaks - another argument in support of Ward Epidemics. The percentage of total complications in Scarlatina is about 40% in cases which are not treated specifically.

Further data, which are important from the point of view of their possible modification by the antitoxin treatment of patients, are Length of Stay in Hospital and Percentage of Return Cases. Both are discussed and in connection with the latter, the part which may be played by coincidence is particularly noted.

THE ANTITOXIC SERUM TREATMENT OF SCARLET FEVER:-

The value of any conclusions reached from observation of the clinical course of Scarlet Fever in patients treated by means of specific antitoxin is modified by certain factors. Of these, the most important are (1) The uniformity of potency of the serum, (2) The dosage, (3) The Method of Administration and (4) The Day of Disease on which the therapy is instituted. In addition, in assessing the usefulness of specific therapy, /

therapy, complications entirely due to the serum, such as serum rashes and anaphylaxis, require to be dealt with.

At first, Scarlet Fever Antitoxin was unconcentrated, but previous experience in concentrating Diphtheria Antitoxin quickly opened up the way for dealing with the new product in a similar way. The result of concentration was, that in a given volume of serum, from four to six times the autotoxic content of the unconcentrated variety became possible; and in addition, the protein was reduced by one half. The standardisation of Scarlet Fever Antitoxin presents great difficulties. Attempts have been made to specify antitoxic value in terms of units of toxin and by means of the Schultz Charlton Reaction. Both are scientifically inaccurate and at best they are largely empirical.

The dose of antitoxin employed varies widely, some workers giving comparatively small quantities, while others use the preparation liberally. Probably 10 cc. are sufficient in ordinary cases; toxic and septic cases should have doses which are judged to be adequate for the particular patients under treatment. Septic cases do better if given polyvalent antistreptococcic serum along with Scarlet Fever Antitoxin. If the throat lesion closely resembles diphtheria, there should be no hesitation in giving Diphtheria Antitoxin/

Antitoxin in addition to the specific treatment, for the evaluation of any therapy necessarily implies that co-existent conditions receive appropriate treatment.

Some authorities consider that Scarlet Fever Antitoxin need not be employed in all cases of the disease. The difficulty in prognosing in Scarlatina negatives such an argument. O'Brien is strongly in favour of treating all cases specifically when he states that, given early, its beneficent action approaches that of the specific antitoxin used in Diphtheria.

With regard to the method of administration, there seems no justification for employing any other than the intramuscular route in ordinary cases. Banks of Leicester records very creditable results from the intravenous administration. Goodall prefers the subcutaneous route, because of the risk of abscess formation after intramuscular injection. The writer has personally never seen an abscess formed, if the necessary and elementary precautions are observed at the time of injection. Sensitised patients may usually be successfully desensitised by giving 0.1 cc., followed by two injections of 1.0 cc. at hourly intervals; an hour later, the remainder of the antitoxin is given. The majority of sensitised persons do not give anaphylactic reactions to subsequent doses of the identical protein, so that simple sensitisation may not be the only/

only requirement for this dramatic phenomenon.

The Day of Disease on which antitoxin serum is given is, of necessity, very important, the prevention of the fixation of toxin by the tissues being more desirable than the neutralisation of toxins already fixed or fixing. The really early treatment of hospitalised cases of Scarlet Fever is almost impossible at present, because the majority of patients are not admitted before the third day of disease. But even if admitted late in the toxic phase, cases of Scarlatina should be given the benefit of antitoxin treatment. Some observers have noted distinct benefit from specific therapy instituted so late as the fifth day.

(66)

Robb of Belfast records that the disease was completely aborted in cases treated sufficiently early. The experimental results of various workers have been quoted, with reference to the period elapsing between the administration of Scarlet Fever Antitoxin and the return of the temperature to normal, according to the Day of Disease on which the serum was injected. The general consensus of opinion appears to be that, the earlier the treatment the earlier the fall of the temperature to normal. But there is one proviso, namely, that when the Day of Disease added to the period elapsing gives a result of five or more days, it is essential to keep in mind that a large proportion of/

of untreated cases will have normal temperatures by then.

In the writer's series of cases, only 10 out of 106 were admitted and treated on the first day of disease; in these, the average period required for the return of the temperature to normal was 2.4 days. Patients treated on the second day of disease had normal temperatures after an average period of 2.8 days. A study of the effect of antitoxin on the temperature in Scarlet Fever in the total (106) cases shows that at the end of the fourth day of disease, 90% of cases treated on the first day, 47% of those receiving antitoxin on the second day and 27% of third day cases had normal temperatures. When given after the third day of disease, specific serum has no appreciable effect on the temperature curve.

The dangers of anaphylaxis must be kept in mind and where there is even the most slender reason to suspect previous sensitisation, appropriate methods should be employed to desensitise the patient. The lymphatic type of child is probably most likely to give anaphylactic reaction. Intracutaneous tests of hypersensitiveness to serum are of little use. It is of particular importance to remember to desensitise patients in whom it is desired to confer a passive immunity to an accidentally introduced mixed infection in a hospital ward, if such patients are in the/

the convalescent stage of a serum-treated disease.

