STUDIES IN THE PATHOLOGY OF STAPHYLOCOCCAL INFECTIONS

BY

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I submit this thesis for the degree of Doctor of Medicine in the University of Edinburgh. It has not already been accepted for any degree, and it is not being concurrently submitted in candidature for any degree.

I certify that I have written this thesis myself, and, except for the acknowledgements made in the preface, the work presented in this thesis has been done by me.

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PREFACE.

The work embodied in this thesis has been undertaken during my appointment as an assistant clinical pathologist at the Welsh National School of Medicine.

Many people have aided me directly or indirectly in various ways. I thank Professor J. Gough, M.D., for the facilities which his department has afforded, and for introducing me to the field of experimental pathology. I also thank my colleagues in the Department of Pathology, for much helpful criticism, whereby I have been aided in the formulation of opinion. Drs. A. G. Heppleston, M.D., M.R.C.P., H. G. Roberts, M.B., and H. W. Whiteley, M.D., have allowed me ready access to their autopsy reports, and pathological material.

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Mr. J. P. Napper took most of the photographs, which form such a considerable portion of the thesis.

Mr. W. E. Wentworth prepared the paper sections of whole lung.

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INTRODUCTION.

The current trend in the investigation of staphylococcal infections is to concentrate attention on the bacterium and its products. Not only does the bacterium receive most attention, but also the prevalent tendency is to experiment in vitro. This thesis presents an attempt to approach the question as a problem in host resistance, rather than one simply of bacterial virulence. Furthermore, partly as a result of inclination, and partly because of the nature of the facilities available, I have limited the study, to the morbid anatomy of the host response, and not its immuno-chemical aspects. The problem has not so much been sought after, but has rather presented itself, in the course of my routine work as a hospital pathologist.

The scope of this thesis falls into three main sections:

1. A study of the type of patient who contracts staphylococcal septicaemia.
2. A study of the morbid anatomical changes observed in fatal cases.
3. A study of the response of the experimental animal to staphylococcal septicaemia.

Whilst the importance and complexity of bacterial variations in the production of disease are realised, this thesis is that host resistance is a major factor in the response to, and outcome of, severe staphylococcal infections. Whilst this may appear to be a truism, the staphylococcus does nevertheless claim, perhaps, more than its share of attention. It may be
the "villain of the piece", but that is no reason for neglecting the "piece".

Early in the course of this work it became apparent that fatal cases, both in their clinical course, and pathological picture, showed features suggestive of a state of hypersensitivity to the bacterium or its products. The kidneys, and to a lesser degree the lungs, were found to be indices of such a state of hypersensitivity. Therefore, this thesis argues that in staphylococcal septicaemia there may arise a state of hypersensitivity to the bacterium or its products, and that this state, mediated principally by its effect on the kidneys and lungs, is often the decisive factor in a fatal outcome.

In presenting this thesis, I am all too well aware of the many questions that have been left unanswered, or questions that have not even been asked. Many new techniques could, with advantage, be utilised in the investigation of this problem. The animal experiments are described, not because they give irrefutable proof of the argument of the thesis, but the findings do provide some comparative and corroborative evidence. I regret the relatively small number of animals that could be used, and the limited scope of the experiments, but I believe that sufficient evidence of structural damage is presented to indicate, and justify, further experimentation - particularly of the serological aspects.

Staphylococcal infections are an example of a field of research, where the "climate of opinion", conditions the direction of such research in an almost exclusive fashion.
Judging from current medical literature, more people are concerned about the staphylococci present in hospital dust, than are concerned with the pathogen in the human body. I trust that it is not too presumptuous to hope that this thesis will, in some small measure, contribute to a re-orientation of thought, and a different emphasis, concerning staphylococcal infections.

The inflammatory response in an area of localized sepsis has been recognized for as long as historical records are available. The Egyptian plagues of boils; the sufferings of Job; the 'signs of Celsus', are well-known examples.

The Italian physician Fracastorius (1453-1553), was the first to discuss the cause of the inflammatory response. He referred to invisible parasites - the seminaria as the cause of the putrefactive disease, (Fracastorius 1546).

This idea was further developed by Kircher (1558). He postulated the existence of contagium animatum. The effluvium is alive and contains imperceptible bodies:

"Since they are very fine and subtle and very light are driven about not otherwise than the atoms by the very movement of the air. But since they have a certain sluggishness, and are of glutinous tenacity, they find it easy to insinuate themselves into the innermost fibres of clothes, ropes and linen sheets. Of a truth, that is full of pores like wood, bones, cork and even metals, they penetrate by their fineness and form new hot beds of contagion."

These were great conceptual advances, but before there could be an objective demonstration of their validity, a technical advance was awaited. This was the discovery of
CHAPTER 1.

HISTORICAL REVIEW.

"And if the bright spot stay in his place, and spread not in the skin, but it be somewhat dark; it is a rising of the burning, and the priest shall pronounce him clean, for it is an inflammation of the burning."

Leviticus, 13. 28.

The inflammatory response in an area of localised sepsis has been recognised for as long as historical records are available. The Egyptian plague of boils; the sufferings of Job; the 'signs of Celsus', are well-known examples. The Italian physician Fracastorius (1483-1553), was the first to discuss the cause of the inflammatory response. He referred to invisible parasites - the seminaria as the cause of the putrefactive disease, (Fracastorius 1546).

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These were great conceptual advances, but before there could be an objective demonstration of their validity, a technical advance was awaited. This was the discovery of
the microscope. The compound microscope was probably discovered sometime between 1590-1610. But it was Antonj van Leeuwenhoek (1632-1723) who designed and made the first efficient magnifying system (although he was really using simply an efficient magnifying glass). He not only provided the instrument, but also in 1676 described the morphology of various animalcules, including the coccal form.

The only noteworthy feature of the following century in the development of the recognition of the causes of specific infections, was the commencement of the debate on spontaneous generation. Louis Joblot's (1645-1723) and Lazzaro Spallanzani's (1729-1799) works were important not only for the reason that they were early champions of the cause that Pasteur was later to vindicate fully, but they also applied the experimental method to the investigation of this problem.

The necessity of the experimental method was given further emphasis and impetus by John Hunter (1812). He made the first fundamental distinction between the causes of inflammation and the results of such inflammation in the tissues - "Inflammation in itself is not to be considered a disease but as a salutary operation, consequent either to some violence or some disease," (Hunter 1812). He also drew attention to phlebitis as a factor in dissemination (Hunter 1793).

The contagious nature of infective processes still, however, awaited demonstration. This was made the subject of clear-cut experiments by Gaspard (1822,1824). He performed a series of over 70 experiments on dogs, sheep, foxes and pigs, with putrid infusions - pus,
vaccine, lymph, blood, bile, urine, sperm, saliva, carbonic acid, hydrogen and hydrogen sulphide, by intrapleural, intravenous, subcutaneous, and intraperitoneal injections. He described the symptoms and lesions, and provided the next major advance when he observed that blood from a dog suffering from putrid intoxication could reproduce the disease when injected into another dog.

Gaspard's findings were confirmed by Magendie (1823), and Virchow (1856), who injected dogs with putrid matter. Virchow's work on thrombosis and embolism also disposed of the commonly held view expressed by Morgagni (1761), that post-wound pyaemia was caused by the carriage of pus to the viscera and its deposition there.

The debate as to the microbic character of the contagious factor continued. Schwann (1837) suggested that putridity might be brought about by microbes. Pasteur (1863) showed that putrefaction could be produced by organised ferments of the genus *Vibrio*. But some continued to look for the chemical causes of putrefaction, whilst others looked for bacteria. It may not be inappropriate, if even somewhat ironical, to state at this juncture that part of this thesis is that insufficient attention may have been paid subsequently to the chemical nature of the bacterial antigen in staphylococcal infections, as the cause of allergic tissue damage in the host during infection.

The next step was the discovery of micrococci in pyaemic lesions, by several people. Von Recklinghausen (1871) found micrococci in the kidneys from a case of pyaemia. Waldeyer (1871) found them in the cardiac and renal abscesses,
as well as peritoneal pus in puerperal fever. Coccii were also identified in lesions, and in the blood stream by Birch-Hirschfeldt (1872). However, even in 1874, Billroth did not think there was enough evidence to conclude that inflammation could be caused by bacteria.

Davaine (1872) experimented extensively on the problem of infection. He noted an increased virulence on repeated animal passage of putrid material. He further found that the virulence of infected blood disappeared on keeping, and also that the minimum lethal dose of putrid material depended more on the species of animal than on its size. Rabbits were found to be the most susceptible.

Coze and Feltz (1872) found bacteria in the blood of animals (ante-mortem and post-mortem) which had received injections of putrid fluids. They also reported the presence of bacteria in cases of typhoid fever, variola, scarlatina, measles and puerperal fever, and alleged that such blood was infective for animals. These extensive claims must, of course, cast considerable doubt on the reliability of their experimental techniques.

Klebs (1871) carried out classical researches on gunshot wounds in the Carlsruhe military hospitals - he performed 115 autopsies, 73% of which showed septicaemia and pyaemia. He found bacteria of different forms in fresh and preserved specimens but he made the mistake of regarding these as different forms of one organism - microsporon septicum.

The term "septicoemia" was first introduced by Pierry (1837). Vulpian (1874) stated that septicaemia was due to bacteria in the blood and that it was, in fact, a parasitic
disease. He used the word "bacteriemie".

Because of the confused terminology, the matter was discussed by a committee appointed by the Pathological Society of London (1879). This committee suggested the various conditions should be grouped into:

1. Septic intoxication - chemical, non-infective.
2. Septic infection - due to some peculiar constituent of putrid matter in the blood. Some thought this a living organism, others a non-organised ferment.
3. Pyaemia - similar to 2, but giving rise to metastases.
4. Thrombosis - with softening of thrombus and embolism.

The recognition of staphylococcal infection with septicaemia as an entity still awaited the researches of two other men. Koch (1878) showed that diseases differing clinically and anatomically can be produced experimentally by the injection of putrid substances. He examined tissues using aniline stains and took clear pictures of the bacteria in the tissue lesions. Furthermore, he differentiated between pathogenic and non-pathogenic bacteria and noted that the smaller the injected dose the longer the animal survived.

The first person, however, to identify the staphylococcus as a cause of clinical infection was Ogston (1880, 1881, 1882, 1883), although due credit is not given to Pasteur, who in 1880 reported that he cultivated small spherical organisms in broth from the pus of boils and osteomyelitis. He also produced infection in the rabbit, and recovered the
organisms. Ogston used Koch's methods in the examination of 100 abscesses for bacteria. No bacteria could be found in the "cold abscesses", whereas the staphylococcus could be seen in the acute variety. Ogston differentiated between "chain micrococci" and "grouped micrococci". In contrast to the clear demonstrations, and lucid deductions of Koch and Ogston, the clinical reports relating to septicaemia at that time show considerable confusion of thought. Reports of what read like cases of staphylococcal septicaemia were recorded by Waller (1882), Fergus (1879), Bradley (1876), Kealey (1885) and Jones (1889), amongst others. Moxon and Goodhart (1875) gave a clear description of three cases of ulcerative endocarditis with "arterial pyaemia", but postulated that the observed "so-called bacteria" were the products of changes occurring in the red blood cells.

Bradley (1876) in a well-documented account, described cross infection in a surgical ward. He distinguished between two types of septicaemia - the one arising "de novo" and the other by direct inoculation from without. Furthermore, when commenting on what was then a frequent source of debate, he stated that he drew no distinction between septicaemia and pyaemia. His concluding remark is distinctly applicable today - "But, gentlemen, it is not enough to isolate our cases, we must purify our wards."

The fulfilment of Koch's postulates came when Garré (1885) infected himself with a strain of Staph. aureus obtained from a fatal case of osteomyelitis, by rubbing a whole slope culture into the skin of his left forearm. After the formation of small pustules, which coalesced, a carbuncle formed which took three weeks to heal.
with considerable scar formation. Bümm (1885) and Bockhart (1887) carried out similar experiments.

This century has witnessed the discovery of the various toxic and enzymic properties of pathogenic staphylococci, and their intimate relationship with staphylococcal bacteriophages. The close correlation found between haemolysin and oagulase production with pathogenicity has aided the identification of the pathogenic staphylococci. The discovery of bacteriophages has greatly facilitated epidemiological surveys (Blair 1956). Nevertheless, there has been surprisingly little advance in the understanding of the pathogenic role of the staphylococcus in the human body.

In the years 1920–1940, the classical methods of Bacteriology and Immuno-chemistry were applied principally to what were then important and frequently encountered bacteria — namely the haemolytic streptococci, Strep. pneumoniae, N. meningitidis, Corynebacteria and M. tuberculosis. The staphylococcus tended to be regarded as harmless even if ubiquitous. Then, at a time when increasing attention might well have been paid to this organism, the discovery of sulphonamides and penicillin introduced an entirely new field of study and even suggested that the problem might soon be one of academic interest alone.

Many reports of isolated instances of staphylococcal septicaemia, as well as larger series, did appear in the medical literature during 1900–1940. Ryle (1930) gives a picture of staphylococcal fever as it occurred in the pre-antibiotic era. He emphasised its protean nature but his view that a "reasonably optimistic
prognosis is justified" and that the majority of people with a "sound physique" should recover, does not appear to have been consonant with other contemporary reports.

Mendell's review (1939) is probably one of the best assessments for the period in question. He regarded the staphylococcus as "the deadliest organism of general sepsis". Other series are those of Bean (1929), Neuhof et al (1934), Scott (1935), Reinman (1936), MacNeal and Frische (1936) and Skinner and Keefer (1941).

Much of the research that was done on the staphylococcus during these years concerned its exotoxins and enzymes. Kraus and Pribram (1906) found that some strains of broth filtrates killed on intravenous injection in a dosage of 1-2 cc. per Kg. bodyweight within 5-30 mins. and also that animals could be protected by antitoxin. Burnet (1929) did detailed work on the toxins of the staphylococcus which had exhibited their virulence in the Bundaberg disaster of 1928, when diphtheria toxin-antitoxin for human immunisation had been contaminated and 12 children died as a result. Burnet analysed the lethal, skin-necrotising and haemolyzing properties of exotoxin, and considered that they were antigenically similar.

Duran-Reynals (1933) postulated a "spreading factor" which might account for the invasiveness of virulent strains. Valentine (1936) correlated the haemolytic and leucocidin properties with pathogenicity. The staphylococcal toxins are considered in more detail in the final chapter of this thesis.

Fewer studies of the antigenic properties of the organism itself, as distinct
from its products, have been reported. Julianelle and Weigherd (1935) developed a precipitin technique for antibody estimation, and a method for extracting bacterial protein. This extracted protein was shown to be antigenic and to stimulate a specific antibody response. The subsequent relative lack of interest in this aspect of the problem is probably explained by the discovery of chemotherapeutic and antibiotic agents.

Julianelle and Weigherd did not examine histological material. As a major portion of this thesis is concerned with histological changes it is necessary to trace the growth of knowledge in this branch of the subject.

The suppurative visceral lesions encountered in staphylococcal septicaemia were the earliest to be described and produced experimentally. Wyssokowitsch (1886) first studied the renal excretion of Staph. aureus in the rabbit. He concluded that after intravenous injection the staphylococcus appears in the urine within 6 hours. Sherrington (1893) confirmed this. The details of embolisation, abscess formation and excretion in the rabbit's kidney were worked out by Dyke (1923). He showed clearly that urinary excretion of cocci is evidence of the presence of an established renal lesion. Other work relating to the suppurative renal lesions is referred to in the clinical and experimental portion of this thesis.

However, the lesions that are of greater interest and relevance in the present context are the non-suppurative renal and pulmonary lesions. Harbitz (1899) listed 16 cases of chronic infective endocarditis and drew attention to the frequency and intensity of renal symptoms.
Aschoff (1909) included ulcerative endocarditis as amongst the commonest causes of glomerulonephritis. Löhlein (1907) was the first to describe focal endocarditic glomerulonephritis. Dispute then arose, and still continues, as to whether these focal lesions were toxaemic or embolic. The principal subsequent reports were those of Baehr (1912), Fahr (1925) and Bell (1932).

Neisser and Levaditi (1900) were the first to produce renal necrosis in the rabbit by the intravenous injection of staphylococcal toxin. After Parker et al (1925-26) described their method of producing staphylococcal exotoxin, further reports appeared by Weld et al (1931), Forssman (1932) and De Navasquez (1938).

Concurrently with these advances, fundamental observations and experiments were proceeding in another field — namely in that of the phenomenon of allergy or hypersensitivity.

Portier and Richet (1902) performed the first classical experiments using glycerin Actinaria extracts on dogs, although previous workers had observed the phenomenon - Magendie (1839) due to repeated injections of albumen in rabbits; Flexner (1894) following injections of dog-serum in rabbits, and Behr (1893) with diphtheria toxin hypersensitivity in the guinea pig.

Richet's great contribution was to provide an explanation, not of the specific causes of given conditions, but a basis for the understanding of the extreme degrees of individual variation that may be observed in any given condition. In few diseases are such extremes of individual variation seen as in staphylococcal septicaemia. Richet's words in
1902 are particularly applicable to the increasing problem of serious staphylococcal infections — "Partly as the result of food that has been taken and partly as the result of multiple microbial infections which have attacked him and most often pass unnoticed, each individual is profoundly different from his neighbour, each has been prophylactised or anaphylactised to different degrees against different substances."

The name "anaphylaxis" was given by Portier and Richet (1902) to the phenomenon they had witnessed. Similar phenomena were described by Arthus (1903) using the rabbit; and by Otto (1907) using the guinea pig, to elicit anaphylactic shock following horse serum injections. The Arthus phenomenon of local anaphylaxis has been used in many guises under differing experimental conditions, for example, Shapiro and Ivy (1926), produced acute gastric ulcers by local anaphylaxis in rabbits and dogs.

The concept of hypersensitive host responses was soon applied extensively in the field of bacteriology, especially in the case of the streptococcus (Clawson 1933), the pneumococcus (Zinsser and Mallory 1924) and the meningococcus (Gerber 1936). It is not germane to this discussion to enter into the argument that then prevailed on the nature of the anaphylactic response — whether it was a humoral or a tissue response.

The investigations into hypersensitivity phenomena were given a further impetus following the description by Sanarelli (1924) and Shwartzman (1929) of the phenomenon of local and generalised tissue reactivity. This phenomenon was shown to be operative under
experimental conditions for E. typhosus and N. meningitidis - (Apitz 1935) and Black-Schaffer et al 1947). A hypersensitivity response has been invoked to explain the pathological lesions found in several clinical infections, for example, in E. coli epidemic gastroenteritis - McKay and Wahle (1955). Gerber (1936) described the renal lesions found in rabbits when a generalised Shwartzman phenomenon was produced by two intravenous injections of meningococcal and E. typhosus filtrate, separated by a 24 hr. interval.

At this time, when clinical and experimental experience of hypersensitivity reactions had advanced rapidly and were being integrated into a coherent scheme with the in vitro and in vivo properties of various bacteria, the picture was further complicated by the arrival of a new concept. The designation of a new pattern of disease, namely the so-called "collagen diseases", appears rather to have complicated, if not confused, knowledge of the pathology and pathogenesis of hypersensitivity states, although at the same time the diverse roles which hypersensitivity reactions could take in human disease, were acknowledged. Gruber (1925), first suggested that periarteritis nodosa might be due to a hypersensitivity process. Vaubel (1932) found in the heart of 5/46 of horse-serum treated rabbits "hyperplasia of the intima, a fibrinoid swelling of the intima and media, and a proliferation of adventitial cells."

Rich and Gregory (1943) demonstrated the close similarity between the lesions found in diseases such as periarteritis nodosa and rheumatic fever, to those seen in the animal made hypersensitive to foreign protein. Then the term "diffuse collagen disease" was used by
Klemperer et al (1942) to include, in addition to rheumatic fever and periarteritis nodosa, other conditions such as disseminated lupus erythematosus, diffuse scleroderma, rheumatoid arthritis, thromboangiitis obliterans, and serum-sickness.

Many publications have appeared describing the renal lesions found in animals rendered hypersensitive to various substances. Masugi (1934) used nephrotoxic serum; Rich and Gregory (1943) used horse-serum; Hawn and Janeway (1947), More and Waugh (1949) and McLean et al (1951), all used large amounts of intravenous bovine gamma-globulin to induce diffuse glomerulonephritis.

Since 1940 the greater portion of work undertaken in the study of staphylococcal infections has been concerned either with epidemiological problems, or with antibiotic relationships. Now, however, that serious hospital staphylococcal infections are recognised to be an urgent medical problem, the time should be ripe to reassess the pathogenesis of such infections. The question is no longer "What is the cause of pyaemia and septicaemia?" but, "Why should one individual develop, or succumb to, a fulminating infection, whilst another may appear to be equally exposed to the ubiquitous staphylococcus, and yet remain unaffected?"

Knowledge gained in the study of "stress disorders" (Selye 1950), the isolation of cortisone and A.C.T.H. (Hench et al 1949), have provided additional concepts and tools with which to approach the problem of host resistance and individual variation.
This thesis attempts to integrate the concepts of hypersensitivity and stress disorders with present day knowledge of staphylococcal septicaemia.

Following Hench's observation (1938) that patients suffering from rheumatoid arthritis frequently gained a remission during pregnancy or when jaundiced, he and Kendall collaborated in the investigation of the activity of certain steroids isolated from the adrenal cortex. Hench et al (1949) used "Compound E" and discovered the dramatic ameliorative effect which these hormones exert on rheumatoid arthritis.

The major therapeutic and ideological advance made by Hench and his colleagues came at a time when, as we have seen, great interest was being taken in the pathology of the "collagen diseases". Thus, after the initial clinical trials on rheumatoid arthritis, the effect of steroid hormones on other "collagen diseases" was soon put to the test - pemphigus vegetans, scleroderma and disseminated lupus erythematosus, (Brodthagen et al 1951). Steroids were also used in experiments which had previously been performed in the production of hypersensitivity states in general. Nelson et al (1950) used cortisone to protect mice from fatal anaphylactic shock when being sensitised with horse serum. Dews and Code (1951) found that steroids did not seem to influence anaphylaxis in the guinea pig. Probably the guinea pig is a poor animal to use for a demonstration of the protective influence of cortisone, because of the ease with which it may be made hypersensitive. Humphrey (1951) did claim, however, that cortisone conferred a definite, although minor, degree of protection
against anaphylactic shock in the guinea pig. He also found that cortisone greatly relieved oedema in the reverse passive Arthus reaction, and that it prevented the Shwartzmann phenomenon in the rabbit.

Germuth and Ottinger (1950) using rabbits, demonstrated that "Compound E" and A.C.T.H. reduced the size and frequency of Arthus reaction, but the animal could still produce a normal Arthus reaction on the passive transfer of antibody. There was a reduction of circulating antibody. The same authors (1951) noted that treatment with Compound E. had no effect on the rate of disappearance of circulating antibody in the presumably immunised rabbit - suggesting that Compound E. and A.C.T.H. reduce the circulating antibody by inhibiting antibody formation rather than by increasing antibody destruction.

It has been shown experimentally (Clawson and Nerenberg 1953) that cortisone suppresses the ability of reticulo-endothelial cells to destroy engulfed streptococci. Streptococci, which would normally have only a limited local action (Thomas 1955), killed rabbits which had been given cortisone.

Several reports have now appeared of the association of cortisone with septicaemia - Slaney and Brooke (1958), Dubois-Ferriere (1951), Hayes and Kushlan (1956), Shaper and Dyson (1955), Smith and Cleve (1957), and Hughes and Truelove (1958). The apparent contradiction between an increased liability to septicaemia during steroid therapy and the proposition that serious staphylococcal infections may be manifestations of a state of hypersensitivity (and therefore might benefit from cortisone), is considered
later in the light of clinical and experimental findings.

It is against this historical background of the increasing knowledge gained in the fields of bacteriology and pathology that the problem of severe staphylococcal infections must be considered. That it is in fact a grave problem is widely recognised. The immediate problem may appear to be that of the ease with which the staphylococcus acquires or exhibits antibiotic resistance. But, as Rogers, D.E., states (1956), "drug resistance alone, has rarely been the cause of therapeutic failure." The high incidence of hospital infections which is exemplified in the clinical portion of this thesis is ultimately a question of host resistance. Modern medical and surgical procedures, both diagnostic and therapeutic, must be evaluated as agents which can be potent causes of a significant lowering of host resistance.
CHAPTER 2.

STAPHYLOCOCCAL SEPTICAEMIA IN A GENERAL HOSPITAL.

"Staphylococcal fever may well be regarded as one of the most protean of infective diseases."

Ryle (1930).

Selection of Cases.

The Cardiff Royal Infirmary is a general teaching hospital of approximately 360 beds.

The years 1950-58 were chosen for study. In compiling a series of cases of staphylococcal septicaemia, rigid criteria must obviously be adopted. Nevertheless, such criteria must not be over-rigid if the series is to be as complete and representative as possible. Thus, an insistence upon a positive blood culture in these days of almost universal antibiotic therapy would eliminate several cases of what were undoubted instances of staphylococcal septicaemia. Apart from this exception of an insistence on a positive blood culture, these cases conformed to Kolmer's definition (1934) - "An infection of the blood by staphylococci, their pathogenic presence and products in the blood, resulting in severe constitutional disturbance with signs of sepsis."

Objection may be made to the very term "staphylococcal septicaemia", as it is not a true disease entity. The use of the term is, however, I feel justified, as it expresses the essential feature of some severe staphylococcal infections - namely the occurrence of metastatic lesions from a recognised or un-recognised primary focus.

Material was collected by inspecting all post-mortem records for 1950-58 for likely cases.
This was supplemented by examining the blood culture reports and clinical notes which had been filed under the heading of "septicaemia" or "pyaemia".

All cases finally accepted into the series had a clinical history which was at least suggestive of septicaemia and, in addition, fulfilled one or more of the following criteria:-

1. Bacteriological examination during life yielded a pure growth of pathogenic staphylococcus on primary subculture from the blood on one or more occasion.

2. A pathogenic staphylococcus was isolated in pure culture from the primary and at least one metastatic lesion.

3. Post-mortem bacteriological examination was positive as in 1 or 2 above. Autopsy in all fatal cases showed clumps of typical Gram-positive cocci in more than one lesion.

Staphylococci were accepted as potentially pathogenic when they grew in yellow colonies; coagulated rabbit plasma; and showed haemolytic activity. Throughout the remainder of the thesis, the term *Staph. aureus* will be used to denote a pathogenic staphylococcus.

By adhering to these criteria, no assessment of the problem of staphylococcal infection in general was possible. Thus, numerous cases of severe post-operative wound, or other localised infections without clear evidence of septicaemia, were eliminated. Similarly, uncomplicated cases of primary staphylococcal pneumonia could not be accepted. It is safe to assume that the true incidence of staphylococcal septicaemia is under-estimated in this series.
Incidence.

Forty-nine cases were accepted. Table 1 shows the annual incidence.

**TABLE 1.**

Annual Incidence of Staphylococcal Septicaemia.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>3</td>
</tr>
<tr>
<td>1951</td>
<td>2</td>
</tr>
<tr>
<td>1952</td>
<td>3</td>
</tr>
<tr>
<td>1953</td>
<td>2</td>
</tr>
<tr>
<td>1954</td>
<td>4</td>
</tr>
<tr>
<td>1955</td>
<td>9</td>
</tr>
<tr>
<td>1956</td>
<td>10</td>
</tr>
<tr>
<td>1957</td>
<td>9</td>
</tr>
<tr>
<td>1958</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>

Therefore, even by adhering to the above criteria, it is noteworthy that 49 cases should have been encountered in the clinical and pathological practice of a 360-bedded hospital during a 9 year period. Some cases would have been missed had not the autopsy records and histological material been scrutinised in addition to the clinical records.

There is an apparent increasing incidence since 1954. Analysis of the series indicates that this is a real increase. It will be shown later that it parallels a greater use of steroid therapy and includes most of the cases developing during hospitalisation.
CHAPTER 3.

ANALYSIS OF CLINICAL SERIES.

Age.

From Table 2 it can be seen that staphylococcal septicaemia is a disease found in all decades.

TABLE 2.

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Cases</th>
<th>Male</th>
<th>Female</th>
<th>Deaths</th>
<th>Recoveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>11-20</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>21-30</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
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<tr>
<td>31-40</td>
<td>12</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>41-50</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>51-60</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>61-70</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>71-80</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
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<tr>
<td>49</td>
<td>21</td>
<td>28</td>
<td>40</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

There are various factors which account for the difference in frequency associated with age. Thus, the finding of only one case in the 11-20 year group is an indication of how relatively infrequently haematogenous osteomyelitis occurs in general hospital practice.

The mortality rate shows no consistent variation with age. The survival of only one patient from a total of 17 in the 31-50 group will be seen to be accounted for by complicating factors such as surgery and malignant disease.

Sex.

There were 28 females with 3 recoveries (M.R. 89.3%) and 21 men with 6 recoveries (M.R. 71.3%). This apparent sex difference may be accounted for by the fact that of 9 instances
(8 of which were fatal) in which septicaemia followed surgery, 8 occurred in women.

Duration of Previous Symptoms.

Four patients died at home and were transferred for autopsy. The duration of preceding symptoms, which was known with reasonable accuracy in these patients, was short, varying from 2-5 days.

Table 3 excludes 16 cases which are believed to have developed whilst in hospital, in addition to those who died at home.

**TABLE 3.**
Probable Duration of Symptoms before Hospital Admission.

<table>
<thead>
<tr>
<th>Probable duration of symptoms in days</th>
<th>No. of fatal cases</th>
<th>No. of recoveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 10</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>11 - 21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>22 - 42</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>43 - 365</td>
<td>3 (c. 1 yr. 6 mths.)</td>
<td>0</td>
</tr>
</tbody>
</table>

From Table 3, it is apparent that the patients who are going to recover are amongst those admitted with a history of a few days' duration only. All whose history was of more than 21 days' duration died.

Duration of Illness.

Table 4 includes the duration of illness in the four home deaths. The duration amongst the cases developing in hospital is gauged approximately in the light of the history. For the patients admitted on account of septicaemia the time given is that of the period of hospitalisation.
TABLE 4.
Duration of Illness.

<table>
<thead>
<tr>
<th>Duration in days</th>
<th>No. of Fatal cases</th>
<th>No. of Recoveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 10</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>11 - 21</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>22 - 42</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>43 - 100</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>101 - 300</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Mortality.

The over-all mortality, as has been seen from Table 1, was 40 deaths in a series of 49 (M.R. 81.6%). This, however, is somewhat misleading. Four autopsies were on patients who died at home. Seven patients (all of whom died) had been transferred to the Cardiff Royal Infirmary from neighbouring hospitals on account of the gravity of their condition. The corrected mortality ratio, after excluding these 11 cases is 76.3%.

The Primary Lesion.

There was presumptive evidence as to the site of the primary lesion in 37 of the 49 cases. This is evaluated on the clinical evidence and does not imply that these were the most important lesions from a prognostic or pathological point of view.

- Skin 13
- Respiratory Tract 10
- Central Nervous System 6
- Osseus System 3
- Genito-Urinary System 3
- Cardiovascular System 2

The 9 recoveries included all 3 patients suffering from osteomyelitis.
**Ante-mortem Blood Cultures.**

Blood culture examination was performed on 28 patients. These were all ill at the time the blood was taken. In 21 patients, culture yielded a pure growth of a coagulase-positive *Staph. aureus* on primary subculture on one or more occasions. Only 2 of the 9 cases that recovered were accepted as staphylococcal septicaemia without a positive blood culture. Both had a typical history, and a pathogenic staphylococcus was isolated from the nervous system and metastatic skin lesions.

Post-mortem bacteriology proved to be a useful supplementary source of evidence. It is referred to later. Of the 14 patients with a positive blood culture who died, macroscopic cardiovascular lesions were found in 6 at autopsy - ulcerative endocarditis in 5 cases, and suppurative thrombophlebitis in one case.

The finding of a positive blood culture did not aggravate the prognosis. Seven of these 21 patients recovered. (M.R. 66.6%). Therefore, if anything, they have an improved prognosis. This, of course, may be related to an increased clinical awareness of the condition.

**Other Ante-mortem Bacteriological Examinations.**

Frequently, when no growth could be obtained by culture of the patient's blood, a pathogenic staphylococcus was isolated from various other sites, although caution is needed in accepting these staphylococci as being identical with the organism giving rise to septicaemia. Nevertheless, it is true that diagnostic assistance may not infrequently be obtained from sites where the staphylococcus is either relatively walled-off, or easier to
to isolate. The sites from which staphylococci were grown, included the central nervous system, sputum, urine, and metastatic cutaneous abscesses.

**Antibiotic Sensitivities.**

A detailed analysis of the sensitivity patterns of the staphylococci isolated in this series is not possible, as the same battery of sensitivity tests was not performed in all cases as a routine. A retrospective analysis such as this, only serves to re-emphasise the well recognised features. A penicillin resistant staphylococcus was isolated from 22 patients. In only one case was the organism noted to be penicillin susceptible. Erythromycin resistance was only encountered twice, but the organism isolated was sensitive in 15. Ten patients had a staphylococcus sensitive to chloramphenicol and three had resistant strains.

**Recognised Related or Precipitating Factors.**

More than one complicating condition was present in several patients. These will be mentioned under each heading. Sixteen instances of septicaemia developing whilst the patient was in hospital for an unrelated disorder were seen.

1. **Surgery.**

Nine cases followed surgery. Only one of these recovered. The operations and survival times are listed in Table 5.
### TABLE 5.

Operations followed by staphylococcal septicaemia.

<table>
<thead>
<tr>
<th>Operation</th>
<th>Survival time (days)</th>
<th>Primary condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hysterectomy and bilateral salpingo-oophorectomy</td>
<td>27</td>
<td>Menorrhagia.</td>
</tr>
<tr>
<td>2. Excision omphalo-mesenteric duct.</td>
<td>10</td>
<td>Congenital abnormality.</td>
</tr>
<tr>
<td>3. Cystectomy and ureteral transplantation.</td>
<td>29</td>
<td>Cervical carcinoma.</td>
</tr>
<tr>
<td>5. Excision of Scapula.</td>
<td>10</td>
<td>Chondroma.</td>
</tr>
<tr>
<td>6. Repair of Diaphragm.</td>
<td>20</td>
<td>Diaphragmatic hernia.</td>
</tr>
<tr>
<td>7. Radical Mastectomy.</td>
<td>41</td>
<td>Carcinoma breast.</td>
</tr>
<tr>
<td>8. Subtotal Thyroidectomy.</td>
<td>51</td>
<td>Thyrotoxicosis.</td>
</tr>
<tr>
<td>9. Partial Gastrectomy.</td>
<td>7</td>
<td>Duodenal ulcer.</td>
</tr>
</tbody>
</table>

Two outstanding facts emerge from a study of these cases. First, only two had inherently fatal primary conditions. The radical mastectomy for carcinoma of the breast was performed on a woman of 62 years, who was in excellent general health with no clinical (or subsequent post-mortem) evidence of metastases. Second, these staphylococcal septicaemias did not present as fulminating infections following on immediately after the operation. The histories showed that the patients made a good immediate post-operative recovery, remaining well and afebrile for several days before
exhibiting signs of septicaemia. The subtotal thyroidectomy shown in Table 6 was performed at another hospital and the patient was transferred on account of septic arterial embolism. It should be re-stated at this stage that this analysis takes no account of several cases of severe localised post-operative staphylococcal infections which occurred during the period under review.

2. Steroid Therapy.

Seven examples of septicaemia are attributed partially, or entirely, to steroid hormone therapy. Table 6 lists the conditions for which steroid were administered.

**TABLE 6.**

<table>
<thead>
<tr>
<th>Primary Condition</th>
<th>Steroid</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rheumatoid Arthritis.</td>
<td>Cortisone</td>
<td>11</td>
</tr>
<tr>
<td>2. Congenital Uro-genital Anomaly.</td>
<td>Cortisone</td>
<td>84</td>
</tr>
<tr>
<td>3. Acute Leukaemia.</td>
<td>Cortisone</td>
<td>90</td>
</tr>
<tr>
<td>5. Acute Leukaemia.</td>
<td>Prednisone</td>
<td>150</td>
</tr>
<tr>
<td>7. Aplastic Anaemia.</td>
<td>Prednisone</td>
<td>65</td>
</tr>
</tbody>
</table>

No cases are common to both the post-operative and steroid groups.

Cases 1–6 developed in hospital. The seventh patient developed septicaemia whilst the
patient was being maintained on out-patient prednisone therapy. All these cases terminated fatally. The development of septicaemia cannot be said to have shortened the lives of the three patients who had acute leukaemia. Cortisone was initially life-saving in a child who collapsed soon after birth. The child showed features of adrenal hyperplasia and pseudo-hermaphroditism. The remaining patients had conditions which were not giving rise to undue concern when steroid therapy was instituted—rheumatoid arthritis; a very dubious case of disseminated lupus erythematosus with little systemic illness; and an aplastic anaemia which for over one month had had a near normal haemoglobin concentration.

This last case had never shown any depression of the white cell series or platelets, and was presumed to have occurred secondarily to a thymoma which had been successfully removed 106 days before death (Dr. William Phillips’ case—to be published). She made a complete recovery from the operation and is, therefore, not included in the post-operative series.

Two other patients were given steroids soon after admission, for what appear to have been already established staphylococcal septicaemia. Both these patients died after 9 and 11 days respectively.

Other Possible Predisposing Factors.

A list of the various diseases found amongst the patients of this series emphasises how frequently staphylococcal septicaemia occurs in association with some other predisposing factor.
Other conditions found were:

- Diabetes mellitus - 2 cases
- Rheumatic heart disease - 2 cases
- Congestive cardiac failure - 2 cases
- Influenza - 2 cases
- Malignant hypertension
- Gastric ulcer with subacute "leak"
- Recurrent pyelitis
- Spontaneous abortion - 1 case
- Varicose ulceration of leg
- Disseminated lupus erythematosus
- Paraplegia following spinal injury

The primary conditions listed in Tables 5 and 6, for which surgery was undertaken, or steroids administered, are additional to this list.

No predisposing factor was recognised in 18 cases, which comprised the younger age group presenting with very severe acute infections of short duration. Several died soon after admission, but this group of 18 also contains 7 out of the total of 9 that recovered. Therefore, the cases which are secondary (and which arise in hospital), carry the highest mortality.
Fig. 1.
X-Ray Chest (Case No. 22). This picture was taken 2 days after admission, when blood urea was 100 mg./100 ml. Some infiltration is seen at the right cardiac border.
Fig. 2.
X-Ray Chest (Case No. 22) - compare with fig. 1. This was taken 42 days later. Blood urea 132 mg./100 ml. It shows the appearances of "uraemic pneumonitis", with the typical clear peripheral zone. This appearance had resolved before the patient's death 20 days later - see fig. 13.
Fig. 3.
X-Ray Chest (Case No. 35). This is a "soft" picture, but shows a slight degree of shadowing near the right cardiac border. The blood urea was 98 mg./100 ml.
Fig. 4.

X-Ray Chest (Case No. 35) - Taken 9 days after fig. 3, and 3 days before death. Blood urea 228 mg./100 ml. This shows the rapidity with which consolidation may develop. Autopsy showed that the consolidated area in the right lung consisted of numerous large abscess cavities, bronchopneumonia, and infarction.
Fig. 5.
X-Ray Chest (Case No. 31). This shows a diffuse right mid-zone mottling. The blood urea was 176 mg./100 ml.
CHAPTER 4.

CLINICAL EVIDENCE DENOTING THE IMPORTANT LESIONS.

The striking feature of the clinical pictures presented in this series is their diversity. The following is only a brief summary of the outstanding features.

Pulmonary Manifestations.

Respiratory abnormalities were prominent in 22 patients. These took the form of cough, dyspnoea, cyanosis, pleuritic pain and haemoptysis. Empyema was found in two cases. Cyanosis was frequently noted. In the cases seen personally, the intensity of the cyanosis appeared greater than would be expected from the severity of dyspnoea.

Renal Disturbance.

In the section of this thesis dealing with the pathology of staphylococcal septicaemia, considerable emphasis is laid upon the extent and severity of the renal lesions. That these are of prognostic importance is borne out in the clinical histories. Table 7, although very incomplete, shows this with reference to the urinary findings and blood urea. The use of these criteria underestimates the frequency of significant renal damage, because accurate urinary records are often not made in such gravely ill patients. Blood urea estimations are not available in some instances where autopsy examination disclosed extensive kidney damage.
# TABLE 7.

Evidence of Renal Disturbance in Staphylococcal Septicaemia.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>235</td>
<td>++</td>
<td>Sl.</td>
<td>++</td>
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<td></td>
<td></td>
<td>D</td>
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<tr>
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<td>22</td>
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</tr>
</tbody>
</table>
A clinical state consistent with the diagnosis of "uraemia" was described in five patients. It can be seen from these investigations that the finding of an elevated blood urea content in a patient suffering from staphylococcal septicaemia is a grave prognostic sign, as all the patients with a blood urea exceeding 100 mg./100 ml. died.

Four patients had chest radiographs, the appearances of which were similar to those of
"uraemic pneumonitis" (see figs. 1-5, and discussion under pulmonary pathology). Radiological examination of the chest in staphylococcal septicaemia is frequently of diagnostic value. The tendency to mid-zone infiltration, found in association with uraemia, is often evanescent. The other changes found in chest radiographs, which can be seen in the illustrations, are abscess cavitation, and extensive pulmonary consolidation. Cystic cavities may also be visible.

This, hitherto unrecognised, association of renal failure with septicaemia might well be called a syndrome in its own right.

Central Nervous System.

Five cases were seen of staphylococcal meningitis. One case each of cerebral haemorrhage and subarachnoid haemorrhage occurred in association with staphylococcal septicaemia.

The mental state of the patient was a poor guide to the presence of cerebral involvement, because clouding of consciousness was a frequent finding and almost invariably a terminal one, even in patients who showed no central nervous system involvement at autopsy.

Cardiovascular System.

Ulcerative endocarditis was diagnosed clinically in three patients. One instance of impaction of an embolus at the bifurcation of the aorta was treated surgically (the patient ultimately died). Four patients had a suppurative thrombophlebitis as one of the earliest manifestations of the disease.
Haemopoietic System.

A normochromic or hypochromic anaemia was invariable, and a leucocytosis usually developed.

Haemorrhagic manifestations were an interesting feature. Petechial or purpuric haemorrhages were seen in no less than 20 patients. In several cases haemorrhage was a presenting sign - haemoptysis, haematemesis, haematuria and vaginal haemorrhages. Probably the two examples of intracranial haemorrhage were of similar genesis.

Representative Cases.

1. Case No. 2. (Hospital No. 123664).

Case of Haematogenous Osteomyelitis with Recovery.

This patient, a man of 54, was admitted on 28/9/50. He had first noticed pain in the left groin, accompanied by pyrexia, one week previously. His general practitioner prescribed sulphonamides. However, his general condition deteriorated quickly, so that he was admitted to hospital in a state of prostration. A diagnosis of osteomyelitis of the body of the left pubis was made, the patient exhibiting extreme localised tenderness over this site. Subsequent radiological examination confirmed the clinical diagnosis. He was immediately put on one million units of penicillin daily. The patient's general condition began to improve slowly but his temperature fluctuated between 102-105°F. The blood urea on 29/9/50 was 100 mg. per 100 ml. Urinary examination: Albumin +, W.B.C.'s +. Blood white cell count on 4/10/50 was 25,000 per cmm.
On 6/10/50 high fever recurred with a generalised uticarial type of skin rash. Diarrhoea was also present. These symptoms were attributed to a penicillin hypersensitivity. But blood cultures on 6/10/50 and 14/10/50 both grew Staph. aureus, coagulase-positive, on primary subculture. The staphylococcus was sensitive to chloramphenicol and sulphonamides but resistant to aureomycin, streptomycin and penicillin. Therapy was changed to chloramphenicol and later aureomycin was given.

The blood urea fell to 73 mg. per 100 ml. on 2/10/50. Between 13/10/50 and 20/10/50 there was a diuresis of 3.7, 3.2, 2.7, 2.4, 3.2, 3.7, 2.6, and 2.2 litres on the respective days.

The haemoglobin was 53% on 27/10/50, at which time the white blood count was 9,000 per cemm.

A femoral vein thrombophlebitis was treated with anticoagulants. An abscess which formed in the left groin was aspirated, but culture of the pus did not grow any organism.

Blood cultures on 6/11/50, 18/11/50, and several subsequent occasions were all sterile.

The patient was discharged cured after 86 days in hospital.

Comment:

A case typical of what was seen so frequently and recorded in the pre-antibiotic era.

2. Case No. 48. (P.M. No. 57/70).

Fulminating Staphylococcal Septicaemia in Association with Influenza.

Admitted 23/1/57. Died about 15 hours later.
The patient was a hitherto healthy woman of 33 years. The onset of illness could be timed to 6.0 p.m. on 20/1/57. She suddenly felt ill and complained of severe pain over the lower right side of the chest and in the right loin. Severe rigors, sweating, vomiting and dysuria followed. The temperature at that time was 104°F. During the three days before admission her husband (who was a medical practitioner) prescribed terramycin, penicillin and "gantrisin".

Generalised urticaria and swelling of the vulva was noticed on the third day of the illness (22/1/57).

On admission to hospital, hyperpyrexia was present with a temperature of 109°F. Extreme tachypnoea and cyanosis were present. It was obvious that the patient was in extremis. Speech was slurred; the blood pressure became unrecordable; the tendon reflexes disappeared; strabismus was noted; and paraplegia became established.

Noradrenaline, cortisone and terramycin had no effect. Tracheotomy was also performed just before death.

Culture of blood and cerebro-spinal fluid grew a coagulase positive Staph. aureus.

Autopsy Findings (57/70).

There was a right-sided empyema. The trachea showed marked congestion and necrosis. Both lungs had several areas of haemorrhagic consolidation, small abscesses and broncho-pneumonia. There were numerous clumps of Gram-positive cocci in the abscesses and pulmonary vessels. The kidneys showed a diffuse
necrotising glomerulonephritis and patchy tubular necrosis.

Gram-positive cocci were present in the spleen.

Detailed examination of the central nervous system showed no histological abnormality.

*Staph. aureus* (phage-type 52a) was isolated from blood, lung and pleural cavity.

Influenza B. virus was isolated from the lung.

**Comment:**

The presence of two organisms complicates the issue, but the outstanding pathological features were the severe suppurative involvement of the lungs, and the toxaemic effect on the kidneys. Unfortunately, no blood urea estimations were performed.

3. Case No. 41 (P.M.No. 58/13).

**Collapse due to Bilateral Adrenal Haemorrhage.**

This patient was admitted on 31/12/57. She was a woman of 61 years. Seven years previously she had had a left hemiplegia from which she made a good recovery.

Three weeks before admission she developed a purpuric eruption over both legs. This was followed by increasing drowsiness, weakness and vague ill-health. She was put to bed and became almost unrousable 24 hours before admission. On admission the body temperature was 97°F. She was semi-comatose and both plantar responses were extensor. The skin rash on the legs consisted of ulcers and small abscesses. Her blood pressure on admission was
95/55 mm. Hg. It later rose to 120/80 mm. Hg.

Investigations on 31/12/57, were as follows: swabs from the skin lesions yielded a pure growth of *Staph.* aureus, coagulase positive. Blood culture gave a pure growth of *Staph.* aureus coagulase positive on primary subculture. The organism was sensitive to erythromycin and resistant to penicillin, streptomycin and terramycin. Urine — albumin +. Occasional red and white blood cells. Blood urea 26 mg. per 100 ml.

Penicillin was prescribed but the patient slipped deeper into coma and died with Cheyne-Stokes respiration.

**Autopsy Abstract (P.M. 58/13).**

At the time of the autopsy, I was unaware of the ante-mortem bacteriological findings and so, unfortunately, did not perform any post-mortem bacteriology.

The cause of death was large bilateral medullary adrenal haemorrhages, which were also disrupting considerable portions of the cortex. Gram-stained sections showed clumps of Gram-positive cocci in the cortical capillaries.

There was a bilateral bronchopneumonia. The alveolar capillaries were very congested and there were focal haemorrhages due to rupture of vessel walls. Several of the smaller vessels and capillaries were thrombosed.

The renal glomeruli were very hyper-cellular. There were numerous foci of congestion and localised haemorrhage in the kidneys.

The skin lesions on the leg showed superficial ulceration and necrosis with numerous pleomorphic Gram-positive cocci in clumps.
The brain revealed only old areas of sclerosis in the internal capsule.

Comment:

It might be argued that the staphylococcal blood-stream invasion in such a case was terminal or incidental, as the clinical picture and autopsy findings were not those of a suppurative process. Nevertheless the "toxaemic" lesions found in the adrenals, pulmonary and renal capillaries, are similar to those found in several other cases in this series, where there was also concomitant suppuration.

4. Case No. 45 (P.M. No. 58/469).

Staphylococcal Septicaemia following Partial Gastrectomy.

This patient was a woman who had had a partial gastrectomy performed in October, 1956, for a chronic gastric ulcer. She was then 41 years. Dyspeptic symptoms continued, and she was re-admitted on 30/5/58, and laparotomy was performed on 2/6/58, when the only abnormality found was dilation of the efferent duodenal loop. An extended partial gastrectomy was carried out. Post-operative progress was slow, but a sudden deterioration occurred on 12/6/58, when the patient became drowsy and uncooperative. The temperature varied between 100-104°F. The white blood count was 25,000 per cmm (91% polymorphs). An extensive purpuric eruption developed and purulent blisters were present, mainly on the skin of the arms. The pus from these blisters, and a blood culture on 14/6/58, grew Staph. aureus, coagulase-positive, sensitive to erythromycin and resistant to penicillin,
aureomycin, terramycin and streptomycin. It belonged to phage-type 80.

The patient died on 14/6/58.

**Autopsy Findings**:

The peritoneal cavity contained a small quantity of pus, but the left subphrenic space contained a large collection of pus.

The heart showed a recent fibrinous pericarditis. There were numerous myocardial abscesses, and there was a small quantity of thrombus adherent to the apex of the left ventricle. The heart valves were normal.

Both kidneys were large and pale. The cortex contained small, discrete haemorrhagic areas. Abscesses were present, and were most numerous at the junction of cortex and medulla. Histologically, embolic infarcts were seen, and extensive fibrin thrombosis of arterioles and capillaries. Numerous examples of focal "embolic" glomerulonephritis were present.

The lungs and brain showed infarction.

**Comment**:

A case of post-operative septicaemia, which is of interest because it provides an example of patchy renal cortical necrosis, and focal "embolic" glomerulonephritis, unassociated with endocarditis. Unfortunately, no blood urea estimation was performed.
CHAPTER 5.

DISCUSSION OF CLINICAL SERIES.