The incidence of Serum Rashes varies greatly in different communities and according to the particular make of antitoxin. The writer has consistently found that sera by Messrs Burroughs, Wellcome and Company give a much smaller percentage of Serum Reactions than do those prepared by Messrs Parke, Davis and Company. Various records of the occurrence of reactions to antitoxin are given in the text and the percentages include Bröcker's ⁽¹⁰⁾ extremely low incidence of 3%, Craig's ⁽¹⁵⁾ 41% and in an intermediate position, Harries' ⁽³³⁾ 20% of cases.

In an attempt to overcome the dangers of anaphylaxis, several manufacturing firms have advocated the use of different animals for the production of each particular antiserum. But unless there is complete agreement in this matter, the resulting confusion would probably add to, rather than reduce, the present difficulties. The writer suggests an International Scheme of tattooing all serum-treated cases. A definite selection of colours could be agreed upon, which, besides giving warning of sensitisation, would give definite information concerning previous attacks of the same disease. The inclusion of a thin sterilised rice-paper wafer, appropriately coloured with a harmless indelible substance, in each package of antitoxin, would be the sole necessary addition to the present outfit/

outfit. When giving the injection, the needle of the syringe would pass through the dyed wafer, previously applied to the area chosen for the administration of the antitoxin.

CRITICAL DISCUSSION OF THE ANTITOXIC SERUM TREATMENT
OF SCARLET FEVER.

The effect on the toxic phase was previously noted in dealing with the benefit derived from the early treatment of Scarlet Fever by means of Antitoxic Serum.

When the study of complications occurring in specifically treated cases is approached, there are, for the most part, three distinct collective opinions to be examined. Whether dealing with complications as a whole, or considering them under separate headings, one group of observers give unqualified praise to serum therapy in Scarlet Fever; a second group can find no reason for resorting to such treatment; while a third relates the effect of antitoxin to the Day of Disease on which it was given. At the outset, the analytical method chosen by the last mentioned appears the most rational.

Notable among the records of those observers who make enthusiastic claims for the unqualified success of the antitoxin treatment of Scarlet Fever, are the findings of MacFarlane, Banks, Birkhaug, Gordon, Cushing/

(49) (3) (8) (28)

(16)
Cushing/

(16) (32 & 33)
Cushing and Harries.

As a member of the directly opposing group,
(20)
Doolittle says "I myself have yet to see the data of
a series treated with intramuscular injections of
Scarlet Fever Antitoxin, which I could not, without
much discredit, match with a series of my own untreated
cases". (34) (82) (30) (75)
Husler, Zingher, Göttsche, Toomey and Dolch,
among others, all contribute to the same or a similar
point of view.

Of these observers who qualify the beneficial
effects of Scarlet Fever Antitoxin by analysing them
according to the Day of Disease on which injection was
carried out, probably the best interpreted results are
those of Drs (17) George and Gladys Dick, (14) Chodzko, (15) Craig,
(66) (6) Robb and Benson and Maciver.

With regard to the incidence of total complica-
tions, which is the aspect of the discussion at the
moment, the writer's findings agree with those records
failing to show a percentage decrease of complicated
cases as a result of specific therapy.

The great majority of complications in Scarlet
Fever are conditions which do not endanger life, but
a proportion consists of such conditions as nephritis,
which, even if not proving fatal, may cause chronic
ill-health. Reduction of the number of serious sequelae
may make little alteration in the figures dealing with
the/

the total percentage incidence of complications, so it becomes necessary to discuss individual causes of protracted convalescence and especially to enquire into their relative frequency in cases of Scarlet Fever treated specifically on various days of disease.

Nephritis and Late Albuminuria:- The incidence varies tremendously in cases not treated with antitoxin.

Several investigators are quoted in the text in support of the beneficial effect of Scarlet Fever Antitoxin on the percentage incidence of nephritis. The series of cases detailed by Banks and Mackenzie is of particular interest, in that no case of nephritis was found in 404 patients treated intravenously. Gordon found that the total incidence of albuminuria was not reduced, but that actual nephritis cases were reduced in number by one half. This probably supports the view of a number of eminent authorities that late albuminuria is a condition quite distinct from nephritis. Cushing, Toomey and Dolch, Göttsche, Husler and Doolittle, among others, are all agreed that the incidence of kidney mischief is not lessened, as a result of the serum treatment of the toxic phase of Scarlet Fever.

Analytical studies of the course of disease in scarlatinal patients, tabulated according to the day of disease when specific therapy was instituted are perhaps the most instructive. The general consensus of opinion of such reliable observers as Birkhaug,⁽⁸⁾/

(8) (6) (66) (14)
 Birkhaug, Benson and Maciver, Robb and Chodzko is that early administration of antitoxin reduces the percentage number of cases of nephritis occurring and that the frequency of this complication varies directly with the day of disease on which antitoxin is given.

The writer's series of cases support the contention that nephritis is very definitely reduced in percentage incidence, if antitoxin is introduced on or before the third day.

Adenitis:- As in Nephritis, qualified and unqualified cases are stated with regard to the effect of specific therapy on the number of cases of late adenitis occurring. Among those workers who were very favourably impressed in respect of the effect on adenitis are (28) Gordon, (69) Schottmüller, (4) Banks and Mackenzie (33) and Harries. Such investigators as (10) Bröcker, (25) Friedemann (77) and Deicher, (12) von Borman and Buschmann were unable to convince themselves of any real benefit on this particular complication.

A third group of statistical surveys indicates that early therapy ensures a lessened percentage incidence of adenitis. These findings are recorded (66) in the treatises by Robb of Belfast, (8) Birkhaug, (51) McLachlan and Hunter and others indicated in the general text of this study.

The writer's series of 106 cases of Scarlet Fever included 11 cases (10.4%) of adenitis and there is no ground/

ground for assuming that the percentage incidence was in any way modified by the early administration of antiserum.

Arthritis:- From 4% to 6% of ordinary Scarlet Fever cases suffer from joint pains. In serum-treated patients, it is essential to keep in mind that joint pains may occur as a manifestation of serum reaction, without any evidence of serum rash. The close correspondence of the periods of onset of both conditions leads to a little difficulty in differential diagnosis.

(4)
Banks and Mackenzie had no case of arthritis in (51) 404 patients treated intravenously. McLachlan and (16) Hunter's cases enjoyed a similar immunity. Cushing and other observers record a favourable influence exerted on the incidence of arthritis.

(74) (29)
Toomey and Gordon, Bernbaum and Sheffield see no reason to believe that arthritis is less common in serum-treated cases. The latter found that polyvalent anti-streptococcic serum gave more favourable results than did specific antitoxin.

Cases treated early are less likely to develop arthritis, according to (15) (14) (17) Craig, Chodzko, Drs George and Gladys Dick and Robb. (66)

No case of arthritis occurred in patients treated during the first two days of disease in the writer's series; one of the 31 patients treated on the third day developed the complication; the other instance occurred/

occurred in a patient treated after the third day. Both patients were females. Probably, antitoxin given early tends to inhibit joint complications.

Arthritis is a toxic complication and as such, should benefit from early specific treatment of the toxic phase.

Otitis Media:- Opinions are again divided as to the effect of Scarlet Fever Antitoxin in controlling complications. (7) " (10) (16) (1) Bipoli, Bröcker, Cushing, Archibald, (35) (28) Harries and Gordon are notable among those who are convinced that the incidence of otitis is definitely less, when antitoxin is used in treating scarlatina. (16) Cushing elaborates his argument by pointing out that only 8% of cases of otitis media occurring in serum-treated patients progressed to mastoiditis, as against 18% prior to the institution of antitoxin therapy.

An imposing group of investigators can also be cited to argue for the direct negative to the above. Included in it are such names as Husler, (34) (77) von Borman, (12) (45) Buschmann and Lunin.

The qualification of specifying the day of disease on which antitoxin was given and grouping cases accordingly enhances the value of the investigations of Robb, (66) (17) (6) (15) (8) The Dicks, Benson and Maciver, Craig and Birkhaug. All of these observers have formed the opinion that otorrhoea is less common in Scarlet Fever, when cases receive/

receive early specific therapy.

Four cases of otitis media occurred in the 106 cases of Scarlet Fever under special review. All were in the age group 1-5 years and three of the four were females. The distribution according to the day of disease when antitoxin was administered was such as to negative the deduction that any definite inhibitory influence was exerted by serum treatment.

Rhinitis:- Whereas about 8% of cases of untreated Scarlet Fever develop Rhinitis, Banks and Mackenzie had only three instances of the complication in 404 patients treated intravenously. Harries, Gordon, Archibald and others mentioned in the full text had either equally or even more encouraging results. Many equally responsible workers could find no diminution of the number of cases of rhinitis, resulting from serum treatment. Such observers as Robb and Chodzko concluded that very early specific therapy of Scarlet Fever completely obviated the complication.

The writer's cases do not show any real reduction in the number of cases of rhinitis as a result of treatment with Scarlet Fever Antitoxin; there is no regular increase in the percentage incidence in cases treated on successive days.

Cardiac Complications:- These are relatively uncommon, even in untreated cases, but their seriousness/

seriousness makes them extremely important.

As is the case in the records dealing with the complications enumerated above, there are great differences of opinion with regard to the merits of Scarlet Fever Antitoxin treatment in the prevention or mitigation of cardiac complications. Harries, Banks and Mackenzie, Robb and Craig all note the complete freedom from cardiac complications of patients treated specifically. McLachlan and Hunter and Gordon and his co-workers were less fortunate in their surveys. The writer had two cases in the series of 106 patients, which, although not occurring in patients treated on the first two days of disease, is a higher incidence than might be expected when ordinary non-specific methods of treatment are employed.

A few minor complications are mentioned in the text but their study allows of no useful conclusion.

Septic and Toxic Cases:- Both varieties are complicated from the time of onset. Theoretically, toxic cases should benefit very materially from a specific antitoxic serum and the findings of such investigators as Schottmüller, Lautier and Dreyfus and indeed, those of the majority, are in keeping with this hypothesis.