"The control of the great plagues and certain of the acute bacterial infections have not delivered man from infectious disease, but they have very decidedly changed the nature of that disease in certain countries of the world including our own." McDermott (1956).

Incidence of Staphylococcal Septicaemia.

It has been seen in the first chapter that severe staphylococcal infections have been recognised, as such, on many occasions since Ogston's identification of the pathogenic role of the staphylococcus (1881). This discovery obviously did not come as an explanation of a rarely seen infective process, but rather as the key to an important problem in clinical practice. I have been able to trace 25 publications on one or more cases of staphylococcal septicaemia published between the years 1881-1899. Numerous series of cases were also published during the years 1900-1940. This would suggest caution in assuming that the incidence of severe staphylococcal infections has subsequently increased. McDermott (1956), points out the lack of comparable series for the present and pre-antibiotic eras. It was initially intended to analyse a comparable series in the Cardiff Royal Infirmary for a nine year period prior to 1940, but the data available were inadequate. McDermott concluded that there has been little, if any, increase in the number of patients admitted to hospital with staphylococcal disease. The present series does seem to indicate a
rising annual incidence in one hospital, although the numbers involved are small. This increase, however, does not result from an increased admission rate, but from a great number of hospital infections.

Florey's findings (1958), are difficult to equate with the results of the present investigation, or with numerous reports from widely separate centres. She investigated the incidence of staphylococcal infections in the New York Hospital for a six month period in 1956–57. During this period 11,670 patients were admitted, but apart from three doubtful cases (two of which recovered), no instance of serious staphylococcal infection was found. This seems to be a little short of amazing, but it may be partly accounted for by the fact that the investigation was a perusal of records and wards during a short-term visit to the hospital.

A recent report by Hassall and Rountree (1959), gives a picture closely akin to the one described in the preceding chapter. They found 86 cases of staphylococcal septicaemia during the years 1950–1957, in the Prince Royal Alfred Hospital, Sydney. As far as the records of their hospital were concerned, there appears to have been a large increase in the number of cases of staphylococcal septicaemia - Kellaway, et al. 1928, could only find 18 cases between 1910–1928. Hassall and Rountree emphasise the importance and gravity in the incidence of septicaemia developing after hospital admission.

Pattern of Staphylococcal Septicaemia.

Against this background, of what has probably been a fairly unchanged incidence of
the rate of staphylococcal septicaemia in the general population, there has been a notable change in the pattern of infection.

Bradley, as early as 1876, divided septicaemia into two types. First, that arising de novo - "the septic material being manufactured by the patient himself." Second, septicaemia arising as a result of direct inoculation from without. This division is particularly applicable today. There has probably been little or no change in the incidence and nature of the first type, of what Bradley termed primary septicaemia. Whilst, however, it is a far cry from the hospital conditions decried, and to a great degree remedied, by Lister, the problem of staphylococcal infections contracted subsequent to hospital admission is one of increasing importance.

Staphylococcal osteomyelitis of the long bones is much less frequently seen than it was prior to the introduction of penicillin in 1942 (Spink 1956; Bunn et al 1958). The three cases of osteomyelitis, all of which recovered, in this series, confirmed the better prognosis in such patients.

The patients who developed septicaemia whilst in hospital provide a good illustration of the importance of host factors in addition to the bacteria. The two major causes of a lowering of host resistance are surgery and steroid therapy.

Post-operative Septicaemias.

The epidemiological approach to the problem of cross-infection in the hospital
environment is being applied increasingly. Nasal (and other body sites) carriers of pathogenic staphylococci are dangerous, especially in surgical wards. A high proportion of hospital staff are nasal carriers of penicillin-resistant Staph. aureus, and these strains are rapidly acquired by new hospital staff after they come into residence (Barber et al 1949, Rountree and Barbour 1951, Barber and Burston 1955). Gould (1958) suggests that hospital inhabitants become carriers of antibiotic-resistant staphylococci as a result of a widespread dissemination of penicillin particles in hospital air. The concentration in the anterior nares may be sufficient to eliminate the normal penicillin-sensitive staphylococci. Caswell et al (1958) question the importance of such nasal carriers of staphylococci as a source of infection in hospital wards. They found an infection rate of 5% in clean surgical wounds. As a result of vigorous aseptic measures the rate of infection in clean surgical wounds fell to between 0.8 and 1.5%. Their outbreak of surgical wound infection coincided with a sharp rise in cutaneous staphylococcal infections among hospital staff. Furthermore, the incidence of both fell simultaneously. The cutaneous infections involved mainly fore-arm, hand or face. Therefore, Caswell et al thought that direct contact was a more important factor in the spread of staphylococcal infections than nasal carriers or airborne dissemination. Hare and Thomas (1956) had already partially anticipated these findings. They showed that Staph. aureus resident in the anterior nares
was not transmitted from person to person by droplets or droplet nuclei, but directly by means of nasal secretions, skin contamination, clothing, bedding, etc. They also found that some carriers give rise to much more neighbouring contamination than the majority of carriers. Jeffrey and Sklaroff (1958) reported from a hospital in this country that serious infection developed in 10% of 673 clean surgical wounds. Howe (1954) found an increase in frequency of infections in clean surgical wounds in the Massachusetts Memorial Hospitals from 2 to 7% between 1929 and 1953. These reports are some of many concerning post-operative staphylococcal infections that have appeared during the last decade; for example, Collins et al (1956), Shooter et al (1957), Barber and Dutton (1958), Godfrey and Smith (1958), Penikett et al (1958), Slaney and Brooke (1958). The question posed by this apparently increased frequency and severity of post-operative staphylococcal infections, is whether these reports reflect an enhanced bacterial virulence. This question is considered later, but the answer with regard to post-operative cases may, in part at least, be simpler. Clarkson (1958) may well be justified in his contention that operating-theatre discipline has slackened in the past 25 years. Another point relevant to this question is the fact that surgery is becoming steadily more complicated and radical. Associated with major surgery are, of course, the ancillary diagnostic and supportive procedures. Spink (1956) quotes septicaemia following a thrombophlebitis arising from a "cut down" intravenous infusion apparatus.
The gravity of this state of affairs is underlined by the fact that in this series seven out of the nine surgical septicaemias occurred in patients who were in a state of good general health pre-operatively, and who survived the surgical trauma with minimal disturbance. That only one patient should have survived under conditions where the earliest symptoms occur under medical supervision, and when antibiotics are given in liberal dosage, is a pointed illustration of a complete breakdown of host resistance. It might be argued that such events are rather an illustration of an enhanced bacterial virulence. But this would not explain the sporadic happening of these catastrophic infections. It is almost certain that in the immediate ward environment of these surgical patients, other post-operative patients would be exposed to the same bacterial species but show only a mild wound infection, or no infection at all.

Steroid Hormone Therapy.

The remarks made above concerning the widespread distribution of pathogenic staphylococci in surgical wards, applies with almost equal force to general medical wards. Barber and Dutton (1958), for example, report an outbreak of staphylococcal infection in a male medical ward. Godfrey and Smith (1958) state that 17% of their series of staphylococcal infections were found among patients in the surgical wards and 12% in the medical wards. However, 7·3% of medical patients had severe staphylococcal infections in contrast to 2·6% of the surgical patients. In the analysis in
Chapter 3, it was seen that nine septicaemias developed post-operatively, and seven developed whilst the patient was undergoing medical treatment.

The association of staphylococcal septicaemia (as well as other bacterial infections), with steroid therapy, has now been recorded many times. Dubois-Ferriere (1951), Shaper and Dyson (1955), Phillips et al (1954-1955), Hayes and Kushlan (1956), Smith and Cleve (1957), Mills et al (1957), Hughes and Truelove (1958), Godfrey and Smith (1958), Slaney and Brooke (1958) and Kellgren et al (1958). The latter reported 12 cases of suppurative arthritis complicating rheumatoid arthritis. Ten of these were due to Staph. aureus, but only two patients had received steroid therapy. One case included in the present series was a woman of 69 years, suffering from rheumatoid arthritis. She was afebrile for three weeks after admission, but then began to show pyrexia six days after the institution of cortisone therapy. The patient became uremic (blood urea 182 mg. per 100 ml.). No antibiotics were given. The principal post-mortem findings were papillitis necroticans and an acute suppurative staphylococcal arthritis of the left knee joint, and left sternoclavicular joints. It is thought there may be a masking of the usual features of infection occurring during steroid therapy. The symptoms and signs, in these patients, on steroid hormones, seem to have been just as striking and indicative of infection as in those to whom steroids had not been given. All these steroid septicaemias terminated fatally.

Thus, 16 cases of septicaemia developed in hospital. Fifteen of these are associated
with two factors: (a) 9 post-operative cases and (b) 6 with steroid hormone therapy (the seventh case was being treated at home).

The other patient, not included in these two groups, was a month old baby delivered in hospital, whose mother had a breast abscess.

Caution should be exercised in attributing too great a rôle for the two factors of surgery and steroid therapy, because these two very factors were found in a group of patients who had an unduly high incidence of other primary systemic disorders.

**The Evidence of an Enhanced Bacterial Virulence.**

McDermott (1956) dismisses the hypothesis that we are dealing with a bacterial species possessing an enhanced virulence in our hospital environments. The cases studied in this thesis by their nature, and course of disease, certainly appear to support this theory. At the risk of equivocating, however, the truth may well lie somewhere between both these theories of an increased bacterial virulence, or a diminished host resistance.

Although complicating factors, such as surgery and steroid therapy for other primary disorders, were present in several of these patients, many of the victims of hospital septicaemia were in a state of good general health - for example, it should be unnecessary to question the rôle of host resistance in an apparently perfectly healthy baby contracting a fatal fulminating septicaemia, whilst the mother had a *Staph. aureus* breast abscess following confinement in hospital.

Elek (1956), and Elek and Conen (1957),
injected suspensions of *Staph. aureus* intradermally into human volunteers in graded doses. A "pus-producing dose" could be estimated. They could not detect any gross difference in the virulence of different strains. Preliminary washing of the coccal suspensions made no difference to the "pus-producing dose". Elek (1959) concludes, "It is very doubtful whether strains isolated from the most serious infections, such as pyaemia, differ in their virulence from strains obtained from minor lesions, or even from the anterior nares." However, their experiments can be interpreted in a completely different manner. Elek and Conen experimented with 26 different strains of staphylococcus. Their human subjects were healthy adults aged 18-30 years - a highly selected group, in fact. In 17 volunteers receiving 45 inoculations, of a minimum pus-forming dose, 40 resulted in some pus formation. Of the five failures, three occurred in one individual (and he produced pus with one out of five strains tested). The other two failures produced pus with other strains. These results could fairly be interpreted as exhibiting both individual host variation and differing bacterial virulence. If it is possible to have a state of heightened resistance to *Staph. aureus*, then it is reasonable to postulate that a state of significant lowering of host-resistance may also be encountered. Furthermore, the problem is not that of the behaviour of an "average" group of people (especially a highly selected, healthy group), but rather it is the problem of comparatively rare individuals who succumb to serious staphylococcal infections.
The question as to whether a staphylococcus which has acquired antibiotic resistance, also acquires a different pathogenic propensity is surprisingly undecided. Howe (1954) correlates the appearance of antibiotic resistant strains with a greater capacity for epidemic spread. Certainly the staphylococci isolated in many serious outbreaks show a common pattern of behaviour - they are always antibiotic resistant (Brit. med. J. 1958), usually to tetracycline as well as to penicillin; they usually belong to phage group III (Williams et al 1953); and the demonstration that certain outbreaks have been caused by one strain of staphylococcus - for example, acute membranous staphylococcal enterocolitis and staphylococcal food poisoning. Blair (1956) linked the groups of phage-types with various types of clinical infection. However, Robinson (1958), in a student's essay, offers some pertinent criticisms of this type of argument. He quotes the British Medical Journal (1958) - "Those staphylococci implicated in serious outbreaks are always antibiotic resistant ..... and are of one, or a few, particular phage types. That these organisms are more dangerous intrinsically, as well as by virtue of their resistance to chemotherapy, there is no doubt." Robinson says there is every doubt. In an epidemic it is not surprising that one strain should be implicated. It would be far more surprising if this were not so. The finding of antibiotic-resistant strains in epidemics may also not be so significant, because the antibiotic susceptible strains are the ones which may be killed at the commencement of any potential epidemic.
Barber and Burston (1955) claimed that strains of staphylococci from the lesions of active staphylococcal disease may be the chief offenders in instances of cross-infection. Wise and Spink (1954) related antibiotic resistance to certain altered biological properties of the bacterium. They produced small colony variants (G-variants) by culturing Staph. aureus in the presence of several antibiotics in varying concentrations. These G-variants, when compared with the more standard colonial forms of normal size, possessed less haemolytic activity; produced less coagulase; their nutritional requirements were greater; they remained viable in the tissues of apparently normal animals and were, in fact, less virulent. When these G-variants were cultured without antibiotics, they reverted to colonies of normal appearance. Wise and Spink then made the interesting and reasonable deduction that, given an optimal concentration of antibiotics, G-variants may survive in human tissues. These may then remain undetected. After cessation of therapy, reversion to a virulent form may occur with clinical relapse.

Barbour and Edwards (1953) also provided evidence of a correlation between antibiotic resistance and biological properties. They found that staphylococci of 6/47 phage group mutate five times as rapidly to streptomycin-resistance as those in group 3A, and twice as rapidly as those in group 29/52. The staphylococci of group 6/47 are genetically less stable.

Barber (1947) however, when using penicillin-resistant, and penicillin-sensitive, strains of staphylococci, could demonstrate no
difference in the survival time of rabbits. After examining 200 strains of coagulase positive staphylococci, she concluded that it was impossible to differentiate penicillin-resistant and penicillin-sensitive strains on the grounds of morphology, cultural characteristics, biochemical reactions, or pathogenicity to rabbits. Recently Barber herself, in collaboration with Wildy (1958) has demonstrated a close relationship between bacteriophage group and antigenic type of coagulase.

Therefore, it is obvious that this question, as to whether an enhanced bacterial virulence is an important factor in currently encountered staphylococcal septicaemia, is one to which no definite answer can be given. By its very nature, the present study is more suited for an evaluation of the role of host resistance; and it certainly serves to emphasise this important factor. Nevertheless, as stated above, it would be foolish to discount the part played by the virulent antibiotic-resistant staphylococcus. Although no controls were available, it was interesting that the clinical bacteriologist reporting on the ante-mortem and post-mortem material submitted for bacteriological examination in this series, should frequently comment on the marked pleomorphism and L-formation shown by the staphylococci. I have been able to confirm this in some of the tissue lesions. Dienes (1951) stated that L-forms of staphylococci have not been observed. But Turchini (1955) described marked pleomorphic changes in the cells of Staph. aureus grown on solid media containing sodium desoxycholate, and stated these were similar to the L-forms of
other bacteria.

**Blood Culture.**

The position of blood cultures in clinical practice has changed considerably since the introduction of antibiotics. Prior to the clinical use of antibiotics, the obtaining of more than one positive blood culture could be made an absolute pre-requisite before making the diagnosis of staphylococcal septicaemia.

Ogston (1881) noted at the time of his initial discovery that micrococci could multiply in abscesses and then pass into the blood stream. The first blood cultures were done on finger prick samples. White, as early as 1899, said that a generalised infection with pyogenic cocci might be the immediate cause of death in chronic diseases. He found that in *Staph. aureus* and *C. welchii* infections the greater the number of organisms in the blood, the more rapidly growth took place during blood culture.

Kyle (1948 report of 1930) differentiated clinically between mild cases showing bacteraemia which recover with the formation of a spontaneous fixation abscess, and the more serious fully developed septicaemia with multiple lesions. Transient, harmless staphylococcal bacteraemia is known to occur, for example, after tooth extraction or tonsillectomy (Fischer and Gottdenker 1936).

Nine patients were shown at autopsy to have staphylococcal ulcerative endocarditis. Five of these had positive blood cultures during life. Post-mortem culture of the affected valve always proved positive. This confirms the findings of Butler (1937) before antibiotics.
were used. I cannot, however, agree with her statement that "Staph. aureus, like Strep. haemolyticus, probably never causes subacute bacterial endocarditis." She attributes the isolation of Staph. aureus from the blood in such cases to a secondary infection. Whether the diagnosis of subacute bacterial endocarditis be made on the subacute course of the disease, or on the pathological grounds of typical cardiac lesions and distant embolic and toxaemic lesions, there were two irrefutable cases in this series. They pursued almost identical courses, and repeated cultures in both (ante-mortem and post-mortem) grew nothing other than Staph. aureus. Furthermore, a large proportion of the section on pathology is devoted to a demonstration that these "toxaemic", non-suppurating lesions, are a frequent feature of staphylococcal septicaemia.

Renal Disorder.

Unfortunately, several cases were so inadequately documented that they did not permit detailed assessment of the renal function during life, but, as can be seen from Table 7, sufficient data were available to show that renal failure is not infrequently the final insult suffered by these septicaemic patients. This is later correlated with the pathological findings. Very little attention has previously been paid to the renal lesions in clinical staphylococcal septicaemia. Four cases in Wilson and Hamburger's (1957) series of 55 cases had blood urea nitrogens of over 60 mg. per 100 ml. No pathological details were given.
Lung Lesions.

It has already been noted how frequently cough, sputum, dyspnoea, cyanosis and pleuritic chest pain were recorded.

Pulmonary involvement is not only of importance in the more conventional acute case of septicaemia, but is also a major cause of prolonged suppuration and blood-stream invasion. Some of these cases pursued a chronic course, interspersed with episodes of an acute nature. This type of case demonstrates how a patient can nurse a localised staphylococcal lesion for a considerable time, without acquiring sufficient resistance to cope with a sudden, fatal, blood stream invasion. As Ryle (1948) pointed out, even a serious staphylococcal infection successfully weathered, does not give rise to immunity. Several examples of human "botryomycosis", or "staphylococcal Actinophytosis", have been recorded, Berger et al (1936) and Drake et al (1943). Blog et al (1955), described a case of 2½ years duration. Fink (1941) described a boy of 16 years, who died one year after his first admission to hospital with purpura, furunculosis, liver and lung abscesses. There was a closely comparable case in the present series. A man aged 45 years developed multiple liver abscesses, a subphrenic abscess and an empyema. He died 10 months later from staphylococcal meningitis.

Cardiovascular Involvement.

Cardiovascular involvement clinically took the form of ulcerative endocarditis, suppurative thrombophlebitis, suppurative myocarditis and pericarditis. The endocarditis
was right-sided in two cases. A higher incidence of right-sided lesions is supposed to be a feature of acute ulcerative endocarditis caused by organisms such as the staphylococcus (Bain et al 1958). In right-sided bacterial endocarditis these authors found that embolisation to the lungs was invariable, whereas peripheral emboli were rare - even though the blood culture was often positive. The two cases seen, both had metastatic pulmonary suppuration and both had positive blood cultures. One had no evidence of peripheral embolisation, whereas the other had numerous visceral metastatic abscesses.

Undoubtedly Staph. aureus can cause subacute bacterial endocarditis - subacute in course as well as in the pathological lesions produced. It is surprising how consistently, and in what great a proportion the staphylococcus has been implicated. Osler (1885) out of ten cases was able to show that one was due to a streptococcus and another to a staphylococcus. Lenhartz (1901) found seven staphylococcal cases in a series of 37. Amongst Horder's 97 cases (1909) there were 19 attributed to Staph. aureus, and one to a combined streptococcal and staphylococcal infection. Clawson (1924) and Thayer (1926) published similar series. Thayer included four due to Staph. albus. Whether Staph. albus can cause endocarditis is still dubious. Stitch (1932), for example, reports a case. He obtained three blood cultures positive for Staph. albus - isolated after 96, 72 and 72 hours. Post-mortem examination of pericardial fluid yielded Staph. albus after three days, and the valve vegetation Staph. albus after seven days.
Such bacteriological reports are unacceptable. Usually in these cases details of the technique used to test for coagulase are not given. A case examined personally illustrated the caution necessary - a case of ulcerative endocarditis in which several blood cultures grew \textit{Staph. albus}, but was later proved by serological tests, post-mortem culture, and histological demonstration, to be a case of \textit{C. burneti} endocarditis (Dr. William Phillips' case - to be published). Furthermore, a few colonies of \textit{Staph. albus} are often isolated from post-mortem material.

Some strains of \textit{Staph. albus} produce coagulase, and these behave in a manner similar to that of any pathogenic staphylococcus. An outbreak of surgical wound infection, due to this type of organism was reported by McDonald and Trimbury (1957). \textit{Staph. aureus} can produce stable white-colony variants (Biggar et al 1927 and Barber 1955). However, it appears that coagulase-negative strains of \textit{Staph. albus} can give rise to septicaemia under certain conditions. The commonest predisposing condition reported is that of mitral valotomoy - Lancet (1956 and 1958), Smith et al (1958). Some dubiety still remains because even in the recent paper by Smith et al, there is no mention of the technique used to test for coagulase production, nor how frequently coagulase testing was performed. It would be interesting to know whether these organisms are typable by staphylophage.

\textbf{Mortality.}

A study of the mortality rates of staphylococcal septicaemia is in itself an interesting reflection of changing trends. It has already been noted that Ryle either saw and
recognised a greater proportion of mild cases than other clinicians, or else he underestimated its gravity. He thought a "reasonably optimistic prognosis is justified", and described five severe septicaemias, four of which recovered. He concluded that multiple cardiac and cerebral metastases are probably always fatal, but pulmonary abscesses, even in great numbers, are consistent with perfect recovery. Mendell (1939), on the other hand, stated that the staphylococcus was "the deadliest organism of general sepsis." The following are some of the "pre-antibiotic" mortality ratios:

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>M.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bean (1929)</td>
<td>9</td>
<td>89%</td>
</tr>
<tr>
<td>Lowenstein (1930)</td>
<td>18</td>
<td>78%</td>
</tr>
<tr>
<td>Neuhof et al (1934)</td>
<td>27</td>
<td>56%</td>
</tr>
<tr>
<td>Scott (1935)</td>
<td>74</td>
<td>79%</td>
</tr>
<tr>
<td>Reiman (1936)</td>
<td>Review</td>
<td>79%</td>
</tr>
<tr>
<td>MacNeal and Frische(1936)</td>
<td>100</td>
<td>75%</td>
</tr>
<tr>
<td>Mendell's own series</td>
<td>35</td>
<td>83%</td>
</tr>
<tr>
<td>Skinner and Keefer (1941)</td>
<td>122</td>
<td>82%</td>
</tr>
</tbody>
</table>

The use of antiserum and sulphonamides did little, if anything, to improve this grim position. An appreciable improvement followed the introduction of penicillin during 1942-1946. The Keefer committee, reporting on 91 cases (1943), recorded the mortality rate to be less than 40%. Anderson (1945) reported a mortality rate of less than 30%. In the years following, the mortality rate returned to above 50% - Knight and Collins (1955). Then, with the increasing proportion of penicillin-resistant strains, the mortality rate has reverted to the region of 70% - for example,
Wilson and Hamburger (1957). These authors found that there was no difference in the mortality rates of those who had had initial blood culture examinations; reported soon in the course of the illness; in whom early empirical chemotherapy had been given; or even who had received "correct" chemotherapy. Hassall and Rountree (1959) recently reported on 86 cases, 36 of which recovered, (M.R. 58%).

In a retrospective analysis such as this, no attempt can be made to evaluate the treatment of the cases.
"At present we are almost totally ignorant of what can go wrong as medical bacteriology in the past has been concerned mainly with the parasite, and very little with the host, or the local conditions of defence."

Elek (1959).

Materials and Methods.

All 40 fatal cases had been submitted to post-mortem examination. I performed six of these and witnessed several others. Paraffin-embedded sections of various organs were available for every case. These were all examined and extra sections cut and stained as necessary. The series was compiled, as explained in Chapter 2, partly by an examination of all the autopsy records for 1950-1958, supplemented by inspection of the histological material available in all cases of septicaemia — indeed this histological confirmation was one of the essential criteria adopted before a diagnosis of fatal staphylococcal septicaemia could be made.

Post-mortem bacteriology was all carried out in the same department of pathology, by a fairly standardised technique. Heart blood was taken off by a needle passed through heat-seared pericardium into the left ventricle. Swabs of the various viscera were all collected by plunging the swab through the seared surface of the organ. Heart blood (as near 10 ml. as possible) was put directly into 50 ml. glucose broth which was then incubated for 24 hours before plating out a loopful of broth on blood-
agar plates. Broths were incubated for three weeks before being declared sterile. Swabs were spread on blood-agar plates which were incubated aerobically and anaerobically for 48 hours. All staphylococci isolated in near pure culture were tested for coagulase production by the slide method (Cadness-Graves et al. 1943), and approximate antibiotic sensitivities determined using antibiotic-impregnated discs. Several of the pathogenic staphylococci were also phage-typed.

Examination of the lungs was by usual naked-eye inspection, and the taking of representative blocks for microscopy. In addition, in 17 cases paper-mounted sections of whole lung, prepared by the Gough-Wentworth technique (1948 and 1949), were prepared.

Special care was taken in the histological examination of the kidneys to inspect an adequate number of blocks - preferably representative ones of cortex, medulla, renal papillae and renal pelvis.

The stains used, included haematoxylin and eosin; Gram's stain; Fraser and Lendrum's (1940, 1949) modified acid-picric Mallory; phosphotungstic acid-haematoxylin; and periodic acid-Schiff. Other special stains being employed when necessary. If adrenal function was suspected of being deranged, the adrenals were weighed after dissection, and frozen sections were stained by Sudan III and IV, and haematoxylin and Sudan.

Analysis of Results.

Most of the pathology section of this thesis is a report and interpretation of the naked-eye and microscopical changes in various
organs in staphylococcal septicaemia. This is obviously a highly subjective procedure, and the danger of "seeing what you are looking for" cannot by any means be entirely eliminated. I have attempted to reduce this danger as much as possible by the following methods:

1. Repeated examinations of all histological material without reference to the clinical details. Sections were also re-examined, and an opinion formed without reference to the notes of the previous histological examination.

2. When a knowledge of the important types of histological lesions had been attained, tables of these were prepared and the sections again examined for the presence or absence of each particular lesion.

3. All doubtful examples of any lesion were classified as negative.

The criterion of an independent opinion, or opinions, is sound in theory at least (and in fact colleagues were consulted over some of the sections), but it is not such a practical proposition when a large series of slides of particular interest to one person only are to be examined.

Liberal use is made of illustrations, as a means of reducing an undue dependence upon a subjective assessment.
**Fig. 6.**

Paper-mounted section of lung from Case No. 20. This shows the widespread distribution of abscesses. There is some tendency to peripheral localisation.
CHAPTER 7.

DESCRIPTION OF MORBID ANATOMICAL FINDINGS
IN STAPHYLOCOCCAL SEPTICAEMIA IN MAN.

Pulmonary Pathology.

None of the 40 patients that died had normal lungs at autopsy.

The lesions found fell into one of three main types:

1. Suppurative – acute or chronic.
2. Vascular – involving either larger vessels or capillaries.
3. Complicated – for example, suppuration in an area of infarction.

Table 8 summarises the frequency and association of the main pulmonary lesions.

**TABLE 8**
Showing the Frequency and Association of Various Lung Lesions in 40 Cases of Septicaemia.

<table>
<thead>
<tr>
<th></th>
<th>Metastatic Abscesses</th>
<th>Arterial or Venous Thrombosis</th>
<th>Infarction</th>
<th>Suppurating Infarcts</th>
<th>Broncho-pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Abscesses</td>
<td>19</td>
<td>4</td>
<td>11</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Arterial or Venous Thrombosis</td>
<td>4</td>
<td>13</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Infarction</td>
<td>11</td>
<td>11</td>
<td>20</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Suppurating Infarcts</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Broncho-pneumonia</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>
Fig. 7.
Area of bronchopneumonia in which clumps of intravascular Gram-positive cocci are seen. (Case No. 15).
H. and E. x 65.

Fig. 8.
Pulmonary abscess which is beginning to become encapsulated. (Case No. 23).
H. and E. x 43.
1. Suppurative Pulmonary Lesions.

Histological material was available for examination in all except one case. Paper-mounted sections of whole lung were available in 17 cases. The latter proved to be most helpful in determining the distribution of the macroscopic lesions.

The lungs may be regarded both as the seat, and source of embolic lesions. Typical metastatic abscesses are easy to recognise. These are circular, well-defined and vary in size from 2-20 mms. Their distribution is widespread, with only a minimal tendency to be peripherally situated in the lung fields, (fig. 6).

On histological examination, the abscesses were made up of three main zones. A clump of Gram-positive cocci occurred centrally, and these were often intravascular, (fig. 7). Surrounding these there was a region of neutrophil polymorphonuclear leucocytic reaction, which in turn was encircled by a narrow rim of demarcating tissue composed of varying proportions of congested capillaries and fibrous tissue, (fig. 8). Metastatic abscesses were found in 19 patients at autopsy. Clumps of Gram-positive cocci (most of which were intravascular), were found in 29 cases.

Post-mortem culture of swabs taken from the lungs grew a pathogenic staphylococcus from three autopsies where no lung abscesses were found. The abscesses seen and examined, were clearly of varying ages. Some were well-encapsulated by thick strands of collagen, whilst others showed no such demarcation.

It was usually easy to distinguish between metastatic abscesses and bronchopneumonia, but occasional cases gave rise to difficulty. This difficulty was encountered in three examples of
Fig. 9.

Right lung from Case No. 8.
Well-developed cystic change is present. The cystic spaces are clearly delineated by coal dust deposition. The main lower lobe artery was completely occluded by thrombus. Thrombi can be seen in the smaller branches in this paper section.
what were labelled "suppurative bronchopneumonia", which showed a less well-developed tendency to localisation, with also less destruction of lung parenchyma in the area involved.

Pulmonary suppuration, in the course of staphylococcal septicaemia, is frequently of relatively prolonged duration. This was noted in the 18 patients who had had bronchopneumonia. In two cases bronchopneumonia and bronchiectasis were associated with cystic disease of the lung, (fig. 9). Paper-mounted sections give a good demonstration of this type of change. Histology served to confirm the chronicity of the suppurative process which had entailed the laying down of large quantities of fibrous tissue around the cystic spaces. One of these was a man of 60 years, whose illness began about 10 months before death, following a mid-thigh amputation for diabetic gangrene. After his operation he had repeated episodes of chest infection. He died from subphrenic abscess, and severe renal pyaemia. The other instance of cystic disease of the lung was seen in a woman of 69 years, who developed septicaemia following cortisone therapy for rheumatoid arthritis. In this case there was only a three week history of chest symptoms, so that presumably the findings in this patient were complicated by pre-existing pulmonary disease.

Five patients had severe purulent bronchitis, and in two there was a necrotising bronchitis associated with a proven influenzal infection.

Empyema occurred in three patients. No example of staphylococcal pyopneumothrax, as usually seen in the new-born, was encountered.
Fig. 10.
Case No. 32. The lung shows extensive infarction, in which secondary fungal infection has occurred. The hyphae are transgressing tissue boundaries.

H. and E. x 65.

Fig. 11.
Hyphal strands from Fig. 10 at x 540 magnification. Cocci are also present.

H. and E.
Recent pleurisy was noted in 16 cases, but this was more often associated with infarction, rather than suppuration.

In one case, where extensive pulmonary infarction had occurred, there appeared to be a secondary fungal infection. Hyphae were growing over the infarcted area in a radiating pattern. The strands were transgressing tissue boundaries, there being no apparent localisation, (figs. 10 and 11).

2. Vascular Pulmonary Lesions.

Thrombosis of the larger vessels was obviously important in many cases, both on account of the resulting infarction, and also because septic venous thrombosis is probably one of the major causes of the perpetuation of the septicaemic state. Major vessel thrombosis was seen at 13 autopsies. In 11 of these a large vein was involved. A few of the thrombi were infective, and the cocci tended to show a characteristic arrangement lying circumferentially in the thrombus, immediately internal to the vascular intima. Some of the thrombi, however, did not have the histological appearance of being infective. There were two examples of complete occlusion of a main pulmonary artery. One was a terminal event, in the diabetic patient referred to above (Case No. 8), who had cystic disease of both lungs. No source for a pulmonary embolus was found, (fig. 9). The second example of complete occlusion of a main pulmonary artery occurred in a woman of 54 years (Case No. 40), who died after a fulminating illness of only six days' duration. Fig. 12, shows the extensive pulmonary involvement in this patient. The infarcts consist of typical wedge-shaped
subpleural areas of 1-2 cm. diameter. The metastatic abscesses are distinct from these. In spite of the occlusion of the main right pulmonary artery, no massive pulmonary infarction occurred. Again, no source for a pulmonary embolus could be found. The smaller branches of the pulmonary artery also contained thrombus. Many of the pulmonary veins and venules contained septic thrombi, which were found in relation to the infarcted areas. Therefore, it seems likely that the arterial occlusion in such a case is one of retrograde thrombosis from an area of infarction. A closely similar lesion is seen in pneumoconiotic lungs, where there can occur a retrograde thrombosis in branches of the pulmonary artery extending to occlude the main artery, from an area of progressive massive fibrosis of the lung.

Apart from the 13 cases of major vessel thrombosis, mentioned above, there were a further 7 instances of pulmonary infarction. No case of extensive infarction involving the major portion of a lobe occurred. The usual size of infarcts varied from 0.5 - 2 cm. diameter. The infarcts were nearly always peripherally situated and were often subpleural. These infarcts are easily differentiated from the infarcts found in association with mitral stenosis. Paper sections of mitral stenotic lungs stained with Perl's stain give a vivid deep blue stain due to the haemosiderin present. Fig. 20, is the lung of a post-operative case of septicaemia (Case No. 45), stained with Perl's stain. No such haemosiderin can be detected.
Fig. 12.

Right lung from Case No. 40. The two processes of metastatic abscess formation, and multiple infarction are distinctive. The pulmonary arteries are thrombosed.
Fig. 13.

Left lung (Case No. 22). This shows classical peripheral infarcts, which contain abscesses in their central portions. The histology from this case is shown in fig. 15.
Fig. 14.

Right lung (Case No. 15). This shows aggregation of abscesses at the sites of infarction.
Fig. 14.

Right lung (Case No. 15). This shows aggregation of abscesses at the sites of infarction.
Fig. 15.
Pulmonary infarction (Case No. 22). A thrombosed artery occupies the top left corner. The thin dark line applied to the intima, is made up of an aggregation of Gram-positive cocci.

H. and E. x 43.

Fig. 16.
This shows conglutination of erythrocytes in a pulmonary vein, the wall of which is necrotic. (Case No. 32).

H. and E. x 130.

Fig. 17.
Fibrinoid necrosis of a pulmonary arteriole, with haemorrhage into surrounding alveoli.

H. and E. x 175.
3. Complicated Pulmonary Lesions.

Suppuration often developed in areas of infarction - see fig. 13. When this occurred it was nearly always associated with obvious septic venous thrombosis; the sequence apparently being infarction, suppuration, and further propagation by means of septic venous thrombi.

Other types of Vascular Damage.

The features of abscess formation and septic infarction are the well-recognised cardinal lesions of staphylococcal septicaemia. In this study, however, other types of vascular lesion were of particular interest, namely, the changes involving the smaller-calibre vessels - arterioles, capillaries and venules. Vascular congestion was, as might be expected, invariably present. In many, the engorged vessels appeared to have contained stagnant blood as evinced by their extreme dilation and engorgement with red blood corpuscles, which had become conglutinated with a loss of their acidophilic staining properties (fig. 16). The other change observed was that of actual thrombosis. The thrombi nearly always stained as fibrin - red with trichrome, dark purplish-blue with phosphotungstic acid - haematoxylin, and red-purple with periodic acid-Schiff. The thrombi found in larger vessels usually contained strands of similarly staining material. Extensive conglutination of red cells, with or without definite thrombosis, was found in 9 cases. These included six of the 21 instances where no lung abscesses were found at autopsy, so that it did not appear to be related to any suppurative process.

Thrombosis of the smaller-calibre vessels
was associated with a change in the vessel walls, which were often the seat of fibrinoid necrosis. Fig. 16, shows this in a small pulmonary arteriole. Such fibrinoid necrosis in its turn, gave rise to focal haemorrhages which were widespread in four cases. Fig. 19, shows a paper section where the size and sparsity of the focal haemorrhages present might cast doubt on its significance, but this is only a mild degree of the more fully developed picture exemplified in fig. 18. On histological examination the affected areas are seen to be foci of 10-20 alveoli, which are occupied by red blood corpuscles, and which are grouped around a small central, necrotic, and sometimes thrombosed, blood vessel, (fig. 17). No organisms are revealed in Gram-stained sections. As will be discussed later, these lesions have a renal counterpart, with which they are usually associated, and they are often found in cases which have bacterial endocarditis. It is suggested that they are the pulmonary version of focal "embolic" glomerulonephritis – the basic vascular pathology is similar in both lesions.

**Lung Changes Associated with Uraemia.**

It has already been seen in the clinical analysis, that there was frequently renal damage of sufficient severity to give rise to acute renal insufficiency. Therefore, "uraemic pneumonitis" would not be a surprising finding. Unfortunately, because of the gravity of the condition of these patients, usually only portable chest radiological examination could be undertaken, and these films were often of very poor quality. However, in three patients mid-zone pulmonary
Fig. 18.

Lung from Case No. 44. The histological appearances are illustrated in fig. 17. The paper section shows that the foci of vascular damage and haemorrhage, are easily visible to the naked-eye, and are distributed mostly in the upper half of the lung field. No suppurative lesions were seen in this case.
Fig. 19.

Lung from Case No. 27, showing a much milder degree of the same change as that illustrated in fig. 18. Cases No. 27 and 44 both had bacterial endocarditis.
Fig. 20.

Right lung from Case No. 45 - a post-operative staphylococcal septicaemia. Suppuration is commencing in the infarcts, but no other evidence of suppuration was found - in fact, no abnormalities were noted at autopsy. This section is stained with Perl's stain, which fails to reveal any haemosiderin.
Fig. 21.
Lung from Case No. 35. The appearances are those of a bronchopneumonic pattern, and infarction. This patient was uraemic, and there is a suggestion of sparing of the anterior margin of the peripheral lung field.
Fig. 22.
Localisation of Gram-positive cocci, in the cells of peribronchial glands. (Case No. 11).

H. and E. x 540.
consolidation was present, the appearances of which were consistent with a uraemic pneumonitis - figs. 1-5.

Whole lung paper sections usually demonstrate uraemic pneumonitis clearly, but none of the sections in this series gave this appearance. Fig. 21, is of a paper section in which the distribution with a clear peripheral zone is suggestive, but the lesions are those of infarction and suppuration. Histology of lungs from these uraemic patients showed nothing more suggestive than severe oedema. This finding is in keeping with the inconstancy of the radiological features, and is probably, in turn, related to the rapid course of the disease. No true instance of "pneumonitis" with a fibrinous alveolar exudate was encountered.

Distribution of Cocci.

Clusters of Gram-positive cocci were found in the central zones of abscesses; in septic infarctions; in septic thrombi; in the vessels of infarcted areas with no surrounding inflammatory cell reaction; and in the cytoplasm of circulating polymorphs. Cocci were also seen in the cells of bronchial glands (fig. 22). These may have been post-mortem invaders.
Fig. 23.
Kidney from Case No. 43. This illustrates how sparsely distributed (and difficult to find), renal abscesses may be. Two small abscesses are present in the two upper medullary rays.
Renal Pathology.

TABLE 9.
Frequency of Principal Renal Lesions.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vascular Thrombosis</td>
<td>30</td>
</tr>
<tr>
<td>2. Positive Fibrin Stains</td>
<td>24</td>
</tr>
<tr>
<td>3. Tubular Necrosis</td>
<td>17</td>
</tr>
<tr>
<td>4. Diffuse Glomerulonephritis</td>
<td>16</td>
</tr>
<tr>
<td>5. Glomerular Necrosis</td>
<td>15</td>
</tr>
<tr>
<td>6. Clumps of Staphylococci</td>
<td>13</td>
</tr>
<tr>
<td>7. Renal abscesses</td>
<td>11</td>
</tr>
<tr>
<td>8. Focal &quot;Embolic&quot; Glomerulonephritis</td>
<td>8</td>
</tr>
<tr>
<td>9. Papillitis Necroticans</td>
<td>2</td>
</tr>
</tbody>
</table>

No histological material was available for examination in five cases. In one of these pyaemic renal abscesses had been noted in the original post-mortem record.

Renal Suppuration.

Metastatic renal abscesses are usually relatively scanty in number, and may be easily overlooked at autopsy – see fig. 23. They often occur at the cortico-medullary junction, or in the actual medullary substance, and their size varies from 2-8 mm. diameter. Suppuration rarely, if ever, seemed to arise within a glomerulus, but was usually situated in the tubules, or the peritubular interstitial tissue. A moderate amount of collagen was deposited around the abscesses in several instances. The abscesses were circular, clearly demarcated, and did not resemble the lesions of pyelonephritis except in four cases which had an acute pyelitis, and in these the pelvic suppuration was continuous with
Fig. 24.

Papillitis Necroticans. A well-marked zone of reaction can be seen. Tubular dilatation, visible to the naked-eye in this photograph, is present in the outer third of cortex, together with many thrombosed vessels. (Case No. 19). Microscopy is illustrated in figs. 25-27.
the suppurative process involving the kidney.

**Papillitis Necroticans.**

Two of the four examples of pyelitis showed the classical features of papillitis necroticans (fig. 24). One occurred in a woman of 40 years (Case No. 3). She was in hospital for 57 days. Unfortunately the blood urea was not estimated in the last month of her illness but she developed widespread erythema, oedema, several hypochronic anaemia (Hb. 26%), and terminal convulsions. The urine contained albumin, pus cells, red blood cells and numerous granular and hyaline casts. There was no evidence of diabetes mellitus. At autopsy, a bacterial endocarditis was found, and numerous focal endocarditic glomerular lesions were present. Renal arterial thrombosis was widespread. A few cortical abscesses were found. The pyramidal tubules contained large masses of Gram-positive cocci, around which there was extensive papillary necrosis. In these necrotic areas all the capillaries contained thrombi, which stained as fibrin.

The other example of papillitis necroticans was in a woman aged 69 years (Case No. 19). She was being treated with cortisone for rheumatoid arthritis, when fever developed. She became confused, and twitching of the limbs was observed. The blood urea four days before death was 182 mg. per 100 ml. and the haemoglobin 51%. Her urinary output appears to have been normal. Post-mortem examination showed the kidneys to be swollen (combined weight 450 g.). There were numerous small, subcapsular, abscesses, and the cortex showed a typical pyelonephritic change; although the polymorph casts in the
Fig. 25.
Polymorph casts, with pyelonephritic change associated with papillitis necroticans. These casts did not contain organisms detectable with Gram's stain. (Case No. 19).
H. and E. x 68.

Fig. 26.
Clumps of Gram-positive cocci in tubules of the necrotic papillae. (Case No. 19).
H. and E. x 68.

Fig. 27.
Zone of reaction, limiting the region of papillitis necroticans. (Case No. 19).
H. and E. x 68.
Fig. 28.
Toxic vacuolation of convoluted tubules of the kidney.
H. and E. x 440.

Fig. 29.
Dilatation of second convoluted tubules with flattening of the epithelium. The first convoluted tubules are also dilated and show vacuolation. (Case No. 15).
H. and E. x 106.

Fig. 30.
Marked renal tubular dilatation, with extreme flattening of epithelial linings. Pigment casts are also present. (Case No. 27).
H. and E. x 100.
cortical tubules did not contain organisms detectable by Gram's stain (fig. 25). The necrotic papillae were identical in appearance with those in the first case described. The large clumps of cocci were again very striking, (fig. 26), but, in addition to being present in the tubules, they were also found within blood vessels. There was widespread intertubular capillary thrombosis, and a well-marked zone of demarcation was present between the necrotic and the viable zones, (fig. 27). Neither of these patients with papillitis necroticans had diabetes mellitus, nor evidence of urinary obstruction.

Non-Suppurative Renal Lesions.

Many varieties of renal necrosis were observed. Indeed, the striking thing about the kidneys examined in this series was not the extent of suppuration present, but the frequency and severity of vascular lesions, together with various types of renal necrosis.

Degenerative Tubular Changes.

Some degenerative tubular change was always present, the milder degrees of which could not be distinguished with any certainty from post-mortem degeneration. The convoluted tubules always showed cloudy swelling, often with granular material in the lumina of the tubules. Severe vacuolation of the tubular epithelium was often present, and probably a more accurate index of toxaemic degenerative changes, than cloudy swelling, (fig. 28).

Dilatation of the distal convoluted and collecting tubules was found under two circumstances - first, as a consequence of
Fig. 31.
Capsular surface of kidney (Case No. 44). Pale areas overlying necrotic cortex, are visible. Subcapsular petechial haemorrhages are also present.

Fig. 32.
Cut surface of kidney shown in fig. 31 above. Localised areas of cortical necrosis are present. One column of Bertini is obviously involved. Numerous petechial haemorrhages are visible.
Fig. 33.
The stage of renal tubular healing. The tubules are dilated; the epithelium is plicated; and hyperchromatic and syncytial type cells are seen. Mitotic figures are present. (Case No. 22).

H. and E. x 130.

Fig. 34.
Kidney from Case No. 32. Blood, pigment and granular casts were found, together with extensive haemorrhage into glomeruli, and the renal pelvis.

H. and E. x 96.

Fig. 35.
Severe renal tubular dilatation. (Case No. 27, also illustrated in fig. 30). The shrunken glomerular tuft in a dilated capsule, could be mistaken for a tubular cast.

H. and E. x 100.
tubular necrosis, especially in the stage of attempted healing; and second, adjacent to areas of renal destruction due to suppuration, (figs. 29 and 30). A significant degree of tubular dilatation was present in 17 cases.

**TABLE 10.**
Renal Lesions Associated with 17 Cases of Tubular Necrosis.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tubular Necrosis</th>
<th>Tubular Dilatation</th>
<th>Patchy Glomerular Necrosis</th>
<th>Vascular Thrombosis</th>
<th>Highest B.U.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>-</td>
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<td>+</td>
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</tr>
<tr>
<td>12</td>
<td>+</td>
<td>-</td>
<td>+ Confluent</td>
<td>+</td>
<td>78</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>186</td>
</tr>
<tr>
<td>16</td>
<td>+</td>
<td>-</td>
<td>+++ Complete Cortical</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>182</td>
</tr>
<tr>
<td>22</td>
<td>+ Healing</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>500</td>
</tr>
<tr>
<td>27</td>
<td>+ Healing</td>
<td>++</td>
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<td>38</td>
<td>+</td>
<td>-</td>
<td>+++ Complete Cortical</td>
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<td>49</td>
<td>+</td>
<td>-</td>
<td>+++ Complete Cortical</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Renal necrosis was a notable feature. It was characteristically patchy, occurring in foci of up to about 1 cm. diameter and involving sometimes the medulla, but more
Fig. 36.
Renal glomerulus showing cubical metaplasia of capsule. The tuft has proliferated, and a hyaline thickening of the capillary walls can be seen. (Case No. 44).
H. and E. x 380.

Fig. 37.
Fibrinoid necrosis of the basement membrane of the glomerular capsule, with splitting of the endothelium. The glomerular tuft is shrunken, and the capillaries are mostly occluded. (Case No. 17).
H. and E. x 400.
Fig. 38. Complete bilateral renal cortical necrosis. (Case No. 16). Numerous intra-vascular coccal plugs are present.

H. and E. x 140.

Fig. 39. Complete bilateral renal cortical necrosis, showing refractile appearance.

H. and E. x 68.

Fig. 40. Thrombosed arcuate vessel at zone of reaction to complete cortical necrosis.

H. and E. x 68.
often the cortex. The foci of cortical necrosis were obvious on naked-eye examination, and occasionally they extended along the columns of Bertini, (figs. 31 and 32). It can be seen from Table 10, that tubular necrosis was closely associated with tubular dilatation; glomerular necrosis; thrombosis of renal blood vessels, and clinical evidence of renal insufficiency.

The stage of attempted healing in necrotic tubules was found in two cases, the tubules being extremely dilated and lined by a markedly thinned epithelium, some of the nuclei of which showed mitotic activity, (fig. 33).

Casts were frequently associated with tubular necrosis. All varieties were seen - hyaline, granular, cellular, blood and pigment casts, (figs. 30 and 34).

Glomeruli were seen to lead into dilated proximal convoluted tubules, (fig. 30). Sometimes this was so marked that the glomerulus appeared as a cast in a tubular space, (fig. 35). Cubical metaplasia of the glomerular capsule, fibrinoid necrosis and splitting of the capsule, were often present, (figs. 36 and 37).

A few necrotic glomeruli, or portions of glomeruli, were found in the foci of cortical necrosis, and appeared to be merely incidental to the necrotic process, in which the damage was mainly tubular. In Case No. 12, however, the cortical necrosis had become extensive in kidneys, the seat of wide-spread suppuration.

Complete Bilateral Renal Cortical Necrosis.

Three examples of this complication were encountered - Cases No. 16, 38 and 49.
Fig. 41.
Patchy cortical necrosis - this picture of complete necrosis is from one of the pale, localised, cortical areas illustrated in figs. 31 and 32.

H. and E. x 75.

Fig. 42.
Wedge-shaped peripheral infarct, with thrombosed artery. Smaller arterioles are patent.

H. and E. x 7.5.
TABLE 11.

Summary of Main Findings in Three Cases of Complete Bilateral Renal Cortical Necrosis.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Glomerular Capillaries</th>
<th>Arteries</th>
<th>Veins</th>
<th>Duration of Illness</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>62</td>
<td>Thrombi</td>
<td>Thrombi</td>
<td>Thrombi</td>
<td>5 days</td>
<td>Death at home</td>
</tr>
<tr>
<td>38</td>
<td>47</td>
<td>Congestion and Conglutination</td>
<td>Thrombi</td>
<td>Thrombi</td>
<td>3 days</td>
<td>? Influenza</td>
</tr>
<tr>
<td>49</td>
<td>47</td>
<td>Thrombi</td>
<td>Thrombi</td>
<td>Thrombi</td>
<td>3 days</td>
<td>? Influenza</td>
</tr>
</tbody>
</table>

It can be seen from Table 11, that these are short-lived, rapidly advancing cases. Two patients gave a history, and had post-mortem findings, suggestive of an influenzal infection, particularly as an influenza epidemic existed at that time. Case No. 16, showed widespread coccal plugs in arterioles, interlobular vessels and glomerular capillaries, (fig. 38). No cocci could be demonstrated in Cases No. 38 or 49. Fibrin thrombi were found regularly in glomerular capillaries, the renal interlobular arteries, arterioles and venules. The arterial walls showed fibrinoid necrosis, (figs. 39 and 40). In the cases of patchy cortical necrosis already described, the histological features in the necrotic areas were identical with the picture found in complete bilateral renal cortical necrosis, (fig. 41).