Bipoli found that septic cases reacted satisfactorily/

satisfactorily to early treatment, as also did Craig⁽¹⁵⁾
 and Zikowsky.⁽⁸¹⁾ On the other hand, Baxter,⁽⁵⁾ O'Brien⁽⁵⁷⁾
 and Benson⁽⁶⁾ and Maciver, among others, were disappointed
 with the serum therapy of Septic Scarlet Fever.

There were three cases of the septic form of the disease among the writer's patients and the clinical course of the disease in these does not suggest any definitely beneficial effect resulting from antitoxin therapy.

Deaths:- Serum-treated patients should only succumb to the disease if it is initially septic or because late septic sequelae develop. The death-rate from toxic cases is definitely less in antitoxin treated patients, if early treatment is possible.

Examination of the records shows that the case mortality is reduced by specific therapy. Archibald⁽¹⁾ had a case mortality of only 1% among severe cases treated. The only deaths recorded by Baxter,⁽⁵⁾ Lenthe,⁽⁴³⁾
⁽⁴⁵⁾ Lunin and Zikowsky⁽⁸¹⁾ occurred in septic cases or from septic complications or where antitoxin treatment was carried out relatively late in the disease. Toomey⁽⁷⁴⁾ records 4 deaths from anaphylaxis in 283 patients treated.

The foregoing discussion on the specific therapy of Scarlet Fever does not offer convincing proof of the usefulness of antitoxin in lessening the incidence of/

of all complications, although nephritis and arthritis appear to benefit. Several theories may be put forward in explanation. Variations in the findings of individual observers may be due to the existence of a number of sub-groups of the *Streptococcus scarlatinae*, in which case some records may be those of cases not specifically treated (unidentical toxin and antitoxin) in the strict scientific sense. The consistently good results recorded on the toxæmia of the disease negative this. The empirical standardisation of antitoxin has also to be remembered, as it implies considerable variation of dosage.

Early fixation of toxins may prevent access by antitoxin for the purpose of neutralisation. Probably such fixation is inversely proportional to the rate of tissue fluid exchange; if so, it can be argued that the kidneys and joints are peculiarly fortunate in possessing the necessary exchange system for speeding up the local concentration of antitoxin. Tissues having a slow exchange of fluids should coincide with those liable to sepsis in the late stage of Scarlet Fever, if the above hypothesis is logical. Such is actually the case.

EFFECT/

EFFECT OF SCARLET FEVER ANTITOXIN ON THE LENGTH
OF STAY IN HOSPITAL.

The failure of antitoxin to reduce septic complications leads to the conclusion that the average duration of stay in hospital can be but little affected as a result of specific therapy.

(15) (28) (33) (2 & 3) (66)
Craig, Gordon, Harries, Banks and Robb are all agreed that patients' residence in hospital was definitely lessened.

Quite a number of workers appear to have taken unjustifiable risks in discharging serum-treated patients. Banks considered the treatment complete in sixteen days in a large proportion of adult patients. It has to be granted, however, that he treated all of them intravenously, which may give results profoundly different from those in intramuscular therapy.

Interpreted from as many points of view as were considered useful, the writer's cases could not be shown to have the average period of convalescence shortened as a result of intramuscular antitoxin treatment.

EFFECT OF SCARLET FEVER ANTITOXIN ON THE PERCENTAGE
OF "RETURN" CASES.

Patients who have had septic complications are chiefly responsible for "return" cases, but coincidence must/

must also be kept in mind. The latter fact is illustrated in the text from personal experiences.

(51)

McLachlan and Hunter give a very useful detailed study of the following up of patients after discharge from hospital. They show that not only were there recrudescences of septic processes but also that "clean" cases developed septic sequelae for the first time after leaving hospital. Their work demonstrates the difficulty of assessing freedom from infection in examining convalescents.

A comparatively rapid laboratory method of dealing with patients whom it is proposed to discharge, would be of inestimable value.

Several investigators quote a very low percentage of "return" cases following early discharge after antitoxin treatment. But this may be partly due to the more rapid and complete recovery from any septic sequela which occurs after discharge on account of removal from the massive sepsis of a Scarlet Fever Ward housing a number of complicated cases.

There should be no time-limit used in calculating the percentage of "return" cases, if definite relation between a discharged case and the "return" case can be established and *Streptococci scarlatinae* can be isolated from the naso-pharyngeal region of the supposed "infecting" case.

More/

More exhaustive search by trained investigators would undoubtedly raise the percentage of "return" cases, if direct relationship between cases were the criterion and the time elapsing disregarded.

THE PROPHYLACTIC USE OF SCARLET FEVER ANTITOXIN.

To ensure any uniform success in this connection, a dose of at least 5.0 cc. is required. If the Dick Reaction is very strongly positive, as much as 10.0 cc. may be required. It is quite safe to assume a period of fourteen days as the duration of the passive immunity conferred; many patients treated prophylactically are still Dick-negative at the end of three weeks. Joe⁽³⁵⁾ states that 10.0 cc. should be used as a routine, if the Dick Reaction is not applied as a control.