Another pattern of renal necrosis observed was that of a typical wedge-shaped peripheral infarct, with a related thrombosed vessel, (fig. 42). The lesions of focal embolic glomerulonephritis were very numerous...
Fig. 43.
Renal glomerulus showing proliferation of the tuft, with a fibrinoid change in the capillary walls, and glomerular capsule. (Case No. 30).
H. and E. x 400.

Fig. 44.
Diffuse proliferative glomerulonephritis. (Case No. 23).
H. and E. x 175.

Fig. 45.
Diffuse glomerulonephritis with severe cortical intertubular capillary congestion and thrombosis. (Case No. 3).
H. and E. x 80.
Fig. 46.
Severe medullary intertubular congestion, surrounding an impacted clump of cocci.
H. and E. x 140.

Fig. 47.
Exudative glomerulonephritis, with organisation showing a crescentic pattern. (Case No. 27).
Reticulin stain x 360.

Fig. 48.
Marked hypercellularity and digitation of glomeruli. Typical focal embolic glomerulonephritic lesions were also present. (Case No. 37).
H. and E. x 140.
in and near, such infarcts.

Glomerulonephritis.

Glomerulonephritis was diagnosed histologically if any, or all, of the three principal types were present — proliferative, exudative, or necrotising. The changes might also be focal or diffuse. Using these general criteria, "glomerulonephritis" was present in 16 patients — these 16 included most of those who have already been studied on account of tubular and glomerular necrosis, (figs. 36, 37, 43 and 44). Haemorrhage and severe congestion often accompanied diffuse glomerulonephritis (figs. 45 and 46). Crescent formation with later organisation also occurred, (fig. 47).

Focal Embolic Glomerulonephritis.

This term is used without prejudging the possible rôle played by embolism in its production. As will be shown, the term "focal endocarditic glomerulonephritis" is also not entirely satisfactory, because some examples of it are found without associated endocarditis.
Fig. 49.
Focal embolic glomerulonephritis. (Case No. 3).
H. and E. x 155.

Fig. 50.
Focal glomerular lesion with a fibrin thrombus in the related arteriole.
P.T.A.H. x 160.

Fig. 51.
Cluster of glomeruli containing focal lesions, arranged around a thrombosed intralobular artery. (Case No. 3).
H. and E. x 106.
### TABLE 12.

**Summary of Eight Cases with Focal Embolic Glomerulonephritis.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Duration of Illness</th>
<th>R-sided Endocarditis</th>
<th>L-sided Endocarditis</th>
<th>B.U.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>40</td>
<td>1 year</td>
<td>-</td>
<td>+ (M.V.)</td>
<td>54</td>
</tr>
<tr>
<td>15</td>
<td>33</td>
<td>6 mths.</td>
<td>-</td>
<td>-</td>
<td>186</td>
</tr>
<tr>
<td>17</td>
<td>38</td>
<td>29 days</td>
<td>-</td>
<td>+ (M.V.)</td>
<td>95</td>
</tr>
<tr>
<td>27</td>
<td>21</td>
<td>24 days</td>
<td>-</td>
<td>+ (M.V.)</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>42</td>
<td>20 days</td>
<td>+ (T.V.)</td>
<td>+ (M.V.)</td>
<td>117</td>
</tr>
<tr>
<td>37</td>
<td>75</td>
<td>32 days</td>
<td>-</td>
<td>+ Nodules of fibrinoid M.V.</td>
<td>120</td>
</tr>
<tr>
<td>44</td>
<td>52</td>
<td>39 days</td>
<td>-</td>
<td>+ (M.V.)</td>
<td>30</td>
</tr>
<tr>
<td>45</td>
<td>43</td>
<td>7 days</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Table 48 shows similar lesions in Case No. 37. Typical focal lesions were also present in this case.

All stages of the lesion were observed. Some were simply hyaline foci amongst the glomerular capillaries, (fig. 49). Others were...
Fig. 52.
Arrangement of focal glomerular capillary congestion, with blood casts in the tubules, and convoluted tubular necrosis. (Case No. 6).
H. and E. x 106.

Fig. 53.
Glomerular capillary congestion, and exudative glomerulonephritis in relation to a thrombosed artery. (Case No. 45).
H. and E. x 106.

Fig. 54.
Fibrinoid change in a glomerular tuft. In this example it appears that the change primarily involves the capillary wall. (Case No. 44).
H. and E. x 600.
more necrotic and fragmented, whilst older ones showed the changes of organisation. The focal lesions were easy to find in these eight cases, although their incidence varied in different blocks of tissue from the one kidney, from approximately 5 - 50% of all glomeruli present. The staining properties of the focal lesions were also variable - some stained similarly to fibrinoid with acid-picro Mallory, phosphotungstic acid-haematoxylin and periodic-acid Schiff, (fig. 60). Others did not stain in this manner.

The lesions were closely correlated with a fibrinoid change in the walls of related arterioles and capillaries. They were frequently observed in glomeruli adjacent to which was an arteriole occluded by a fibrin thrombus, (fig. 50), and the wall of which showed fibrinoid necrosis. Thrombosis of an inter-globular artery was sometimes seen with a cluster of glomeruli showing focal lesions arranged in relation to it, (fig. 51). A similar arrangement was sometimes seen, except that the focal glomerular lesions consisted of localised engorged capillary loops, (Figs. 52 and 53).

An interesting correlation was drawn between these renal lesions and the pulmonary vascular damage found in nine patients, (figs. 17 and 18), in whom thrombosis of alveolar capillaries and pulmonary arterioles with surrounding focal haemorrhages occurred. Five of these also had focal embolic glomerulonephritis - that is, in only three patients in whom focal glomerular lesions were found, were no such pulmonary changes recorded. Unfortunately, I did not perform these autopsies, and paper
Fig. 55.
The fibrin-staining material in this glomerulus, appears to be within the lumina of the capillaries. (Case No. 44).
A.P.M. (Lendrum) x 320.

Fig. 56.
The fibrin-staining material is continuous with a thrombus in the related arteriole. (Case No. 44).
A.P.M. (Lendrum) x 320.

Fig. 57.
This illustrates the staining properties of the capillary and arteriolar thrombi. (Case No. 44).
A.P.M. (Lendrum) x 180.
Figs. 58, 59 and 60. These three pictures, all from the same patient, illustrate a gradation from fibrin thrombosis involving the afferent arteriole, to involvement of capillary loops, and finally, a focal, circumscribed distribution of fibrin in a greatly dilated capillary loop.

A.P.M. (Lendrum).
**Fig. 61.**
Coccal embolus in a glomerular capillary. The glomerulus shows no change other than that of diffuse proliferation. (Case No. 32).

H. and E. x 546.

**Fig. 62.**
Proliferation, with vacuolation of the glomerular tuft. (Case No. 15).

H. and E. x 260.

**Fig. 63.**
Vacuolation of tuft associated with hyalinisation.

H. and E. x 260.

**Fig. 64.**
Fibrinoid arteriolonecrosis, without thrombosis. The glomerular tufts show hypercellularity and digitation. (Case No. 37).

H. and E. x 140.
sections of whole lung were not available. It is a lesion which is difficult to detect in the autopsy room, even when specifically sought after.

No bacteria were seen in the lesions, and bacterial emboli were seen without any focal lesion, (fig. 61).

Renal Vascular Lesions.

This is an opportune stage at which to raise a question of terminology, which will be discussed more fully in the next chapter. The terms, "hyaline", "fibrin", and "fibrinoid", are used rather indiscriminately and the latter two often interchangeably. There are, of course, grounds for questioning their separate identities. For the descriptive purposes of this chapter, fibrinoid is taken to be "an intensely acidophilic, homogenous, dense and refractile substance, with staining characteristics similar to those of fibrin, that is, red with trichrome or azan, dark, purplish-blue with phosphotungstic acid-haematoxylin, and red-purple with periodic acid-Schiff" - Movat (1958). Fibrin was differentiated in this description by an absence of the optical properties mentioned. Broadly, fibrinoid was found in the supporting structures - basement membranes and arterial walls, and fibrin was found intravascularly.

The use of special stains such as acid picro-Mallory and phosphotungstic acid-haematoxylin, is helpful in the recognition of fibrin and fibrinoid. Lendrum's modification of the acid picro-Mallory, using a light green counterstain (Lendrum 1949, Fraser and Lendrum 1940 and 1949), proved to be a most useful stain. This stain, and the phosphotungstic acid-
haematoxylin stain, demonstrated the presence of fibrin in no less than 24 cases. The positively staining material included the basement membrane of glomerular capsules, capillary endothelium, focal glomerular lesions, and arterial walls, (figs. 50, 58, 59 and 60).

Arterial, venous, or capillary thrombi were present in 30 cases. This figure does not include the almost constant finding of congestion and conglutination of red cells. When the red cells become conglutinated and lose their eosinophilic staining properties, it may be difficult to distinguish them from true thrombi. This is where fibrin stains are invaluable—particularly Lendrum's modification, in which the bright yellow colouring of erythrocytes contrasts vividly with the red-staining fibrin, although a gradual merging from yellow to red in a mass of conglutinated red cells, was sometimes discernable, (fig. 59).

The vessels most often involved were the glomerular and intertubular capillaries. The lumina of glomerular capillaries, contained an interlacing network of fibrin thrombus, which was at times difficult, or impossible, to distinguish from a fibrinoid degeneration of the capillary endothelium, (figs. 54 - 56). The phenomenon was observed so frequently that it was not possible to correlate it with any of the other renal manifestations. The glomeruli sometimes showed vacuolation associated with hyaline deposition,(figs. 62 and 63). Only paraffin-embedded material was available in these cases, so that the nature of the vacuolation could not be determined.

Involvement of the larger vessels was
not as common as capillary thrombosis, but arterial and venous thromboses were often observed when renal necrosis was extensive. No constant pattern could be discerned, except that thrombosis of interlobular and arcuate arteries were primarily associated with cortical necrosis; whereas the arcuate veins and venae rectae were thrombosed where tubular necrosis and especially papillary necrosis were the major parenchymal lesions. Sometimes fibrinoid necrosis of arteries was seen unassociated with thrombosis or necrosis of the renal parenchyma, (fig. 64). Focal embolic glomerular lesions were closely correlated with fibrinoid degeneration, and with thrombus formation in the afferent arterioles, (fig. 50).

Series of Control Kidneys.

In order to assess the specificity, and utility, of the lesions to which significance is being attached, and also to evaluate the reliability of the staining methods, a control series of kidneys were examined histologically. Forty consecutive autopsy examinations provided the material. Sections of kidney were stained by haematoxylin and eosin, Gram's stain, acid picromallory, phosphotungstic acid—haematoxylin and periodic acid—Schiff. The following lesions were amongst those studied:

"Congestion" and intravascular conglutination of erythrocytes.

This is a histological feature which is an extremely common finding in post-mortem kidneys.

Hypercellular glomeruli.

This was noted as being present in only six of the 40 patients. It is, however, one of the most subjective and, therefore, one of
the most fallible criteria.

**Capillary Thrombi.**

The presence of glomerular capillary fibrin thrombi (or of a fibrinoid change in capillary endothelium) is an uncommon event. It was only present in three patients - one case of multiple myelomatosis with renal vein thrombosis, one case of miliary tuberculosis, and one case of acute glomerulonephritis.

Fibrin stains were found to be distinctly helpful, although care had to be taken when using the phosphotungstic acid-haematoxylin stain, not to confuse the deep blue staining property of erythrocytes when conglutinated, for fibrin thrombi. Lendrum's modification of the acid picric-Mallory is of real value in this differentiation of fibrin from masses of erythrocytes.

**Possible Role of Hypertension in the Aetiology of Fibrinoid Lesions.**

The possibility that a coincidental state of essential hypertension might be implicated, obviously must be considered, before attaching too great a significance to fibrinoid necrosis in renal blood vessels.

It would appear justifiable, however, to say that hypertensive disease, was not a factor in the production of the renal lesions studied in the material available. Only two patients were hypertensive - either on ante-mortem blood pressures, or post-mortem heart size. These were Case Nos. 15 and 37. Case No. 15 showed malignant arteriolonecrosis. A few of the glomeruli also showed a fibrinoid change of the basement membranes, but fibrin capillary thrombi were present. Case No. 37 had extensively diseased kidneys - acute proliferative glomerulonephritis,
focal embolic glomerulonephritis, tubular degeneration and fibrin thrombi in arterioles and glomerular capillaries – a general picture quite unlike that of hypertension, with its striking arteriolar involvement. The finding of fibrin thrombi in glomerular and intertubular capillaries does not resemble the changes in hypertension.

Cardiovascular Lesions.

Bacterial Endocarditis.

Involvement of the heart valves was present in ten cases. Two of these also had infected thrombi attached to the endocardium of the heart chambers. Table 13 summarises these lesions together with incidence of focal glomerulonephritis. Cases 31 and 34 had evidence of rheumatic heart disease with mitral stenosis.

It can be seen from Table 13 that the cases in which ulcerative endocarditis was found at autopsy accounted for six out of the total of eight instances of focal embolic glomerulonephritis. In one of the two cases of focal embolic glomerulonephritis unassociated with bacterial endocarditis, the only heart lesion was the presence of numerous myocardial abscesses, many of which were subendocardial. In the other case (where I performed the autopsy), careful naked-eye and microscopical examination of the heart valves was undertaken, so that it can be definitely stated that valvular bacterial endocarditis was not present. Nevertheless, thrombus was found attached to the left ventricle and numerous subendocardial abscesses were present.
### TABLE 13.

**Showing Frequency of Bacterial Endocarditis and Associated Renal Glomerular Lesions.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Heart Valve with Endocarditis</th>
<th>Heart Chamber Thrombus</th>
<th>Peripheral Vasc. Occlusions</th>
<th>Focal Glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M.V. T.V.</td>
<td></td>
<td>Femoral Vein</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>M.V.</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>T.V.</td>
<td>R.V.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>M.V.</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>T.V.</td>
<td></td>
<td></td>
<td>Digitation of glomerular tufts</td>
</tr>
<tr>
<td>27</td>
<td>M.V.</td>
<td></td>
<td>Carotid Artery</td>
<td>+</td>
</tr>
<tr>
<td>31</td>
<td>M.V.</td>
<td></td>
<td>Common Iliac Vein</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Popliteal Artery</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>M.V. T.V.</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>33</td>
<td>M.V. (Fibrinoid only)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>34</td>
<td></td>
<td>L.V. L.A.</td>
<td>Bifurcation of Aorta</td>
<td>-</td>
</tr>
<tr>
<td>43</td>
<td></td>
<td>R.A.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>44</td>
<td>M.V.</td>
<td>L.V. L.A.</td>
<td>Femoral Artery</td>
<td>+</td>
</tr>
<tr>
<td>45</td>
<td></td>
<td>L.V.</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Fig. 65.
Metastatic abscesses in the pons. A central intravascular, clump of cocci is surrounded by a rim of polymorph infiltration.
H. and E. x 68.

Fig. 66.
Liver showing portal tract infiltration by lymphocytes and plasma cells.
H. and E. x 130.

Fig. 67.
Thrombosis in a case of splenic infarction.
H. and E. x 86.
Major-vessel occlusion was an important cause of serious complications in the course of staphylococcal septicaemia. Table 13 above, has already listed five of these complications. Further examples were thrombosis of the inferior vena cava, innominate vein thrombosis, and saphenous vein thrombosis. In one case there was thrombosis of the vasa vasora of the coronary artery. Suppuration developed in the arterial and venous thrombi.

Pericarditis occurred in ten patients. This was usually fibrinous and not obviously purulent. Metastatic myocardial abscesses were distributed mainly in the left ventricle. These consisted of a central clump of Gram-positive cocci, surrounded by a zone of infarction with a variable degree of polymorph invasion, which in its turn was surrounded by a zone of reaction and acute congestion.

Central Nervous System.

The lesions observed in the central nervous system were those of suppuration, ischaemia and haemorrhage. Fig. 65, shows metastatic abscess formation. Two zones, as in myocardial abscesses, are clearly visible.

Five cases of staphylococcal meningitis were found at autopsy. The meningitis was in these a more localised process, than is customary in the purulent meningitides, for example - localisation to the middle cerebral fossa on one side. This localisation, together with the finding of small cerebral metastatic abscesses in three cases, suggested that the meningitis was a localised reaction to cerebral suppuration, akin to the Rich focus in tuberculous meningitis.
Intracerebral haemorrhage was sufficiently extensive in three patients, to have been the immediate cause of death. In addition, there was one instance each of subdural haemorrhage and subarachnoid haemorrhage.

Vascular involvement was once again seen to be a significant factor. Four patients had small multiple areas of cerebral softening - no organisms were found in such areas. These lesions, and the instances of intracerebral haemorrhage, were probably associated with primary vascular occlusion. Thrombosis of pial vessels was associated with one case of cerebral haemorrhage and another of subarachnoid haemorrhage. In a case of meningitis the smaller arteries and arterioles showed fibrinoid necrosis associated with thrombosis.

**Hepatic Lesions.**

Suppuration is a rare event in the liver during the course of staphylococcal septicaemia. Three examples were recorded as having been found in this series of 40 autopsies. Histological material for confirmation was only available in one of these. The abscesses in this case were found in the liver lobules and portal tracts.

Fatty change of the liver, and a moderate - to - marked degree of portal tract infiltration with lymphocytic cells, were often encountered - the latter being noteworthy in 14 cases, (fig. 66).

Two of the livers examined showed widespread necrosis. One of these was associated with the presence of large masses of intravascular Gram-positive cocci in the necrotic areas. The other, was a massive necrosis involving the left lobe of the liver in a patient who had a
Fig. 68.
Severe congestion of adrenal cortical capillaries, several of which show disruption and haemorrhage.

H. and E. x 130.

Fig. 69.
Gram-positive cocci in the cortical capillaries of an adrenal gland which contained a large medullary haemorrhage.

Gram's stain x 130.

Fig. 70.
Acute renal tubular necrosis from a case of Rickettsial endocarditis.
staphylococcal endocarditis of the mitral valve; who was in congestive cardiac failure; and in whom multiple arterial embolism was occurring. Therefore, presumably, both these liver necroses were of ischaemic origin, even though the liver is supposed to be able to withstand simple arterial occlusion without ensuing infarction.

Thombosis (the thrombi staining as for fibrin) of the sinusoids and radicles of the portal vein was seen in a patient who showed similar thrombi in meningeal, pulmonary and renal vessels, (Case No. 35).

**Splenic Lesions.**

The spleen behaved similarly to the liver, in that suppuration was a distinctly rare event. It was noted in the autopsy records of two patients, but neither could be verified by recourse to histological material.

Infarction was the cardinal lesion found in the spleen - this was present in nine cases. None of the infarcts suppurated, although a polymorphonuclear proliferation of the splenic pulp, together with the presence of occasional Gram-positive cocci, might be mistaken for suppuration. Thrombosis, usually of the larger arteries, was found in these nine cases of splenic infarction, (fig. 67).

**Adrenals.**

Focal necroses of adrenal cortical tissue were found at four autopsies. Severe congestion was a frequent feature, (fig. 68). One case of massive bilateral adrenal haemorrhage was seen - Gram-stained sections demonstrated cocci in the disrupted cortical capillaries in this case, (fig. 69).
Summary of Principal Pathological Findings in Human Series.

The lesions found can be grouped under three headings:—

1. Suppurative.
2. Ischaemic.
3. "Toxaemic".

Suppurative lesions occurred, either in the form of metastatic abscesses, or infection in an area of infarction — the latter was especially prone to occur in pulmonary infarcts. Metastatic abscesses were found in the lungs, kidneys, and central nervous system. The myocardium was less frequently involved. The liver and spleen were only very exceptionally involved.

Infarction was observed in the lungs, brain, spleen and kidneys.

The type of lesion to which particular attention was paid in this study was the "toxaemic" lesion. "Toxaemia" is used in this context, in a non-specific sense. The interpretation of the lesions is considered later.

Changes in both blood vessels and parenchyma were commonly seen. The organs showing such lesions most frequently, and in the clearest fashion, were the lungs and kidneys. The capillaries of pulmonary alveolar septa, renal glomerular tufts, and amongst the renal tubules, showed occlusion by thrombi which stained in a manner similar to fibrin and fibrinoid. The arteries and veins also, although less frequently, were occluded by fibrin thrombi. These larger vessels often developed fibrinoid necrosis of their walls. The parenchymal changes associated
with the vascular lesions were those of severe degeneration or frank necrosis. In the lungs, localised areas of intra-alveolar haemorrhages were grouped around thrombosed, and often necrotic, arterioles or capillaries. The kidneys showed patchy cortical necrosis in which the damage was mainly tubular. The glomeruli on the other hand were found to illustrate various types of non-specific glomerulonephritis.

This discussion is confined to a consideration of the material examined from human cases. Some of the numerous animal experiments which have thrown considerable light upon the pathogenesis of infections are discussed following a description of the lesions found in animals, in Chapter 19.

The surprising fact that emerges from a study of the literature dealing with clinical accounts of severe staphylococcal infections, is the scanty attention that is usually paid to the pathology. Individual lesions have been studied in detail - for example osteomyelitis, and the renal lesions in bacterial endocarditis, but it has seldom been considered as a systemic disease suitable for detailed pathological study. In this respect more attention has been paid to the experimental animal than to man. In many clinical reports no pathology is described. A detailed report such as that of Kendall (1939), is content to describe the pathological findings in 15 autopsies out of 29 fatalities with statements such as, "The heart showed 26 lesions and the lungs 59 lesions." Certainly, current
"Actually there is an appreciable number of diseases that leave their diagnostic label in the kidney, a label that is clearly detectable with the microscope. Sometimes the label is a self-sufficient, specific histological change; at other times the definitive histological picture is made up of a composite of changes, no one of which may establish the diagnosis until all are evaluated together."

Allen (1952).

This discussion is confined to a consideration of the material examined from human cases. Some of the numerous animal experiments which have thrown considerable light upon the pathogenesis of infections are discussed, following a description of the lesions found in animals, in Chapter 10.

The surprising fact that emerges from a study of the literature dealing with clinical accounts of severe staphylococcal infections, is the scanty attention that is usually paid to the pathology. Individual lesions have been studied in detail - for example osteomyelitis, and the renal lesions in bacterial endocarditis, but it has seldom been considered as a systemic disease suitable for detailed pathological study. In this respect more attention has been paid to the experimental animal than to man. In many clinical reports no pathology is described. A detailed report such as that of Mendell (1939), is content to describe the pathological findings in 16 autopsies out of 29 fatalities with statements such as, "The heart showed 26 lesions and the lungs 59 lesions." Certainly, current
reports are even less concerned with the morbid anatomical changes found in generalised infections. The reason for this neglect may be the impression that is commonly held that staphylococcal septicaemia is the classical example of "pyaemia", so that its lesions are those of metastatic suppuration and little more remains to be said about it.

The suppurative lesions are, in fact, the lesions least germane to this thesis, except in so far as their frequency and distribution provide a clue as to the local host factors, which permit implantation and growth of Staph. aureus.

**Pulmonary Suppuration.**

The pulmonary capillaries must be the first capillary bed to which the invading staphylococci are exposed — except possibly in the case of primary pulmonary suppuration. It is difficult to evaluate the "filter bed function" of pulmonary capillaries in this disease. Certainly, staphylococci were observed to have been ingested by intravascular neutrophil polymorphonuclear leucocytes. The finding of two distinct types of suppurative lung lesions (not including primary staphylococcal pneumonia) — namely discrete metastatic abscesses and suppurating infarcts, suggests that the lungs may be involved as a result, both of the initial invasion of bacteria, and also secondarily when circulating bacteria or infected thrombi lodge in already infarcted areas. The mechanism of infarction, in these cases, is probably dependent on pulmonary vein thrombosis. The infarcts observed could be easily differentiated from those found in mitral stenosis by the absence of
a Prussian-blue reaction around the infarcts, presumably because of their shorter duration. Infarcts are more readily produced following arterial obstruction when there is also an impediment to the venous return - as in mitral stenosis (Belt 1934). Karsner and Ghoreyeb (1913) demonstrated that occlusion of the second and third orders of the pulmonary arterial system produced infarcts if the lungs were already the seat of chronic congestion from cardiac insufficiency. Thromboses of pulmonary veins and venules were often noted, in several of which no organisms could be detected. Therefore, it is possible that the vascular lesions discussed below may be influential also in the development of the pulmonary infarcts.

One of the two examples of cystic disease of the lung cannot be attributed to prolonged staphylococcal infection. It is more likely that in Case 19 the chronic lesions were already well established and may, indeed, have provided the avenue of infection. Heppleston (1956) in his description of the pathology of honeycomb lung, included six cases due to prolonged suppuration of a bronchopneumonic type, three of which were tuberculous. The cystic type of staphylococcal pneumonia found in infancy was not seen in this series. Case 32, which showed a radiating hyphal growth, conforms to the description of pulmonary mucormycosis described by Baker (1956). He described seven cases in which non-septate hyphae 4-20 μ wide and up to 200 μ long occurred - in none of the cases was a fungus isolated on culture. They were diagnosed on morphological grounds; the tendency to thrombosis and infarction; and the penetration of arterial walls.
The cases of pulmonary suppuration associated with influenza differed from the others by showing severe necrotising bronchitis and tracheitis.

Renal Suppuration.

Suppurative renal lesions were, as might be expected, found frequently. Papillitis necroticans was an interesting complication of suppuration in two patients. This condition was first described by Friedrich (1877) in a man aged 70 years, with prostatic disease and hydronephrosis. He noted necrotic sequestration of the papillae. Subsequently several cases were reported in association with urinary obstruction. The other clinical association noticed was that of diabetes mellitus, Edmondson et al (1947) reported 13 instances in diabetics, and 20 in non-diabetics. They added a further 50 hitherto unreported occurrences - 29 in diabetics and 21 in non-diabetics.

Schomer (1931) described three cases. The first was a diabetic man of 48 years, who had mandibular abscesses and septicaemia due to Friedlander's bacillus. The second case was that of a woman of 68 years, with a carcinoma of the stomach and bacteremia from no known focus. Bacterial thrombosis of the vessels in the renal medullae, in and around areas of necrosis, were outstanding. The third case was probably a staphylococcal septicaemia - ulcerative endocarditis of the aortic valve and skin abscesses in a man of 48 years.

In the series described by Edmondson et al pyogenic infection was a common finding. It was present in 26 out of 29 diabetic cases and they classified the manifestations of these infections
into septicaemia, renal tract infection, and acute renal failure. *Staph. aureus* was isolated in five cases. Cortical abscesses were present in two-thirds of the cases. They emphasised the vascular lesions - hyaline capillary thrombosis and extensive thrombophlebitis.

In the two cases from this series, the sequence of events could have been firstly the formation of cortical abscesses, then the excretion of large numbers of staphylococci, which lodged and multiplied in the collecting tubules and ducts of Bellini. These bacterial aggregates were often surrounded by zones of coagulative necrosis in which vascular thrombosis was likely to develop.

Dawson and Langley (1944) and Allen (1952) postulate an ascending infection from a diffuse pyelonephritis. Such a view must presuppose that pyelonephritis itself is not the result of haematogenous infection. Dawson and Langley found no evidence of vascular occlusion, although it is not stated that fibrin stains were used. In fact, one of the illustrations in article shows a clear focal, hyaline glomerular capillary occlusion. The question of capillary damage is all-important because no vessels larger than capillaries are found in the distal two-thirds of the renal pyramids. Apparently, the entire papillary blood supply consists of arterial capillaries leading down, and venous capillaries leading up the pyramid with only poor anastomoses. Robbins et al. (1946) emphasised the importance of this in their study of four cases of papillitis necroticans. All four had septicaemia. These authors, in the light of their own cases, and other descriptions, for
example, Sheehan (1937), grouped cases of papillitis necroticans into two groups—firstly, the acute, fulminating in the course of severe generalised infection with pyuria, rising blood urea, and possibly oliguria; and secondly, a group which has a protracted course. Swartz (1954) described a case associated with meningitis. Thrombosis of the interlobar veins had occurred. No case of recovery from this complication has been reported, (the diagnosis can be made during life with the assistance of pyelography).

A rising blood urea in the course of a staphylococcal septicaemia may well be indicative of the development of papillitis necroticans.

**Renal Infarction and Necrosis.**

Examples were encountered of what were typical wedge-shaped infarcts resulting from arterial occlusion. The renal parenchyma within these areas was completely necrotic, and the margin of the infarct was formed by the customary zone of reaction. Cortical infarcts of this type were expected, but the more surprising fact that emerged during this study was the importance of other patterns of renal necrosis. There are grounds for believing ischaemia to be the ultimate cause of the renal necroses, but to term them 'infarcts' would lose sight of several important differences between the two types of lesion both in morphology and pathogenesis.

Two main types of renal necrosis were observed—one in which the necrosis was principally cortical and involved the glomeruli, and the other in which the necrosis was solely tubular.

Necrosis of glomeruli was observed in
15 cases. Usually the glomeruli were involved in areas of patchy, localised, cortical necrosis, but in three cases, complete bilateral cortical necrosis had occurred. The pathogenesis of this condition is still controversial. It was first described by Jubel-Rénoy (1886) - this was in a girl of 16 years suffering from scarlatina. The first large review was that of Ash (1933). Renal cortical necrosis which is found in diethylene glycol poisoning, can be distinguished from the "disease" variety by the presence of concomittant liver lesions (Barber 1934). De Navasquez (1935), initially claimed there to be an "almost invariable association with pregnancy." This, however, was soon realised to be incorrect.

Dunn and Montgomery (1941) in a paper on "acute necrotising glomerulonephritis" described in detail the findings in eight patients, none of which were pregnant. One of these died ten days after appendectomy. Diarrhoea was noted in four of the others. No other histories of infections were given. These authors emphasised the importance of using specific fibrin stains. They listed 18 cases of extensive necrosis of the renal cortex not due to blockage of the larger arteries, and not associated with pregnancy - amongst these the organisms associated with the primary disease were streptococcus, diphtheria bacillus, tubercle bacillus and pneumococcus. Dunn and Montgomery found that in the early stages, the glomerular capillaries were engorged, and later, fibrin thrombi formed. Thrombosis extended to afferent arterioles, and then the intralobular arteries.

The primary diseases in cases of bilateral
renal cortical necrosis are diverse. Some of these have already been mentioned. Other reports of various conditions are:— with pregnancy (Gaspar, 1938, and Sheehan and Moore 1952), diphtheria (Stoeckemius 1921), influenza (Beneke 1894), dysentery (Fahr 1925), burns (Pollard 1907), trauma (Naueuberger 1927), and post-operative (Penner and Berheim 1940). In view of the ease with which bilateral renal cortical necrosis can be produced experimentally, using staphylococcal exotoxin, it is interesting that there should be such a dearth of references to staphylococcal infections clinically associated with condition. Gareiss-Dollitzturm (1928), described it in the case of a para-8 woman who died 25 days post-partum, after developing a staphylococcal septicaemia.

Duff and Murray further reviewed the condition in 1941. They analysed 71 cases that came to autopsy. Of these 48 were pregnant and 23 non-pregnant. Amongst the non-pregnant, in one case bacteria were noted in the vessels of spleen, liver and pancreas, and in another pneumonia with abscess formation was present. Post-partum infection was present in six of the pregnant cases (three after induced abortion). In their description of the pathological findings it was noted that the arteries and veins visible to the naked eye, (that is, the larger arcuate vessels) were free from any form of occlusion, except in two where renal vein thrombosis was found. Whilst it is now generally agreed that renal cortical necrosis occurs secondarily to ischaemia, the manner in which this is mediated is still disputed. The capillaries are usually described as empty, but the following workers describe finding fibrin thrombi:— Bowes (1933-34),
Gaspar (1938), Hirst (1926), Lanza (1938) and Dunn and Montgomery (1941), as mentioned above. Scriver and Oertel (1930), found conglutinated red blood cells and fat droplets. Cortese (1935) also described fat droplets. Duff and Murray (1941) emphasised the significance of lesions in larger vessels, especially the intralobular arteries (up to 150 µ diameter). They postulated a primary fibrinoid necrosis in the arterial walls, with subsequent thrombosis - the thrombi being made of fibrin or hyaline substance.

Acidophilic, homogenous, amorphous, masses were seen and the question was raised whether these were true thrombi or conglutinated erythrocytes. This question posed itself during the examination of material in this series. Frequently a gradation could be observed from erythrocyte collections where the cells were still discrete, to areas where complete homogeneity had resulted. Furthermore, such masses did not stain specifically as did fibrin thrombi, although a gradual merging with fibrin-staining material sometimes occurred. Nevertheless, they probably represent vascular stagnation during life. These authors also made the most interesting observation, and one that is highly relevant to this discussion, that the condition could be associated with liver cell necrosis (in spite of the statement made by Barber above, concerning diethylene glycol poisoning); multiple haemorrhagic ulceration of the small intestine; multiple thromboses and small infarctions of the spleen; minute haemorrhagic necrotic areas in the adrenals; and cerebral petechial haemorrhages. Lelong (1955) also records this among 33 cases occurring in children. Such a list of lesions is suggestive
of a systematised reaction akin to the generalised Shwartzman phenomenon. Such a mechanism can hardly explain the cases occurring from simple traumatic shock, but details are not given, and whilst infective cases form an appreciable proportion of their series, it would have assisted in this matter if an attempt had been made to correlate the pathological findings with the diverse primary conditions. It is immediately obvious that renal cortical necrosis is not a specific feature of generalised staphylococcal infections, but the probability that a fundamental type of host response may be involved, in no way lessens the significance of the finding.

Sheehan and Moore (1952), in their monograph on renal cortical necrosis, gave the morbid anatomical lesions in detail. They examined 67 fatal cases of concealed accidental haemorrhage. Their conclusions were that vascular spasm was the primary factor giving rise to renal necrosis, and that vascular thrombosis was secondary and was not found until 14 hours after the establishment of tissue necrosis. They postulated a sequence of glomerular spasm; the first stage of reflow; later arterial spasm; the second reflow, and then the stage of final permanent circulatory arrest. However, even if these are, in fact, the stages that take place in the development of renal cortical necrosis following accidental uterine haemorrhage, they may well not apply to the cases described in this series. They described renal cortical necrosis in seven non-pregnant patients - this was labelled "confluent focal renal cortical necrosis", and the description given conforms very closely to
the lesions observed in this series. Their state of "benign glomerular thrombosis", is the same as the histological features observed in many of the present series, although it is not possible to be so confident about its "benign" import. The starting point of the present investigation is completely different from that of Sheehan and Moore's. In any case, even if vascular spasm plays a primary rôle, it is still not a final answer. Sheehan and Moore thought an "eclamptic toxin" might be implicated, but the frequency of renal necrosis unassociated with pregnancy seems to indicate a more "common" factor. They did not observe any examples of renal medullary or papillary necrosis.

The pathological findings in the three cases described in this series underline the importance of vascular fibrinoid necrosis and fibrin thrombus formation. In one case the extent of coecal vascular plugging suggested that this mechanical factor may have initiated the process. It can be argued, as do Sheehan and Moore (1952), that the thrombi found in these, and the reported cases, are formed subsequent to the cortical necrosis. This argument rejects positive structural evidence, and has little other evidence to advance except equally debatable experimental procedures. Also, inspection of the kidneys in this series gave a picture of a process ranging from the finding of capillary thrombi in 30 cases (24 of which stained as fibrin), amongst which occurred 15 examples of patchy cortical necrosis of varying degrees of severity, to three examples of the fully developed condition of bilateral renal cortical necrosis. The basic lesion in all these was a fibrinoid change in the vascular endothelium and fibrin thrombus formation.
Acute Tubular Necrosis.

Necrosis of different portions of the renal tubules was found as part of cortical necrosis, and also, of course, in the areas involved by papillitis necroticans. Apart from these, a relatively pure acute tubular necrosis was a major immediate cause of death in at least four cases. The term "acute tubular necrosis" is used in the sense in which it has been defined by Dible (1953).

These lesions have been closely studied by Bywaters and Dible (1945) in their description of the kidney in the "crush syndrome". The glomeruli showed eosinophilic debris in their capsular spaces. Cubical metaplasia of the glomerular capsule gave the appearance of an extension of tubular epithelium into the capsule as a funnel-like opening. This was a striking feature in one of the cases studied, as illustrated in fig. 35. The proximal convoluted tubules exhibited intense catarrh with an amorphous debris in their lumina. The most severely damaged portions of the tubules, however, were those of the wide ascending limb of Henle's loop, and the second convoluted tubules, in which complete necrosis affected small areas, chiefly in the boundary zone.

Pigmented tubular casts were frequently observed. Bywaters and Dible also found that a polymorphonuclear leucocytic invasion of casts (in which no organisms could be found) appeared to be associated with a high incidence of tubular necrosis. All these features were confirmed in the present series.

This type of tubular necrosis resembles that of "lower nephron nephrosis" described by
Lucké (1946), and the changes found in some cases of septic abortion by Bratton (1941).

Dible (1953) further classified the causes and types of tubular necrosis. First, tubular necrosis caused by the direct action of poisons, such as mercury and carbon tetrachloride. Second, the "shock kidney" of acute renal ischaemia. Third, cases of uncertain or mixed aetiology, such as the crush syndrome and criminal abortion. He states that cases of simple chemical poisoning show necrosis which is most marked in the first convoluted tubules. No definite localisation of tubular necrosis could be discerned in this series. Forty of the 62 cases examined by Dible showed selective tubular damage. Two of these were cases of criminal abortion, two followed burning and a further two were due to blackwater fever. Apart from these there was no hint of an infective factor in any of the others. He made a clear differentiation between symmetrical cortical necrosis, which was due to ischaemia, and tubular necrosis which was due to the direct effect of toxins.

Most of the cases in this series, in which tubular necrosis was present gave histories of brief duration with a fulminating disease process. One patient (Case No. 22) however, presented as a case of acute tubular necrosis with anuria and uraemia. He had a high swinging temperature from the commencement, and survived 64 days in hospital. At autopsy the kidneys showed tubules in the stage of attempted healing. It must again be emphasised that acute tubular necrosis is a non-specific change. A typical example was encountered in a case of Rickettsial endocarditis (fig. 70).
Focal Embolic Glomerulonephritis.

In 1907 Löhlein, in a monograph on inflammatory glomerular changes, described 35 cases of primary glomerular disease. Included in these were two cases which showed focal glomerulonephritis. Both occurred in patients who had chronic ulcerative endocarditis. In this original description he thought the lesions were toxaemic. However, when he later reported eight cases of chronic ulcerative endocarditis, all of which showed the same focal glomerular lesions, he thought they must be embolic, (Löhlein 1910). He stated they were probably small infarcts resulting from the lodgement of minute infected emboli.

Baehr (1912) supported the suggestion that focal lesions resulted from embolism. He examined the kidneys from 34 cases of subacute bacterial endocarditis and observed in minute detail the development of the lesions. Typical lesions were seen in 21 of 25 cases (in which the endocarditis was caused by Strep. viridans). Five of the 21 showed bacterial emboli in the very early glomerular lesions. Also of interest is the fact that Baehr noted the association of blood in the tubules, tubular atrophy and dilatation.

Baehr also studied the kidneys from 54 cases of acute endocarditis. No focal glomerular lesions were discovered in a single glomerulus, from any of these cases. This, he stated, rather as a presupposition and not as a result of observation, was due to the fact that when staphyloccoci lodge in the glomerulus, suppuration takes place. Therefore, Baehr concluded that the focal glomerular lesions were caused by emboli of
Strep. viridans. Fahr (1925) also believed the lesions to be embolic.

The fact that focal embolic glomerulonephritis is not restricted to Strep. viridans endocarditis was shown by Miller and Branch (1923), who found typical focal embolic lesions in a case of endocarditis of 50 days' duration due to H. influenzae.

Another step in the argument was the observation that focal glomerulo-nephritis could occur in the absence of endocarditis (Fahr 1925; Baehr and Sacks 1923; Bell 1932). Fahr believed that embolic lesions occurring in the absence of endocarditis were caused by bacterial emboli.

The next detailed study was that of Bell (1932). He examined the kidneys from 104 cases of active rheumatic endocarditis and 233 cases of bacterial endocarditis. Three cases of 164 examples of "primary bacterial endocarditis" were staphylococcal. The 164 cases were subdivided into 56 acute (duration less than 6 weeks) and 108 subacute (duration over 6 weeks). Embolic lesions were present in four of the former and in 57 of the latter. No indication was given of the infecting organism in these. There were 69 cases of "secondary bacterial endocarditis"—that is, where endocarditis was incidental to a septicaemia. Two of these were known to be staphylococcal. Focal embolic glomerulonephritis was present in four, but the organism was not noted. Bell stated that the duration of endocarditis was of great importance, the focal lesions being rarely found when the endocarditis was of less than six weeks' duration. He also said that "staphylococcal infections cause glomerular abscesses and not
embolic lesions of the type under discussion." Bell deduced that the focal lesions were, in fact, due to intracapillary thrombosis and were not due to embolism.

Allen (1952) summarises the reasons believing the focal lesion to be non-embolic:—

1. **Bacteria** are found only with extreme rarity.

2. Vegetations of acute bacterial endocarditis are large and friable yet focal glomerular lesions do not occur.

3. It is not to be expected that emboli should be restricted to one organ.

4. With true septic emboli, clusters of bacteria fail to produce the lesion. Neither do other solid particles on injection.

Allen goes on to conclude that the lesions result from an immuno-allergic response. The evidences adduced in the course of this study is of a conflicting nature. Allen's reasons given above for thinking the lesions to be non-embolic, are hardly adequate, because focal embolic glomerulonephritis is found in association with staphylococcal endocarditis. It is no objection to question why the lesions should only be found in kidneys because this organ is the most likely to be examined histologically and in any case the arrangement of the glomerular capillaries is unique. It appears that the production of lesions of this general type and morphology is a feature of the renal glomerulus in various diseases, for example, in disseminated lupus erythematosus and diabetes mellitus. Furthermore, it was shown in the previous chapter that a basically similar "vasculitis" often does, in fact, occur in the pulmonary blood vessels.
Any theory as to the production of these lesions must not only be based on their invariable association with the presence of endocarditis, but also take into account the exceptions to this rule. The factor common to all cases is a septicaemia. Bain et al (1958) describe focal lesions in a case where the endocarditis was confined to the tricuspid valve. This case had a positive blood culture.

It can be seen from Table 12, that the lesions are not limited to cases of over six weeks' duration, as stated by Bell (1932). It is also an undoubted fact that bacterial emboli can lodge in the glomerular capillaries without producing focal lesions. Contrary to the statements of Baehr and Bell, suppuration very rarely, if ever, originates in a glomerulus.

Bearing in mind the findings and statements of the workers to which reference has been made, and considering the evidence of the present study, the nature and aetiology of focal embolic glomerulonephritis is still an undecided question. Yet I would support Allen's conclusion (if not his reasons for reaching the conclusion) that the lesions are in the nature of an immuno-allergic response for the following reasons: -

1. The lesions are associated with fibrinoid change in related arteriolar and capillary walls.
2. Fibrin thrombi are present in related arterioles and capillaries.
3. The lesions are only restricted to the kidney in so far as their morphology is conditioned by their peculiar location. A basically similar pulmonary vascular lesion
was frequently associated with focal glomerular renal lesions.

This conclusion, for the reasons given, leaves much still unexplained. As is so often the case, the real answer may incorporate both views. Fahr (1925) may have been near to the truth when he stated that focal lesions occurring in the absence of endocarditis are caused by bacterial emboli. Bacterial emboli may well provide the local antigenic stimulus. The customary absence of discernable bacteria is no objection, because, as will be shown experimentally, bacteria can be cleared extremely rapidly. Hale and Smith (1945) stained films of staphyloococi in citrated blood. The coagulase negative varieties had clear outlines, but the coagulase positive strains were obscured, and Weigert's fibrin stain suggested that fibrin had been deposited around the individual cocci. It is interesting to conjecture whether such fibrin-coated cocci could be the cause of the fibrin thrombi.

The lesions of focal embolic glomerulonephritis are certainly associated with fibrinoid change in the related arterioles. Fibrinoid necrosis of the arterioles, with or without occluding fibrin thrombi, could often be seen adjacent to glomeruli showing focal lesions. Focal lesions were occasionally seen in glomeruli encircling a larger thrombosed artery, and they were also found with particular frequency near infarcted areas. This feature has been described by Russell (1929). Therefore, it seems that ischaemia is an important factor in the production of focal lesions.

The final answer awaits the application of new techniques - such as the fluorescent
antibody technique, which should lend itself to a demonstration of any local union of antigen with antibody.

**Acute Glomerulonephritis.**

The finding of histological evidence of glomerulonephritis in 16 cases is another item of evidence supporting the thesis that a hypersensitivity reaction is a means of tissue damage in generalised staphylococcal infections.

Dunn and Thompson (1921), in the course of 660 post-mortem examinations, found evidence of acute glomerulonephritis in 13 patients who had suffered from serious septic infections - 6 ulcerative endocarditis, 3 complicated otitis media, 2 septicaemia, 1 empyema and 1 retroperitoneal cellulitis. The pathological findings included a focal distribution of miliary thrombi in the glomerular tufts and diffuse intracapillary glomerulonephritis. They thought that nephritis is common in serious infections, but rarely causes renal insufficiency. Bell (1932; 1936), found an acute diffuse glomerulitis in a high proportion of all types of bacterial endocarditis.

The distinction between diffuse and focal glomerulonephritis in the present context is of doubtful value. Focal glomerulonephritis is supposed to arise at the height of the primary infection, and the diffuse variety only after a latent interval. This distinction could not be made in the present series.

Fishberg (1939) differentiates between focal glomerulonephritis due to the direct action of bacteria, and diffuse glomerulonephritis as an allergic reaction. Allen criticises this view and points out that the focal lesions resemble
the individual glomerular pattern of diffuse glomerulonephritis - "in other words the form of acute focal glomerulitis are also regarded as a toxic or allergic response to the products of organisms or drugs. To deny, as some do, that focal allergic reactions occur in the kidney, is to fail to give interpretive consideration, not only to these lesions, but to others such as those of lupus erythematosus, focal endocarditic glomerulonephritis, acute vascular alterations and, of course, acute focal interstitial nephritis." (Allen, 1952).

The Significance of Fibrin and Fibrinoid.

A study of the literature relating to hypersensitivity reactions is made somewhat more confusing than it might be, because of the variable connotation of certain terms. Some of the worst offenders in this respect are the terms "hyaline", "fibrin", "fibrinoid" and "fibrinoid necrosis".

The term "fibrinoid" was introduced by Neumann (1880) who described it as "an intensely acidophilic, homogenous, dense and refractile substance with staining characteristics similar to those of fibrin."

The development of thought, and a summary of the work done on the nature of fibrinoid has been recently reviewed by Movat (1958).

Neumann and Klinge (1929-30) believed that fibrinoid developed from degenerating collagen. Marchand (1896) and Meyer (1950) put forward the view that fibrinoid is an end-product of a fibrinous inflammation. Altshuler and Angevine (1949) claimed that fibrinoid is not altered collagen or exuded fibrin, but a precipitated acid mucopolysaccharide of connective
tissue ground substance.

Much recent work has involved the use of new techniques in the differentiation of fibrinoid from fibrin. Glynn and Loewi (1952) found that fibrinoid differed in possessing a fibrillar structure and resistance to digestion with trypsin. Kellgren et al (1951) differentiated between the two using histochemical methods, X-ray diffraction, and electron-microscopy. Gitlin et al (1957) however, using the fluorescent antibody technique, found that fibrin could be localised in all lesions containing fibrinoid.

Another line of research in this topic has been the identification of fibrinoid as a feature of lesions resulting from hypersensitivity reactions - this is not to say that fibrinoid is any way specific for hypersensitivity. Klemperer (1950), for instance, emphasises this lack of specificity, fibrinoid being found in the bases of peptic ulcers, in the placenta and in arteries in hypertensive and renal disease. However, fibrinoid remains a useful index of a hypersensitivity reaction. The concept of the collagen diseases by Klemperer et al (1942) has emphasised the diagnostic value of fibrinoid degeneration as indicative of a disease in which the union of antigen and antibody plays an essential part in the pathogenesis and production of tissue damage. The utility of this index in a condition such as staphylococcal septicaemia may be compared with its utility in a pure "collagen disease". Baehr and Pollock (1947) discuss the significance of the fibrinoid degeneration found in disseminated lupus erythematosus and scleroderma. They stated that the occurrence of fibrinoid degeneration in the Arthus phenomenon, and in serum sickness, is insufficient basis for the assumption that
disseminated lupus erythematosus and diffuse scleroderma must be the result of a hyperergic state. They also point out that they have never seen a patient with disseminated lupus erythematosus and diffuse scleroderma with eosinophilia, urticaria or asthma, this being in striking contrast to the findings in polyarteritis. However, it seems hardly justifiable to dismiss fibrinoid degeneration as a useful criterion in the detection of hypersensitivity reactions, because it is found in some lesions where there is no recognised reason to suspect a state of hypersensitivity. One might in similar manner dismiss the finding of an eosinophilia because it can be found in diverse conditions. Furthermore, the apparently non-allergic conditions may well involve some unknown antigen-antibody reaction. For example, Apitz (1934) considered pregnancy to represent a state of generalised reactivity as evinced experimentally when only a single intravenous injection of bacterial filtrate succeeded in producing the generalised Shwartzman phenomenon in pregnant animals. Certainly, fibrinoid degeneration is a constant feature of the Shwartzman phenomenon. Several recent publications give results indicating that fibrinoid found in the generalised Shwartzman reactions derives from fibrin - Miller and Bohle (1957) and Pappas et al (1958). Brunson et al (1955) detected a marked, abrupt, depletion of blood fibrinogen when fibrinoid is deposited in the tissues.
The Possible Role of the Shwartzman Phenomenon in Human Disease.

"Under the heading of bacterial allergy or bacterial hypersensitiveness is included an altered reactivity of the host to bacteria and their products." (Shwartzman 1937).

The possible rôle of Shwartzman's phenomenon in human bacterial infection is considered fully in Shwartzman's book. He describes similar lesions in acute thrombocytopenic purpura, bilateral renal cortical necrosis, and generalised miliary tuberculosis. He suggests that "toxic thrombosis" is a manifestation of the phenomenon. Several illustrations are given of glomerular capillary thrombi, and thrombi in the renal arterioles. He summarises his conclusions on the possible rôle of the phenomenon in human disease - "Production of severe lesions through the synergistic effect of biologically unrelated micro-organisms, and also through the synergistic effect of micro-organisms and non-bacterial antigen + antibody complexes, suggests explanations for the pathogenesis of certain secondary and mixed infections, and also for exacerbations of bacterial diseases."