⁽³⁷⁾ Kirkhope's experimental work shows that 5.0 cc. of Scarlet Fever Antitoxin is a suitable average prophylactic dose for a child-contact. The general consensus of opinion is that 5.0 cc. and 10.0 cc. are adequate minimum and maximum doses respectively.

The well-known "immunity" enjoyed by a large proportion of very young children may be a simple failure of the immature organism to react specifically to certain infections.

CONCLUSIONS.

1. Experimental evidence is overwhelmingly in favour of a definite haemolytic streptococcus as the causative organism of Scarlet Fever. There may be sub-groups of the *Streptococcus scarlatinae* which are toxigenically identical.
2. Acute and chronic carriers are probably pre-eminently important in the method of spread of Scarlet Fever.
3. The diagnosis of mild and atypical cases of Scarlet Fever remains a clinical proposition. Serological methods are seldom helpful, except that the definite change from a positive to a negative Dick Reaction during the course of the disease is proof that the condition undergoing treatment is Scarlet Fever. It is presumed, of course, that antitoxin has not been administered.
4. Considerable help in the diagnosis of difficult cases would be afforded if every child were submitted to the Dick Test on entering school and periodically thereafter. Close co-operation between the School Medical Services and Infectious Diseases Hospital Authorities would then make it possible to have useful information regarding the personal/

personal history of every child suspected of having Scarlet Fever.

5. Scarlet Fever is, on an average, diagnosed too late for the full benefit to be derived by the majority of serum-treated patients.
6. Scarlet Fever Antitoxin is specifically antitoxic.
7. The lack of a scientific method of standardising Scarlet Fever Antitoxin is a serious handicap to experimental therapy with this particular immune serum.
8. The average intramuscular dose of 10 cc. of concentrated Scarlet Fever Antitoxin is a suitable one. Toxic cases should receive at least 20 cc. intramuscularly.

The appropriate treatment of co-existent diseases (e.g. Diphtheria) does not detract from the value of observations on the results of the specific treatment of Scarlet Fever.

9. The antitoxic treatment of the toxic phase of Scarlet Fever is valuable. The earlier the administration of the serum, the more rapid is the amelioration of the toxicity.

10. The problem of sensitisation to horse serum requires attention. An International Scheme which would permit of harmless indelible substances being used for tattooing the site of injection would be a valuable safeguard against anaphylaxis. Accurate records of second and subsequent attacks of a particular zymotic disease would also be made possible by such a procedure, if an agreed colour represented a particular disease.
11. Specific Antitoxic Therapy does not reduce the percentage of total complications appreciably, but the incidence of nephritis is definitely lessened and probably it could be entirely obviated by adequate early antitoxin treatment of Scarlet Fever. Arthritis is less evident in cases receiving early specific therapy.
12. Toxic Scarlet Fever is markedly benefited by treatment with antitoxin. The treatment has no appreciable effect on cases of Septic Scarlatina.
13. Antitoxin treatment lowers the case mortality by its great curative influence on toxic cases and by preventing nephritis in patients subjected to the therapy early in the toxic phase.

14./

14. The Length of Stay in Hospital is not reduced as a result of antitoxin treatment. This is explained by the fact that the serum appears incapable of preventing or mitigating septic sequelae, which are the most important causes of protracted convalescence.
 15. "Return" cases may be less common in Hospitals practising antitoxin treatment of Scarlet Fever, but if so, the reason for the reduction is probably the early discharge of patients. By this means, massive sepsis occurring in wards is avoided. If septic complications develop after discharge, recovery is more rapid and more complete than is the case when complicated cases are housed in the same hospital ward.
 16. There is no room for argument as to the outstanding value of Scarlet Fever Antitoxin as a prophylactic. With adequate dosage, a passive immunity lasting for at least fourteen days can be guaranteed to contacts of the disease.
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VIII. APPENDIX I. ANALYTICAL TABLES.106 Cases of Scarlet Fever.1. Age- and Sex- Distribution.

Age Period	0-1	1-5	5-10	10-15	15-25	25-35	35-45	Totals.
Males	-	17	9	2	9	3	-	40
Females	-	15	17	6	22	5	1	66

2. Day of Disease on Admission; arranged in Age and Sex Groups.

Age Group	Sex	1st Day of Disease	2nd Day of Disease	3rd Day of Disease	After 3rd Day of Disease.
1-5	M	2	7	3	5
	F	5	2	2	6
5-10	M	1	5	2	1
	F	2	7	5	3
10-15	M	-	-	2	-
	F	1	3	1	1
15-25	M	-	2	3	4
	F	1	5	6	10
25-35	M	-	-	2	1
	F	-	3	-	2
35-45	M	-	-	-	-
	F	-	1	-	-

3. Average Day of Disease on Admission; for each
Age and Sex Group.

Age Group	1 - 5		5 - 10		10-15		15-25		25-35		35-45	
	M	F	M	F	M	F	M	F	M	F	M	F
Average Duration of Disease (in Days)	3	4	2.5	2.25	3	2.5	3.25	3.5	3.25	3	-	2

4. Number in each Age and Sex Group, treated with
Scarlet Fever Antitoxin on various Days of Disease.

Age Group	1-5		5-10		10-15		15-25		25-35		35-45	
	M	F	M	F	M	F	M	F	M	F	M	F
1st Day of Disease	2	3	1	2	-	1	-	1	-	-	-	-
2nd Day of Disease	6	2	5	5	-	3	1	4	-	3	-	1
3rd Day of Disease	4	3	2	7	2	-	4	7	2	-	-	-
After 3rd Day of Disease	5	6	1	3	-	2	4	10	1	3	-	-

5. Average Day of Disease, on which Scarlet Fever Anti-
toxin was given: Arranged in Age and Sex Groups.

Age Group	1-5		5-10		10-15		15-25		25-35		35-45	
	M	F	M	F	M	F	M	F	M	F	M	F
Average Day of Disease	3.0	4.0	2.5	2.5	3.0	2.5	3.5	3.5	3.25	3.0	-	2.0

Average Day of Disease for Total Cases = 3.2

6. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal, when the Serum was given on the 1st Day of Disease. (a) For Total Cases. (b) For Total Males. (c) For Total Females.

Description and Number of Cases	Period Elapsing						Average Period Elapsing.
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
Total (10)	2	4	3	-	1	-	2.4 Days
Males (3)	1	2	-	-	-	-	1.7 Days
Females (7)	1	2	3	-	1	-	2.7 Days

7. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal, when the Serum was given on the 2nd Day of Disease. (a) For Total Cases. (b) For Total Males. (c) For Total Females.

Description and Number of Cases	Period Elapsing						Average Period Elapsing.
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
Total (30)	4	10	10	4	-	2	2.8 Days
Males (12)	2	6	4	-	-	-	2.2 Days
Females (18)	2	4	6	4	-	2	3.2 Days

8. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal, when the Serum was given on the 3rd Day of Disease. (a) For Total Cases. (b) For Total Males. (c) For Total Females.

Description and Number of Cases	Period Elapsing						Average Period Elapsing
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
Total (31)	8	14	3	3	1	2	2.5 Days
Males (14)	4	5	1	1	1	2	2.9 Days
Females (17)	4	9	2	2	-	-	2.1 Days

9. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal, when the Serum was given after the 3rd Day of Disease. (a) For Total Cases. (b) For Total Males. (c) For Total Females.

Description and Number of Cases	Period Elapsing						Average Period Elapsing
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
Total (35)	14	7	5	3	3	3	2.8 Days
Males (11)	7	1	1	-	2	-	2.0 Days
Females (24)	7	6	4	3	1	3	3.0 Days

10. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal: Analysis of each Age and Sex Group.

Age Group	Sex	Period Elapsing						Average Period Elapsing
		1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
1-5	M	9	5	3	-	-	-	1.7 Days
	F	5	7	2	-	-	1	2.25 Days
5-10	M	3	4	2	-	-	-	1.9 Days
	F	5	6	5	1	-	-	2.1 Days
10-15	M	-	2	-	-	-	-	2.0 Days
	F	1	2	1	1	1	-	2.8 Days
15-25	M	2	3	1	-	2	1	3.0 Days
	F	2	6	6	5	1	2	3.3 Days
25-35	M	-	-	-	1	1	1	5.7 Days
	F	1	-	-	2	-	2	4.8 Days
35-45	M	-	-	-	-	-	-	-
	F	-	-	1	-	-	-	3.0 Days

11. Periods and Average Periods elapsing between the Administration of Scarlet Fever Antitoxin and the Return of the Temperature to normal. (a) For Total Males. (b) For Total Females. (c) For Total Cases.

Description of Cases	Period Elapsing						Average Period Elapsing
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days	
Total Males	14	14	6	1	-	2	2.3 Days
Total Females	14	21	15	9	2	5	2.8 Days
Total Cases	28	35	21	10	5	7	2.6 Days

12 Percentages of Cases, in which the Temperature reached normal in the various Periods noted after the administration of Scarlet Fever Antitoxin, when analysed for (a) Total Males (b) Total Females (c) Total Cases (d) Each Age Group.

Description or Age Group.	Percentages of Temperatures reaching normal in:-					
	1 Day	2 Days	3 Days	4 Days	5 Days	6+ Days
Total Males	35.0	35.0	15.0	2.5	7.5	5.0
Total Females	21.2	31.8	22.7	13.7	3.0	7.6
Total Cases	26.4	33.0	19.8	9.4	4.7	6.7
1 - 5	43.75	37.5	15.63	-	-	3.12
5 - 10	30.8	38.6	26.9	3.8	-	-
10 - 15	12.5	50.0	12.5	12.5	12.5	-
15 - 25	12.9	29.0	22.6	16.1	9.7	9.7
25 - 35	12.5	-	-	37.5	12.5	37.5
35 - 45	-	-	100.0	-	-	-

13. Course of Disease and Length of Stay in Hospital.Age Group 1 - 5 years. Males. 17 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.			Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Rhinitis	Otitis	Adenitis		
2	2	5	27			53	52
2	2	5	33			67	65
3	3	5				* 48	45
2	2	3				28	26
3	3	4		26		47	45
5	7	9	30			92	88
6	6	6				29	23
3	3	3			16	31	29
2	3	4				31	30
2	2	4				28	26
4	5	6	27			31	27
1	1	2				28	27
4	4	5				28	24
2	2	4	23			40	38
4	4	5				*45	41
2	2	5				27	25
1	1	3				28	27

* Debilitated after the toxic phase.