McKay and Wahle (1955) describe identical lesions of widespread fibrin capillary thrombosis in various viscera in nine cases of epidemic gastro-enteritis due to E. coli OIII B4 in infants. Their illustrations of fibrin capillary thrombi resemble exactly the ones described in this series.

Role of Cortisone.

In view of the suppressive effect of
cortisone on hypersensitivity reactions (Rich et al 1950) and on the Shwartzman phenomenon (Marcus and Donaldson 1952) it is of interest to note whether the incidence of the thrombotic renal and pulmonary lesions varied in those patients who were receiving steroid therapy.

In addition to the seven patients who developed septicaemia, three others were treated with steroid therapy on account of the fulminating nature of their infections. Ten is too small a number to analyse in detail, but reference back to tables constructed of renal and pulmonary lesions, provides suggestive evidence that steroid therapy does have some effect in preventing the formation of fibrin capillary thrombi. Of the nine patients in whom pulmonary capillaries were seen to be thrombosed, only one was from the group of ten on steroid therapy. One of the eight cases showing focal embolic glomerulonephritis was on steroid therapy. Only this one of the ten steroid cases in fact had the lesion of focal embolic glomerulonephritis, although these ten included two cases of endocarditis. These isolated observations are, of course, no demonstration of a protective effect on a state of hypersensitivity by steroids, but the findings are, at least, suggestive. This aspect is investigated further in later animal experiments.

Summary of Pathological Evidence in Human Cases which indicates a State Hypersensitivity.

Hypersensitivity is used as an inclusive term – including the reaction of the Shwartzman phenomenon.
1. The frequent finding of multiple fibrin capillary thrombi especially in lungs and renal glomeruli.


3. Acute renal tubular necrosis, and patchy renal cortical necrosis.


5. Fibrinoid necrosis of blood vessels, and basement membranes (for example kidney glomerulus).

Other possibly relevant findings were the "shock lesions" of bilateral renal cortical necrosis, and massive bilateral adrenal haemorrhage, and also the possibility of a suppressive effect on the development of hypersensitivity lesions by the administration of cortisone.

All intravenous injections were performed on the marginal ear veins, and subcutaneous injections and intradermal injections into the shaved flank skin.

A single strain of Staph. aureus isolated from a case of recent sepsis was used throughout the period of experiment – a duration of just over six months. During this time it was kept alive on agar slopes in screw-capped universal containers, and subcultured at ten day intervals. The organism was a haemolytic Staph. aureus, sensitive to penicillin, erythromycin and...
CHAPTER 9.

STAPHYLOCOCCAL SEPTICAEMIA IN THE RABBIT.

Scope of Experiments.

1. A study of the morbid anatomical changes in experimental staphylococcal septicaemia.
2. Observations on the modifications of host response by concurrent hypersensitivity states, and steroid therapy.
3. Attempted production of hypersensitivity lesions by immunisation with staphylococcal bacterial protein.
4. Notes on weight changes and blood urea levels in experimental staphylococcal septicaemia.

Materials and Methods.

Male albino rabbits of weights varying about a mean of 2 Kg. were used throughout. They were fed alternately on four days of cabbage and three days of bran and oats, and housed in individual cages.

All intravenous injections were performed on the marginal ear veins, and subcutaneous injections and intradermal injections into the shaved flank skin.

A single strain of Staph. aureus isolated from a case of recent sepsis was used throughout the period of experiment - a duration of just over six months. During this time it was kept alive on agar slopes in screw-capped universal containers, and subcultured at ten day intervals. The organism was a haemolytic Staph. aureus; coagulase-positive; sensitive to penicillin, streptomycin, chloramphenicol, erythromycin and...
terramycin. It belonged to phage-type 52A/79.

Suspensions of the organism for intravenous injection were prepared immediately before the anticipated time of injection. The organism was suspended in 0.85% saline and diluted to match an opacity standard corresponding to 1,895 million organisms per ml.

Blood samples were collected from the marginal ear veins.

Horse-serum, used in foreign protein sensitisation, was provided by Wellcome, No. 2 (No. E.3225A). It was kept frozen solid when not in use.

Cortisone was administered as "Cortelan" (Glaxo), each millilitre of suspension containing 25 mg. cortisone acetate.

Animals were weighed at intervals on the same balance, at approximately the same hour of the day.

**Animal Autopsy Technique.**

Rabbits were allowed to die, or killed as indicated in the text. Killing was effected with intravenous "Nembutal". Autopsy was performed immediately thereafter. Heart, lungs, adrenals, kidneys, spleen and liver were removed and placed in formal-saline for fixation.

The left kidney was bisected in a horizontal (coronal) plane, and the right kidney in a vertical plane prior to fixation. In the first ten animals, the brain was removed, but this examination was abandoned later.

Blocks of tissue from the organs listed were put through for histological examination. The lungs were cut in a coronal plane to include the hila. Two large blocks were taken from the heart - one through the anterior wall of the left
ventricle and left atrium, and the other through the pulmonary conus. These blocks gave a good representation of all the heart chambers, and included the mitral, pulmonary, and tricuspid valves. The blocks were processed by hand, and stained routinely with haematoxylin and eosin, Gram's stain, Lendrum's modification of the acid-picro Mallory stain, phosphotungstic acid-haematoxylin, and periodic acid-Schiff.

The actual examination of the histological material was carried out in a manner similar to the human series. Having noted the lesions of interest, tables were drawn up, and the presence or absence of such lesions was recorded without reference to the experimental groups to which the animal belonged.

Significance of Results.

In presenting the results of these animal experiments, I realise that they are open to criticism on the grounds that the numbers involved are small — too small to allow of tests of statistical significance. I used as many rabbits as the facilities available and cost would allow. Naturally, if smaller equidae had been studied, then more animals could have been used. However, rabbits were chosen because they are good subjects for the production of hypersensitivity states, and are also suitably susceptible to staphylococcal infections.
Graph 1. This shows the pattern of weight loss in rabbits suffering from staphylococcal septicaemia. Two phases of weight loss occur - between 0-4 days, and between 10-14 days.

Graph 2. This shows the changing blood urea levels in 7 rabbits during staphylococcal septicaemia.
Graph 3. This shows the changes in weight and blood urea level in one rabbit during staphylococcal septicaemia. This rabbit developed papillitis necroticans.
CHAPTER 10.

DESCRIPTION OF ANIMAL EXPERIMENTS AND PATHOLOGICAL FINDINGS.

Experiment 1.

Control Staphylococcal Septicaemia in the Rabbit.

Object.

To study the distribution and types of lesions in the rabbit following an intravenous injection of Staph. aureus.

Method.

It was first necessary to obtain a knowledge of the effect of variation in the dose of the inoculum.

Three rabbits (R.23, 24 and 25), were injected intravenously with 0.5 ml. 1.0 ml. and 2.0 ml. respectively. The survival times were 13 days, 9 days and 15 hours respectively. One millilitre was then taken as the dosage for all subsequent experiments, unless otherwise stated. Four additional rabbits (R.19, 20, 21, 22), were given 1.0 ml. by intravenous injection – that is 7 animals were given an uncomplicated staphylococcal septicaemia.

Results.

Survival Times. The five rabbits that received 1.0 ml. intravenously, survived 6 days, 8 days, 9 days, and 2 survived approximately 36 hours. Death was preceded by anorexia, weight loss and often diarrhoea. The temperature was usually elevated. Graphs 1-3, illustrate the change in weights and blood-urea levels observed during life. The trend with animal weights was
Fig. 71.
Kidney from a rabbit which survived 36 hours. No abscesses were found. The vessels are congested, but the cortex itself is pale. (R. 20).  
\[ x \ 1.5 \text{ approx.} \]

Fig. 72.
This animal survived 5 days. Abscesses have aggregated in the renal pelvis. (R. 16).  
\[ x \ 1.5 \text{ approx.} \]

Fig. 73.
This kidney shows a radiating "pyelonephritic" pattern. Foci of congestion and haemorrhage are apparent. (R. 19).  
\[ x \ 1.5 \text{ approx.} \]
that of an initial rapid fall following the intravenous injection of *Staph. aureus*, succeeded by relative stability for some days, terminating in a second fall when renal suppuration became established. Most animals showed a gradually rising blood urea level. The highest levels were observed in the animals which subsequently showed papillitis necroticans at autopsy.

**Autopsy Findings.**

**Kidneys.**

The kidneys bear the brunt of the suppurative manifestations of staphylococcal septicaemia, following intravenous injection in the rabbit. In the course of this, and subsequent experiments, a total of 19 rabbits were given intravenous injections of *Staph. aureus*, with regular production of renal abscesses. The only limiting factor was the survival time. Animals dying within 36 hours of injection (3 out of the 19 died within this time), did not show renal abscesses, (fig. 71). The longer the duration of survival, the more extensive was the extent of renal suppuration, thus, rabbits surviving 14 days showed numerous, large, abscesses. Abscesses were found in the cortex and medulla, but a pattern was usually discernable – they were arranged in a linear manner, converging in wedge-shaped areas (on cross-section) from the cortex to the renal papilla, (figs. 72 and 73). The abscesses in the medullary portion of these suppuring areas were often of a linear "pyelonephritis type" contrasting with the circular abscesses found in the cortex. The kidney tissue forming the margins of the suppurring areas were visibly congested, and in
Fig. 74. Renal tubular dilatation adjacent to an area of suppuration. (R. 18).
H. and E. x 50.

Fig. 75. Renal tubular dilatation occurring in the absence of neighbouring suppuration. The only change nearby is that of perivascular foci of lymphocytes and plasma cells. (R. 23).
H. and E. x 90.

Fig. 76. Rabbit lung in staphylococcal septicaemia. White intravascular material gives a superficial resemblance to abscesses. (R. 24).
x 2 approx.

Fig. 77. Patchy haemorrhagic consolidation of the lung in a rabbit dying 36 hours after infection. (R. 17). For histology see fig. 80.
x 2 approx.
several, the surrounding zone of tubular dilation was so marked as to be easily detectable on naked-eye examination, (fig. 74). Tubular dilation sometimes occurred in the absence of neighbouring suppuration, (fig. 75). The kidneys were enlarged and of a deep red-purple colour. It was also possible, as a rule, to detect the cases with pyelitis by the naked eye.

One rabbit, where the suppuration was of an especially severe degree, showed perirenal haemorrhage and suppuration.

Lungs.

Pulmonary suppuration does not occur in the rabbit following the intravenous injection of virulent staphylococci. None of the 19 animals receiving injections in the course of these experiments, developed pyaemic abscesses in the lungs.

Two examples were seen of pulmonary changes which resembled abscesses, (fig. 76), but further examination, including microscopy, showed that these consisted of an unusual intra-vascular material, described below.

Five cases occurred (3 out of the 7 "uncomplicated" cases) of patchy pulmonary consolidation. The consolidated areas were deep red in colour, and imparted a tough texture to the entire lung, (fig. 77).

Heart.

Abscess formation occurs less frequently in the heart than in the kidney. The kidneys and heart are the only two organs in which abscesses may be found with any degree of regularity. Myocardial abscesses were present in 3 out of 7 rabbits. Abscess formation was associated with a sero-fibrinous pericardial reaction.
Fig. 78.
Solid, white intracardiac mass in a rabbit dying 8 days after infection. (See also fig. 76).

x 1.5 approx.

Fig. 79.
Gram-positive cocci in the cytoplasm of intravascular polymorphs, in the lung.

Gram's stain x 440.

Fig. 80.
Pulmonary oedema and congestion appearing within 36 hours of infection. (R. 17).
See fig. 77.
H. and E. x 320.
A striking appearance was seen on cutting into the ventricle, on two occasions. An extremely firm greyish-white material filled the ventricles. This was partially adherent to the endocardium and quite unlike post-mortem clots seen at autopsy, (fig. 78). This is, in fact, the same substance as might have been mistaken for abscesses in the lung, and illustrated in fig. 76. Its possible nature is considered later.

Liver.

The liver varied considerably in appearance and size. Some livers were pale and mottled, whilst others were of a uniformly deep red-purple colour.

Other Organs.

Nothing of note could be discerned at autopsy from examinations of the spleen, adrenals, and brain. Examination of the brain was discontinued after the first 10 rabbits had been examined without any significant result.

Microscopic Examination.

Lungs.

The absence of any suppurative process, as deduced from naked-eye examination, was confirmed by microscopic examination. Gram-positive cocci were seen in the lungs of 2 animals - in one they formed large intravascular clumps, and in the other were seen in the cytoplasm of neutrophil polymorphs, (fig. 79). Both these animals were found dead within 36 hours of infection.

Table 14 shows that intravenously-injected cocci are found in the immediate post-injection period. Furthermore, they do not subsequently give rise to pulmonary suppuration.
**Fig. 81.**
Thrombosis in a dilated pulmonary capillary or venule. Fibrinoid necrosis with haemorrhage is involving a smaller branch.

H. and E. x 170.

**Fig. 82.**
Intra- and peri-bronchial haemorrhage, in a rabbit which survived for 5 days. (R. 15).

H. and E. x 90.

**Fig. 83.**
Destruction of a glomerulus, with deposition of fibrinoid, resulting from heavy lodgement of cocci, in a rabbit surviving 5 days. True suppuration has not developed.

H. and E. x 170.
TABLE 14.
Summary of Principal Histological Findings
in Lungs of Control Rabbits.

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Dosage of Staph. Suspension</th>
<th>Survival Time (Days)</th>
<th>Gram Positive Coci in Lungs</th>
<th>Pulmonary Oedema</th>
<th>Capillary Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>1.0 ml.</td>
<td>8</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>1.0 ml.</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>1.0 ml.</td>
<td>6</td>
<td>-</td>
<td>+</td>
<td>Conglutination.</td>
</tr>
<tr>
<td>22</td>
<td>1.0 ml.</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>0.5 ml.</td>
<td>13</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>24</td>
<td>1.0 ml.</td>
<td>9</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>2.0 ml.</td>
<td>15 hours</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

The lungs invariably showed pulmonary oedema, (fig. 80). The other significant finding was that of alveolar capillary thrombosis. These thrombi did not stain constantly with fibrin stains. Thrombosis also involved the smaller arteries and veins in two rabbits. Thrombi were usually associated with foci of haemorrhage into the neighbouring lung parenchyma, (fig. 82).

Intra-bronchial and bronchiolar haemorrhage was also often present, (fig. 82).

Kidneys.

The kidneys were the organs which were most constantly involved, and to which the most detailed attention was given.
TABLE 15.

Summary of Main Renal Lesions in Control Infected Rabbits.

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Dose of S. Suspn.</th>
<th>Survival Time (Days)</th>
<th>Abscesses</th>
<th>Glomerulonephritis</th>
<th>Cortical Necrosis</th>
<th>Vascular Occlusion</th>
<th>Tubular Dilatation</th>
<th>Casts</th>
<th>Pyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>1.0</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>1.5</td>
<td>-</td>
<td>+</td>
<td>Patchy</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>1.0</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>Patchy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>1.0</td>
<td>1.5</td>
<td>Slight</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>0.5</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>Patchy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>Patchy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>2.0</td>
<td>15 hrs.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Fig. 84. Coagulative necrosis, without suppuration, surrounding a glomerulus which has been almost completely replaced by cocci. (R. 17). H. and E. x 170.

Fig. 85. Masses of cocci have aggregated in the renal pyramid, with ensuing papillary necrosis and sequestration. Tubular dilatation, and vascular thrombosis are also widespread and severe.

H. and E. x 3 approx.
Fig. 86. Portion of a necrotic renal papilla completely sequestrated, and lying detached in the renal pelvis.

H. and E. x 4 approx.

Fig. 87. Extensive deposition of fibrinoid in, and around, glomeruli, and in the intertubular capillaries.

(R. 15).

A.P.M. x 170.
Suppurative Lesions.

Table 15 summarises the main histological features in the 7 control rabbits. Abscesses were found in all animals that survived more than 36 hours. The distribution of these abscesses varied from a diffuse pattern, to the definite wedge-shaped pattern seen with the naked-eye. Even though cocci were frequently found in glomerular capillaries, only very rarely was a glomerulus seen to be involved in a suppurative process. Coagulative necrosis occurred around glomeruli in which many cocci were present, (figs. 83 and 84), still without suppuration. Abscess formation plainly follows the lodgement of cocci in the intertubular capillaries, and also follows excretion of the organisms within the lumina of tubules. The occurrence of pyelitis in 4 out of 7 rabbits was correlated with this predilection to form "excretion abscesses". In 2 rabbits, suppuration had become very extensive, with the formation of prominent tubular coccal masses, necrosis and subsequent sequestration of the renal papilla, that is, papillitis necroticans, (figs. 85 and 86).

Vascular Lesions.

Vascular lesions were found constantly, although they took several forms. All animals showed occlusion of glomerular capillaries with eosinophilic hyaline material. Sometimes this material stained as fibrin, as indeed did the basement membranes of glomerular tufts and capsules, (fig. 87). This last feature made it difficult, if not impossible, at times, to distinguish between capillary occlusion due to thrombosis, from occlusion due to a fibrinoid change in the capillary wall. Usually, however,
Fig. 88. Fibrin strands in glomerular capillaries. (R.20). Compare with fig. 55 in a human case.

P.T.A.H. x 440.

Fig. 89. Thickened glomerular capsules.

P.A.S. stain.
Fig. 90.
Renal periarteritis in rabbit which survived 9 days after infection. (R. 24).

H. and E. x 170.

Fig. 91.
Renal glomerulus showing capillary loop dilatation in a rabbit which survived 36 hours. (R. 17).

H. and E. x 640.

Fig. 92.
Exudative glomerulonephritis in a rabbit surviving 5 days. (R. 15).

H. and E. x 155.
it was possible to observe that the fibrin-staining strands were continuous with thrombus at the site of the entering arteriole. Fig. 88 shows the typical appearance of this glomerular capillary occlusion. Material of exactly similar appearance occluding glomerular capillaries, sometimes did not stain as fibrin. The thickened glomerular capsule frequently did not stain as fibrin, but it was nearly always P.A.S. positive (fig. 89).

Intertubular capillaries, both cortical and medullary, were also often occluded by fibrin-staining thrombi. The other larger blood vessels were less frequently involved. The intralobular and arcuate arteries were sometimes thrombosed, and also showed a fibrinoid degeneration of their media. These arterial changes were found near areas of suppuration, whereas the capillary lesions did not show any such relationship. Three animals, ones that had survived 8, 9 and 13 days, showed a well-developed renal periarteritis, (fig. 90). The periarteritic foci were composed of mostly lymphocytes, plasma cells and appreciable numbers of eosinophils. As this feature was found in the rabbits that had survived for the longest duration, they were also found in kidneys which exhibited the most extensive suppuration, but in each particular kidney they bore no obvious positional relationship to the areas of suppuration.

Glomerulonephritis.

The estimation of the presence, absence, and especially the degree of diffuse proliferative glomerulonephritis, is particularly subjective and, therefore, fallible. Cell counts fail to estimate the other manifestations of glomerulonephritis. Subjective error in this matter was
Fig. 93.
Renal glomerulus showing fibrinoid material amongst the capillary loops.
(R. 23).
H. and E. x 640.

Fig. 94.
Renal glomerulus showing a proliferative and exudative response. A few small clumps of cocci are present.
H. and E. x 640.

Fig. 95.
Wedge-shaped peripheral renal infarct, showing aggregation of cocci in the infarcted area.
(R. 15).
Gram's stain x 27.
reduced as much as possible by repeated examination, and careful comparison with a non-infected control series (to be described below). In these infected animals various combinations of proliferative, necrotising, and exudative glomerulonephritis were found in all but one animal, (figs. 91-94)- this was the rabbit that died within 15 hours of injection. Any one glomerulus may only be partially affected, especially in the necrotising variety, when one or two loops of the glomerular tufts were shrunken. The irregular involvement of glomeruli sometimes appeared as crescent formation, although only very few examples were seen of adhesion between the tufts and Bowman's capsule. One rabbit showed a clear marginal zone of fibrin-staining material surrounding the tufts. In the examples of exudative glomerulonephritis, the exudate was made up of red blood cells and a granular acidophilic material.

These lesions were not the direct result of suppuration, as there was no evidence of leucocytic infiltration, and no cocci were usually found in the lesions. Furthermore, as pointed out above, when large numbers of staphylococci were found to be lodged in glomerular capillaries, the only observable change was that of surrounding coagulative necrosis.

Renal tubular changes.

Marked cloudy swelling and fragmentation of the epithelium of the convoluted tubules, with granular debris in the lumina, was a common feature.

Patchy cortical necrosis was present in 4 of the 7 rabbits. The necrotic areas, which involved tubules and glomeruli, were frequently
Fig. 96.
Myocardial abscess in the rabbit. The muscle fibres between the central clump of cocci, and the encircling zone of inflammatory cells, are necrotic. (R. 17). H. and E. x 170.

Fig. 97.
Section of mitral valve of rabbit. Infected intracardiac thrombus is present, and a few adherent thrombi are seen in the top left-hand corner. H. and E. x 90.
situated in the strip of cortex included in the wider portion of the wedge-shaped zones of suppuration. They were usually associated with thrombosed arcuate or intralobular arteries and, in fact, conformed to the classical description of renal infarcts.

Intravascular staphylococci without surrounding reaction were often present in infarcted areas, (fig. 95).

Damage to the more distal parts of the nephron was obviously a direct consequence of local suppuration. The two examples of papillitis necroticans have already been mentioned. These two rabbits had severe sepsis in the medullary portions of their kidneys. Intratubular and peritubular suppuration was giving rise to considerable local destruction of tissue, and also the majority of the intertubular capillaries were occluded by fibrin-staining thrombi. With the exceptions of papillitis necroticans, and the patchy cortical necrosis described above, no other types of tubular necrosis were seen. The other type of tubular damage, which was often very prominent, was that of dilatation, which was always well-developed at the margins of suppurating areas, (fig. 74).

Microscopical Examination of Other Organs.

Heart.

Myocardial abscesses appeared as foci of suppuration surrounding a clump of intravascular staphylococci. The encircling zone of reaction was made up of neutrophil polymorphs and lymphocytes. The muscle fibres in the region between the central cocci and encircling zone of reaction were completely necrotic, (fig. 96).

Subendocardial fibrinoid degeneration was observed—particularly in the valves sectioned,
Fig. 98.
Interlacing structure of the white intracardiac substance illustrated in fig. 78.

P.T.A.H. x 106.

Fig. 99.
High power view of fig. 98.

P.T.A.H. x 440.

Fig. 100.
Large clump of cocci in a rabbit's adrenal gland - 5 days after infection. (R. 15).

Gram's stain x 730.
The smaller intramuscular branches of the coronary arteries sometimes showed a suppurative thrombosis and arteritis.

The nature of the firm grey-white intraventricular substance observed in 2 rabbits is debatable. In haematoxylin and eosin-stained sections it appeared as an eosinophilic mass in which interlacing strands of a more strongly eosinophilic substance could be seen. Occasional leucocytes were entangled in the interstices of this fibrillary network. The fibrillar strands were best demonstrated with acid-picro Mallory staining red; with phosphotungstic acid-haematoxylin staining blue; and with periodic acid-Schiff staining pink-red. Star shaped structures were seen from which fibrils radiated, (figs. 98 and 99). The underlying endocardium showed a definite, although slight, cellular reaction with fibrinoid change in the subendocardial tissue. The material observed in branches of the pulmonary artery possessed similar histological, and staining, characteristics.

Liver.

Portal tract infiltration with large numbers of lymphocytes and smaller numbers of plasma cells was a noticeable feature.

The other significant histological feature in the examination of brain, adrenals, and spleen, was the finding of scattered thromboses of arterioles and capillaries. Clumps of cocci also occurred in various viscera. It was obvious that many cocci passed through the pulmonary bed soon after intravenous injection. Fig. 100 shows large intravascular clumps of cocci in the adrenal 36 hours after
injection. In the later stages, only smaller clusters of mostly intracellular cocci could be found in the adrenals, (fig. 101).

Control Uninfected Animals.

It was felt that uninfected animals should be examined with special reference to the non-suppurative renal lesions found in the septicaemic animals. These control animals (admittedly only six in number) were examined after tabulation of the lesions found in the septicaemic rabbits, and the lesions specifically sought.

Six albino rabbits of approximately similar weights and ages, had been used in another unrelated experiment, for which they had received one intratracheal injection of silica. The kidneys (and other organs) were examined in the same manner as described above.

Two of these six rabbits showed a mild necrotising glomerulonephritis, and a further one proliferative glomerulonephritis - that is, according to the criteria adopted for the assessment of the experimental lesions. Occasional arteries showed mild periarteritis, with small collars of lymphocytes.

The lesions which were not observed were: marked proliferative and exudative glomerulonephritis; glomerular and intertubular capillary thrombosis; and fibrinoid degenerative vascular lesions.
Fig. 101.
Few, scattered, intracellular cocci in the adrenal gland of a rabbit dying 5 days after infection. (R. 15).
Gram's stain x 730.

Fig. 102.
Hyaline thrombi in the glomerular capillaries of a rabbit sensitised to horse serum. (R. 4).
H. and E. x 640.
Experiment 2.

A study of the morbid anatomy of a known instance of hypersensitivity, and the lesions produced in the septicaemic rabbit made hypersensitive to foreign protein.

Object.

The object of this experiment was to observe whether the lesions (especially the renal lesions) observed in septicaemic rabbits, which were being attributed to a hypersensitivity reaction, were in fact similar to the lesions produced in the rabbit known to have been made hypersensitive to foreign protein. Furthermore, it was thought that if an animal was first made hypersensitive to foreign protein, and then given Staph. aureus by intravenous injection, that the altered state of host reactivity (particularly that of the reticulo-endothelial system) might affect the course of the infection, and the lesions produced by it.