14. Course of Disease and Length of Stay in Hospital.Age Group 1 - 5 years. Females. 15 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.		Day of Disease when occurring			Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Rhinitis.	Otitis.	Serum Rash.	Adenitis.	Myocarditis.		
5	5	7						* 53	48
2	2	3	22					29	27
4	4	7		9				76	72
7	7	9			16			29	22
1	2	5						26	25
2	3	5					8	28	26
10	10	19		32				108	99
1	1	1						* 80	79
3	3	3						32	30
1	1	3	37		18	24		87	86
4	4	5					7	51	47
10	10	11						29	19
1	2	4		15				58	57
1	1	3			17			31	30
3	3	5						33	30

* Debilitated after toxic phase.

15. Course of Disease and Length of Stay in Hospital.Age Group 5 - 10 years. Males. 9 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications. Day of Disease when occurring.				Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Rhinitis.	Serum Rash.	Adenitis.	Endocarditis		
2	2	4	26				33	31
2	2	3					43	42
2	2	4					30	28
3	3	4					* 42	39
5	5	6	24				45	41
2	2	4				19	78	76
2	2	5	28		6		53	52
1	1	3		11	18		40	40
3	3	6		20			31	28

* Pre-existing Chronic Otitis Media.

16. Course of Disease and Length of Stay in Hospital.Age Group. 5 - 10 years. Females. 17 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications. Day of Disease when occurring.			Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Rhinitis	Adenitis.	Anaphylaxis		
3	3	5				28	25
4	4	5				30	26
4	4	5				29	25
3	3	5				28	25
2	3	5				29	27
1	1	4				27	26
3	3	4	24	6		37	34
2	2	3				* 43	41
2	2	6				30	28
1	1	4				44	43
2	2	5				29	27
2	2	4	27		2	42	40
2	3	4	12			36	34
3	3	5				28	25
2	2	5				28	26
3	3	6				33	30
4	4	6		8		28	24

* Post-operative Abdominal Wound.

17. Course of Disease and Length of Stay in Hospital.Age Group 10 - 15 years. Males. 2 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complication.	Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Day of Disease when occurring.		
			Conjunctivitis.		
3	3	5		30	27
3	3	5	21	49	46

18. Course of Disease and Length of Stay in Hospital.Age Group 10 - 15 years. Females. 6 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Rhinitis.	Serum Rash.	Adenitis (A) and Peritonsillar Abscess (P).	Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
3	4	7				30	27
1	1	6			14(A). 21(P)	32	31
2	2	4		8		28	26
2	2	6		14		28	26
2	2	4				28	26
5	5	6	21			34	29

19. Course of Disease and Length of Stay in Hospital.Age Group 15 - 25 years. Males. 9 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.				Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Day of Disease when occurring.					
			Rhinitis.	Serum Rash.	Peritonsillar Abscess.	Nephritis.		
2	3	5	22	8			47	45
2	2	4					28	26
3	3	5					* 56	53
4	4	5				21	36	33
5	5	5					30	25
4	4	7					28	24
3	3	8					29	26
3	3	9					30	27
4	4	9			18		28	24

* Debilitated after Toxic Phase.

20. Course of Disease and Length of Stay in Hospital.Age Group 15 - 25 years. Females. 22 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.			Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Day of Disease when occurring.				
			Serum Rash.	Adenitis	Arthritis		
3	3	7				29	26
2	2	5				30	28
4	4	8				33	29
2	3	5				39	37
4	4	6		10		32	28
6	6	7			9	35	30
1	1	4				* 39	39
3	3	7				32	30
2	2	9		11		32	30
2	2	5		14		31	29
6	6	11				30	25
7	7	10				29	23
5	5	7				31	26
3	3	5			6	28	25
3	3	4				31	28
4	4	8				28	25
3	3	6				28	26
4	4	7				28	25
3	3	5	8			35	32
4	4	13				33	29
2	2	6				28	26
4	4	6				28	24

* Increased Length of Stay due to Septic Finger.

21. Course of Disease and Length of Stay in Hospital.

Age Group 25 - 35 years. Males. 3 Cases.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.	Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Day of Disease when occurring		
3	3	11	Nil	29	26
3	3	7	Nil	28	26
4	4	9	Nil	28	24

22. Course of Disease and Length of Stay in Hospital.

Age Groups 25-35 years and 35-45 years. Females.

5 Cases in former Age Group and 1 Case in latter.

Day of Disease on Admission.	Day of Disease on giving Antitoxin.	Day of Disease when temperature reached normal.	Complications.	Day of Disease on Discharge from Hospital.	Number of Days in Hospital.
			Day of Disease when occurring		
			Serum Rash.		
Age Group 25 - 35 years					
2	2	8		28	26
5	5	14		29	25
2	2	6		28	26
2	2	5	11	32	30
4	4	8		28	24
Age Group 35 - 45 years					
2	2	5		29	27

23. Average Course of Disease. Percentages of Individual Complications and Average Length of Stay in Hospital for each Age and Sex Group.

Age Group.	Sex.	Number of Cases.	Average Day of Disease on admission.	Average Day of Disease on giving Antitoxin.	Average Day of Disease when temperature reached normal.	Percentages of Individual Complications.										Average Day of Disease on Discharge.	Average number of Days in Hospital.	
						Rhinitis.	Otitis.	Adenitis.	Arthritis.	Nephritis.	Peritonsillar Abscess.	Conjunctivitis.	Endocarditis.	Myocarditis.	Serum Rash.			Anaphylaxis.
1-5	M	17	3.0	3.0	4.7	29.4	6.0	6.0									40.5	37.5
	F	15	4.0	4.0	6.25	13.3	20.0	13.3					6.6	20.0			50.75	46.75
5-10	M	9	2.5	2.5	4.4	33.3		22.2									44.5	42.0
	F	17	2.25	2.5	4.6	17.6		11.6				11.1		22.2			32.25	30.0
10-15	M	2	3.0	3.0	5.0												39.5	36.5
	F	3	2.5	2.5	5.3	16.6		16.6			50.0						30.0	27.5
15-25	M	9	3.25	3.5	6.5												34.75	31.5
	F	22	3.5	3.5	6.8	11.1		13.6	9.1								31.75	28.25
25-35	M	3	3.25	3.25	8.95												28.5	25.25
	F	5	3.0	3.0	7.8												29.25	26.25
35-45	M	-	-	-	-												-	-
	F	1	2.0	2.0	5.0												29.0	27.0

24. Average Course of Disease. Percentages of Individual Complications and Average Length of Stay in Hospital for (a) Total Males (b) Total Females (c) Total Cases.

Description of Cases.	Percentages of Individual Complications.		
	Total Males	Total Females	Total Cases
Number of Cases.	40	66	106
Average Day of Disease on Admission.	3.0	3.0	3.0
Average Day of Disease on giving Antitoxin.	3.0	3.3	3.2
Average Day of Disease when temperature reached normal.	5.5	6.1	5.8
Rhinitis.	22.5	9.0	14.2
Otitis.	2.5	4.5	3.8
Adenitis.	7.5	12.0	10.4
Arthritis.	-	3.0	1.9
Nephritis.	2.5	-	0.9
Peritonsillar Abscess.	2.5	1.5	1.9
Conjunctivitis.	2.5	-	0.9
Endocarditis.	2.5	-	0.9
Myocarditis.	-	1.5	0.9
Serum Rash.	7.5	10.5	9.4
Anaphylaxis.	-	1.5	0.9
Average Day of Disease on Discharge.	39.0	35.5	37.0
Average Number of Days in Hospital.	36.0	32.5	34.0

25. Shortest, Longest and Average Periods in Hospital of Cases in the under-noted categories, when Scarlet Fever Antitoxin was given (a) on the 1st Day of Disease, (b) on the 2nd Day of Disease, (c) on the 3rd Day of Disease, (d) after the 3rd Day of Disease.

Age Groups etc.	Sex.	1st Day of Disease			2nd Day of Disease			3rd Day of Disease			After 3rd Day of Disease.		
		Shortest Period.	Longest Period.	Average Period.	Shortest Period.	Longest Period.	Average Period.	Shortest Period.	Longest Period.	Average Period.	Shortest Period.	Longest Period.	Average Period.
1-5	M	27	27	27	25	65	38.7	29	45	37.3	23	88	40.6
	F	30	86	71.7	25	57	36.3	26	33	29.7	19	99	51.2
5-10	M	40	40	40	28	76	45.8	28	39	33.5	41	41	41
	F	26	43	34.5	26	41	32.4	25	34	28.6	24	26	25
10-15	M												
	F	31	31	31	26	26	26	27	46	35.5	27	29	28
15-25	M				26	26	26	26	53	37.8	24	35	26.5
	F	39	39	39	26	30	28.3	25	37	29.1	23	30	26.4
25-35	M							26	26	26	24	24	24
	F				26	26	26				25	30	27.5
35-45	F				27	27	27						
Total Males		27	40	31.3	25	76	40.7	26	53	35.1	23	88	34.0
Total Females		26	86	50.6	25	57	30.0	25	37	29.0	19	99	32.9
Total Cases		26	86	44.8	25	76	34.3	25	53	31.8	19	99	33.3

26. Septic Cases. Details of Course of Disease and Length of Stay
in Hospital. 3 Cases. Percentage 2.8%.

3	F	10	19	32	61	55	7	108	98	64	
$\frac{6}{4 \frac{12}{12}}$	M	5	17								
4	F	4	12					51	47	13	
				Day of Disease when occurring.							
				Otitis.	Rhinitis.	Adenitis.	Cardiac Failure.				
								Day of Disease on Discharge from Hospital.	Number of Days in Hospital.	Increase of Stay in Hospital over average Stay for all Cases.	

IX. APPENDIX II. BIBLIOGRAPHY.

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