Method.

Rabbits were sensitised to horse serum. The method was basically that of Rich and Gregory (1943).

Eight albino rabbits (R.1-8) were sensitised using 10 ml./Kg. bodyweight, of horse serum intravenously. This was followed by 1 ml. at 15 days; the original dose at 16 days; 2 ml. at 40 days; 2 ml. at 47 days and half the original dose at 54 and 89 days. Objective evidence of sensitisation was obtained with intradermal skin tests using horse serum and positive precipitin serological reactions. Also there were 2 anaphylactic deaths. Animals were killed, or died, at the following intervals after the first intravenous dose of horse serum: 27, 30, 37, 57, 61, 75, 96 and 110 days.
Post-mortem examination and preparation of tissue for histological examination were carried out as described in the first experiment. A further 4 albino rabbits (R.15, 16, 17, 18), each of approximately 2 Kg. body weight, were similarly sensitised to horse serum over a period of 45 days. The injections of antigen were then stopped, and 1.0 ml. \textit{Staph. aureus} suspension given intravenously. This suspension was the same as that used for rabbits 19-22 in the first experiment. All injections were made within about one hour, so that all animals receiving 1.0 ml. received approximately the same number of organisms. The 4 rabbits which had been sensitised and infected were allowed to die.

**Results.**

Various hypersensitivity lesions were seen in rabbits 1-8, but the only ones relevant to this thesis are the kidney changes.

The Renal Lesions in Hypersensitivity to Foreign Protein.

Although the renal lesions following foreign protein sensitisation have often been described, a brief description is given here in order that the criteria of histological assessment being applied in the examination of septicaemic animals, may be used on a more generally known, and described, type of histological change.

The two striking changes were those of diffuse glomerulonephritis and periarteritis. All 8 rabbits showed the various types of glomerulonephritis - all kidneys contained glomeruli whose contents were proliferating, hypercellular and ischaemic. Three of these animals also showed features of a necrotising glomerulonephritis with marked digitation and
Fig. 103.
Periarteritis in the kidney of a rabbit sensitised to horse serum. There are moderate numbers of eosinophils.
H. and E. x 520.

Fig. 104.
Similar appearances to fig. 103, with many eosinophils, in a septicaemic rabbit. (R. 23).
H. and E. x 640.

Fig. 105.
Renal artery showing fibrinoid necrosis, with haemorrhagic disruption, in a rabbit sensitised to horse serum.
H. and E. x 125.

Fig. 106.
Similar appearances to fig. 105, in a septicaemic rabbit, which had survived for 9 days.
H. and E. x 170.
shrinkage of the tufts. In one animal exudate in capsular spaces was a striking feature.

In 6 of the 8 rabbits, the capillaries of the glomerular tufts were completely or partially occluded by hyaline thrombi, (fig. 102). Periarteritis was marked in 6 rabbits, and was present to a slighter degree in a seventh, (figs. 103-107). The arteries most frequently involved were the intralobular arteries and the glomerular arterioles. The larger aterial arteries were less often involved. The cellular component of the reaction was fairly constant, lymphocytes being the predominant cell type. Eosinophils were present in appreciable numbers and plasma cells least frequently. The arterial and arteriolar walls usually showed some fibrinoid change in haematoxylin and eosin-stained sections. Fibrin stains showed positively-staining material in the glomerular and intertubular capillaries, as well as a fibrinoid change in the walls of arteries, and basement membranes. The hyaline, intracapillary, glomerular thrombi, however, often failed to stain positively with fibrin stains.

Cortical necrosis was not observed. Severe tubular dilatation occurred in two animals. Results in Infected Hypersensitive Rabbits.

The four rabbits (R.15-18) that had previously been sensitised to horse serum before the administration of intravenous Staph. aureus suspension, survived 5 days, 36 hours and 14 days respectively, so that their survival times were comparable with the non-sensitised group that had been given the staphylococcal injection only. Animals in both groups fell into two types in respect of their survival times - either death
within 36 hours or survival for 5-14 days.

Post-Mortem Findings.

The lesions found in the four sensitised rabbits were similar to those found following septicaemia only, but they were much more severe and extensive. Systematised capillary damage was a feature. Capillary fibrin thrombosis and endothelial fibrinoid degeneration was present in all 4 rabbits, and was found to be widespread in kidneys, lungs, spleen and meninges.

The kidneys showed typical diffuse glomerulonephritis. Exudate in the capsular spaces was more marked than in the simple infected, or hypersensitive animals. Fibrin thrombi were occluding many of the glomerular tufts in all rabbits. Marked glomerular crescent formation was present in R.18, which had survived 14 days. Three of the 4 showed renal periarteritis with fibrin thrombi, and fibrinoid necrosis. Venous thrombosis of arcuate branches had occurred in 2.

Tubular degenerative changes were severe, and prominent tubular dilatation was a feature in 2 rabbits.

Papillitis necroticans occurred in R.16, which had survived 5 days.

Widespread capillary thrombosis can occur long before suppurrative lesions develop – for example R.17 died within 36 hours of injection of staphylococcus. At post-mortem the lungs showed irregular dusky red purple blotches. Petechial haemorrhages were visible in the pericardium. The liver was very pale, and the kidneys deep red. Microscopy demonstrated large coccal masses occupying some glomerular capillaries, with no surrounding reaction. Other
glomeruli showed marked capillary dilatation, but there was little evidence of fibrin thrombus formation. In contrast, however, capillary thrombosis was a marked feature in lungs, pericardium, cerebral meninges and spleen. The lungs also showed severe pulmonary oedema and localised areas of congestion and haemorrhage.

The overall picture in these horse-serum-sensitised rabbits, given intravenous Staph. aureus, was that of the previously observed vascular damage arising as a result of the intravenous injection of Staph. aureus, but the reaction was accentuated and more widespread. The associated (or ensuing) parenchymal damage in the form of cortical necrosis, infarction, tubular degeneration and the deposition of fibrinoid was also definitely more severe in the horse-serum sensitised rabbits.
Fig. 107.
Classical arteritis involving a renal arteriole in a septicaemic rabbit surviving for 13 days. (R. 23).

H. and E. x 170.

Fig. 108.
Granulomatous reaction in a rabbit lung following the injection of crude bacterial antigenic suspension.

H. and E. x 96.
Experiment 3.

The Effect of Previous Immunisation on the Course and Results of Staphylococcal Septicaemia in the Rabbit.

Object.

The first object was to prepare an antigen from the strain of Staph. aureus which was being used in these experiments, in an attempt to immunise rabbits with the production of hypersensitivity lesions. The second object was to ascertain whether previous immunisation modified the lesions produced in the course of experimental staphylococcal septicaemia.

Method.

**Preparation of Bacterial Antigen.**

It was felt that the attempted immunisation procedure should utilise the bacterial body protein, rather than any of its exotoxins. The bacterial antigen had to be prepared with as little alteration of its protein as possible. The method adopted was that of Walker (1916). Large quantities of the Staph. aureus in use, were inoculated on agar slopes in 0.5 litre containers which were then incubated at 37°C for 24-48 hours. The growth was washed off the slope surface with 0.85% saline solution, and the washings centrifuged. The supernatant was decanted, after which the process of washing and centrifuging was repeated. The residue was broken up in absolute alcohol and 0.5% phenol and centrifuged. This was repeated. Then the same process was repeated but using ether. The residue was dried and broken up into a fine grey powder.

The nitrogen content of this powder as estimated by the micro-Kjeldhal method was 11.9% - that is equivalent to a protein content of 74%
The powder was made up as a 1% (w/v) suspension in 0.85% saline solution for injection. Sterility was always checked before use. No free coagulase could be detected, and no haemolytic activity. Gram-stained films showed cocci arranged in clumps, about 80% of which were still Gram-positive.

Seven albino rabbits (R.26-32), were used in this experiment. The suspension of bacterial antigen was injected intravenously in the following dosage:

- 1st day: 2 ml.
- 7th day: 0.5 ml.
- 14th day: 0.5 ml.
- 21st day: 1.0 ml.

R.26 and 27 were given 1.0 ml. 24 hours after the first dose, and R.27 was killed at 48 hours – this was a pilot attempt to produce a generalised Shwartzmann reaction. R.30 was killed after 22 days.

The remaining five rabbits were given Staph. aureus suspension 1 ml. intravenously. Three of these were allowed to proceed and the other two were started on 12.5 mg. cortisone acetate by daily subcutaneous injection.

The original intention was to allow these five rabbits to die of their septicaemias, but it was found that the Staph. aureus culture had presumably lost some of its virulence since it was used in the first and second experiments, which had been performed four months previously. (This was confirmed by injection into other animals). No early deaths occurred – in fact only one natural death took place – at 14 days. The others were killed at 8, 10, 13 and 14 days.

Table 16 summarises these procedures.
TABLE 16.
Procedures Adopted in Experiment 3.

<table>
<thead>
<tr>
<th>Rabbit Number</th>
<th>Number of Immunising Injections</th>
<th>Staph. aureus Injection</th>
<th>Cortisone Time of Killing after Infection</th>
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<tr>
<td>26</td>
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<td>28</td>
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<td>Died at 14 days</td>
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<td>30</td>
<td>4</td>
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<tr>
<td>32</td>
<td>4</td>
<td>+ +</td>
<td>8 days</td>
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</table>

Results.
R. 27, the animal that was killed 24 hours after the last of two injections of bacterial antigen given intravenously, with a 24 hour interval between the injections, did not show any definite lesions on naked-eye examination. Histological examination showed intracellular Gram-positive cocci in the reticulo-endothelial cells of the splenic pulp, hepatic sinusoids, and cells in the interstitial tissues of the lung. The lungs showed plugging of smaller branches of the pulmonary artery with cocci and inflammatory cells and some surrounding reaction. Capillary thrombosis had occurred in the lungs, liver and kidneys. Fibrin stains demonstrated numerous fibrin capillary thrombi in the glomerular and renal intertubular capillaries. The only other notable findings in this animal were that the splenic pulp contained many eosinophils, and that the portal tracts of the liver showed a very
marked cellularity.

R.26 also received two intravenous injections with a 24 hour interval between the injections. As neither R.26 or 27 animal appeared to be ill, R.26 was allowed to proceed with the others and was given repeated injections. R. 30 was given four weekly intravenous injections of bacterial protein suspension, and the animal was then killed. Autopsy examination did not show anything abnormal, but histological examination again showed capillary thrombi in the kidneys and lungs. The renal arterioles were often surrounded by a collar of mononuclear cells - lymphocytes, plasma cells and eosinophils. The lungs, in addition to showing thrombosis of alveolar capillaries, also showed a granulomatous reaction surrounding thrombosed branches of pulmonary arteries and arterioles, (fig. 108) - these thrombi contained numerous polymorphs with intracellular and extracellular Gram-negative and Gram-positive cocci, (fig. 79). Collars of lymphocytic cells surrounded several of these vessels. There was no evidence of suppuration. These vascular and granulomatous lesions were found in all animals which received the bacterial protein suspension. The pulmonary arterial thrombi were obviously the result of embolism. Several of the rabbits became dyspoeic and cyanosed immediately after their injections.

The rabbits usually developed a pyrexia of up to 106°F, four hours after intravenous injection. This, of course, may have been a pyrogenic reaction, and no evidence of a hypersensitivity response.

The embolic lung lesions make it advisable to limit the detailed analysis of histological findings to the kidneys. Table 17 summarises the principal renal lesions.
### TABLE 17.

The Renal Lesions following Bacterial Immunisation.

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</table>
The number of animals used is too small to allow of any accurate quantitative assessment. The 3 rabbits which were given intravenous viable Staph. aureus, without accompanying cortisone therapy, following previous injection of bacterial protein suspension, showed the usual suppurative lesions. Capillary thromboses were widespread in all three. The other renal lesions observed were fibrinoid arteriolar necrosis, diffuse glomerulonephritis, dilation of glomerular capillaries, cubical metaplasia of the glomerular capsules, and periglomerular fibrosis in areas of suppuration. An extreme degree of tubular dilatation was found adjacent to foci of suppuration. Preliminary injection by bacterial protein suspension then does not result in any change in the type of non-suppurative renal lesions, but it may enhance the animal's response, as the capillary and glomerular lesions observed were severe and widespread.

R.31 and 32, which received 0.5 ml. of "Cortelan" daily, following their injection of Staph. aureus, differed from the others described above, in that there was no histological evidence of glomerulonephritis. Both rabbits showed dilatation of the glomerular capillary loops, and in R.31 there were a few hyaline capillary thrombi, but these did not stain with fibrin stains. Again, few animals are involved, but the appearance of diffuse glomerulonephritis seen in R.28 and 29, contrasted with the absence of any such change in R.31 and 32. Suppuration was less extensive than usual in these two animals - indeed in R.31 renal abscesses were only found with difficulty.
Experiment 4.

The Effect of Cortisone on the Development of Non-suppurative Lesions of Staphylococcal Septicaemia in the Rabbit.

Object.

To observe whether cortisone administered before, and during, the course of a staphylococcal septicaemia modified the non-suppurative lesions in the rabbit.

Method.

R.31 and 32, which had been previously immunised with bacterial protein suspension, were given cortisone after intravenous injections of Staph. aureus - the method and results are given as part of Experiment 3, above.

Rabbits 34, 35, 36 and 37, were given daily subcutaneous injections of 1.0 ml. "Cortelan" for 9 days. On the tenth day 1.0 ml. of Staph. aureus suspension was given intravenously to R.34, 35, and 36. R. 37 was killed after 12 days of cortisone therapy only. Cortisone therapy was continued in R.34 and 35, and the animals were killed 8 days and 12 days respectively after infection. Cortisone therapy was stopped in the case of R.36 on the day of administration of Staph. aureus and the rabbit was killed 12 days later.

Results.

All 3 infected animals were obviously ill by the time it was decided to kill them. Anorexia was almost complete; weight loss was progressive; and diarrhoea was present. Blood urea levels were elevated in all three.

At autopsy, the kidneys were enlarged, and cutting of the renal capsule showed that the kidney substance was under tension. Renal
abscesses were numerous, and showed the usual distribution. Renal suppuration was particularly extensive in R. 35, and the renal papillae of both kidneys were distended with pus. The right kidney in this animal was surrounded by an area of extensive haemorrhage at the upper pole of the kidney. Some pus formation had taken place in the extravasated blood. This finding of interstitial, as opposed to visceral, suppuration, is of great interest as this rabbit (R.35) was the only animal in a series of 19 given intravenous Staph. aureus suspension, which showed a typical peripheral pulmonary infarct.

Histological Examination in Cortisone-treated animals.

Kidneys.

Suppuration was confirmed as being extensive in R.34, 35 and 36. Papillitis necroticans was present in R.34 and 35. Tubular dilatation was prominent adjacent to areas of suppuration.

The other non-suppurative lesions, which were observed in the preceding experiments, were just as obvious in the cortisone-treated rabbits - namely, diffuse glomerulonephritis, capillary thrombosis, fibrinoid change in basement membranes, and patches of tubular necrosis. Periarteritis, with thrombosis was also present. Following the results of cortisone therapy on the course of septicaemia in previously immunised rabbits (R.31 and 32), it had been expected that non-suppurative lesions would be absent or less obvious. They were, in fact, if anything, much more severe.

Lungs.

The histological changes seen in the lungs, were those of acute interstitial
inflammation, and arterial and capillary thrombosis in R.35.

Liver.
The liver showed marked glycogen accumulation. R. 35 showed capillary thrombosis.

Other Lesions.
The spleens were atrophied. Myocardial abscesses were present in R.34. The myocardium in this animal also showed foci of large mononuclears, multi-nucleated cells, and eosinophils. Strands of collagen were infiltrating and surrounding these foci. Sub-endocardial collagenous thickening was present in R.35, as well as intracardiac thrombus formation.

R.37, which had received only a 12 day course of cortisone, showed no specific features, apart from a very minor degree of exudation into glomerular capsular spaces. Fibrin stains gave negative results. The liver again showed marked glycogen accumulation.

The Effect of Intramuscular Injections of Staph. aureus.

Two male albino rabbits were given 2 ml. Staph. aureus suspension in the thigh muscle mass. One rabbit died 13 days later. The other is still alive at the time of writing, three months later, although it still has a fluctuant mass at the site of injection. The rabbit that died showed typical peripheral pulmonary infarcts. The lungs also showed severe bronchopneumonia and pulmonary oedema. No renal suppuration could be found. The kidneys, however, showed a very severe proliferative and exudative glomerulonephritis. There were numerous capillary thrombi, with a fibrinoid change in the renal basement membranes.
The Effect of Staphylococcal Alpha-haemolysin.

Only one rabbit was given staphylococcal toxin. This was done purely as a pilot experiment as only a limited number of animals were available. The rabbit was given 1 ml. alpha-haemolysin (Wellcome, K.1202), containing 23 international units. The toxin was injected intramuscularly. The rabbit died 5 days later. The blood urea level rose to 160 mg. per 100 ml. Congestion and erythrocyte conglutination was marked in pulmonary and renal blood vessels. The lungs showed interstitial consolidation. The adrenals showed patchy cortical necrosis. The kidneys did not show glomerulonephritis, vascular thrombosis or fibrinoid degeneration. Foci of renal cortical necrosis were present, but these were small and isolated. The parenchymal damage was tubular.
Summary of Principal Lesions Observed in Experimental Staphylococcal Septicaemia.

Staphylococcal septicaemia following the intravenous injection of Staph. aureus in the rabbit is a disease process during which the kidneys bear the brunt of the attack. The renal lesions are of two main types: first, the suppurative lesions, which include cortical and medullary abscesses, pyelitis, and papillitis necroticans; and second, the non-suppurative renal lesions, which include diffuse glomerulonephritis; fibrinoid change of basement membranes; fibrin thrombus formation in capillaries and arteries; periarteritis, and patchy necrosis of cortical tubules.

The morbid anatomical changes could be modified in several ways. Concurrent sensitisation to horse-serum resulted in an accentuation of the vascular component of the non-suppurative lesions. This caused a more widespread parenchymal damage, in the form of tubular necrosis. Two out of four horse-serum hypersensitive rabbits developed papillitis necroticans.

Previous immunisation with Staph. aureus bacterial protein extract seemed to give rise to an increase in the histological severity of the diffuse glomerulonephritis. Suppurative lesions were less extensive, and tubular necrosis found less frequently. When two, immunised, infected, rabbits were also given cortisone, no histological evidence of glomerulonephritis, vascular occlusion, fibrinoid change or significant tubular necrosis was found.

Cortisone therapy alone, however, did not appear to have any influence on the type or extent of the renal lesions.
Evidence of capillary damage and thrombosis during staphylococcal septicaemia was also found in the lungs, liver, heart and spleen. The only organs which showed abscess formation were the kidneys and heart. Pulmonary infarction was only seen once after intravenous injection of Staph. aureus - in an animal in which perirenal haemorrhage and suppuration had occurred.
<table>
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<th>Rabbit Number</th>
<th>Cortisone Abscesses</th>
<th>Glomerulonephritis</th>
<th>Vasculitis</th>
<th>Fibrinosis</th>
<th>Necrosis</th>
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CHAPTER 11.

DISCUSSION OF EXPERIMENTAL FINDINGS AND CORRELATION WITH FINDINGS IN HUMAN SERIES.

Distribution of Suppurative Lesions.

The fate of staphylococci following intravenous injection involves a study of the distribution of inanimate particulate matter. All venous blood-borne organisms must pass through the lungs, and the sites at which, and the degree to which, such organisms are arrested are dependent in part, at least, upon mechanical factors. Drinker and Shaw (1921) using particles of manganese dioxide 1 μ diameter suspended in 0.4% acacia found that particulate matter was removed very rapidly from the blood stream. The chief points of removal were the lungs, spleen and liver and this localisation was not the result of embolism but the result of the specific activity of the reticulo-endothelial cells in these organs. The Kupffer cells were particularly active in this "mopping-up" operation. The lung showed less of this activity than the liver, although Nye and Parker (1930) stressed the role of the lungs in the rabbit as a member of the reticulo-endothelial system. They suggested that the pulmonary capillary endothelium may have phagocytic powers. Particles were scattered diffusely through the splenic pulp but were not found in the Malpighian corpuscles. The kidneys were of minimal importance in this clearing function. When using lycopodium spores 27 μ x 25.5 μ in size, Daley (1957) found that injection via a cardiac catheter in dogs did not give rise to any generalised vascular constriction consequent on local embolism. When the catheter was passed into a pulmonary end-artery, spores were generally distributed in the lung, but no
spores were found in blood leaving the lungs. The reason for this was supposed to be dissemination by a reflux past the catheter. The conditions in this experiment were so artificial, and the size of the particles so much larger than the staphyloccocus, that the results may not be applicable. Confirmation of this selective "take-up" of injected particles was obtained in this study by observing the distribution of dead staphyloccoci in Experiment 3.

Rich (1946) in his consideration of the mechanical factors responsible for the degree of involvement of different tissues in tuberculosis postulated that the tubercle bacillus was arrested as foreign particulate matter. The liver, spleen, marrow and lungs arrest most of circulating particulate matter - the former three organs have large numbers of intravascular mononuclear phagocytes, whereas the lungs do not have fixed intravascular phagocytes. Rich, therefore, concluded that the tendency of particulate matter to stop in pulmonary capillaries appeared to be due to the tortuosity of these vessels. Thus, while foreign particulate matter is arrested in pulmonary capillaries, non-particulate colloidal materials pass freely through, but are rapidly removed from the circulation by the phagocytes of the liver, spleen and bone marrow. Confirmation of this hypothesis in man is given by the distribution of intravenously injected saccharated iron oxide.

Elek (1959), discussed "organ tropism" and the factors which may influence this, but he did not refer to the actual distribution of suppurative lesions found in man and animals. Consideration of the suppurative lesions found
in both the human and animal series brings out the striking fact that the organs which possess the greatest reticulo-endothelial cell activity, on the whole display the least tendency to develop suppuration. The only important exception to this was that of the human lung. Lung suppuration was common in the human series. This contrasted with the animal series where pulmonary suppuration was not observed. However, of the organs mentioned, it has been found that the lungs have the least efficient reticulo-endothelial system for dealing with circulating particulate matter. The tortuosity and length of pulmonary capillaries would tend to increase the chances of suppuration developing. The reason for the difference observed between the human and animal series is probably related to the route of infection. The single, intravenous, injection of a large inoculum of Staph. aureus in the rabbit ensures a rapid uptake by the reticulo-endothelial system. Pulmonary suppuration in man is likely to be a secondary infection from an already established visceral lesion. Under these conditions pulmonary venous thrombosis may be the conditioning factor allowing bacterial emboli to lodge in an environment favourable for suppuration. The paper sections of lung showed changes which supported this contention. In this connection, it was particularly noteworthy that the only rabbits to show pulmonary infarction were two animals, one of which had very severe renal and perirenal sepsis, and the other was one of two rabbits in which the Staph. aureus was injected intramuscularly.

Dutton (1955) demonstrated the lethal effect of varying the route of inoculation. He used a variety of organisms including
Staph. aureus and found it was less lethal when injected intravenously than when injected intraperitoneally or subcutaneously. He points out that the doctrine of localisation of organisms at the site of primary lodgement being a desirable event, may not always be true. Localisation may not be the most effective defence against infection, as it protects the bacteria from the action of the reticuloendothelial cells in the liver, spleen and bone-marrow.

Another method of investigating the way in which the body copes with circulating organisms is the counting of viable cocci in the blood stream, and various viscera, at intervals following infection. Wyssokowitsch (1886) was the first to observe the very rapid removal of injected bacteria from the blood stream after intravenous injection. He used Micrococcus tetragenus and E. typhosus, and found that following intravenous injection numerous organisms could be obtained from the lung at a time when the blood culture was sterile. Arima (1911) injected Staph. aureus into the rabbit and ground up the organs prior to bacteriological culture. He seldom found bacteria in the blood half-an-hour after intravenous injection. Organisms were most abundant in the liver, spleen and bone marrow. He stated that the organs which attract most destroy most—probably a truism because the method of destruction involves phagocytosis. Bartlett and Ozaki (1916-1917) counted the bacteria in histological preparations. It is difficult to believe that this could be done with any reasonable degree of accuracy. They made, however, the important observation that following
injection of *Staph. aureus* into the left ventricle of dogs, cocci are taken up immediately by the polymorphonuclear leucocytes in the lung capillaries. This was denied by Hopkins and Parker (1918), although they confirmed the presence of large numbers of bacteria in the lung immediately after intravenous injection. Furthermore, their argument seems to be conditioned by the fact that they found in vitro that leucocytes "have little bactericidal power even for the bacteria they ingest" — in this they anticipated Rogers' theory of what might be called "sheltering intravascular staphylococci" referred to below. Hopkins and Parker, however, were using haemolytic streptococci, and experimental results are difficult enough to interpret without deducing too much from an experiment in which another organism is used. Leucocytic ingestion of staphylococci was a feature in both humans and rabbits in the present investigation. Hopkins and Parker also found that cocci are stored in large numbers in the liver and spleen as the numbers in the lungs decrease. Finally, the bacteria undergo rapid autolysis in the liver and spleen so that it was not possible to find them in these organs after 48-72 hours. This fact was confirmed in this work. Recently Rogers, D.E. (1956) has suggested that strains of staphylococci phagocytosed by circulating leucocytes may remain viable and protected from the antibacterial action of the reticulo-endothelial system. These intra-leucocytic staphylococci may be responsible for the persistence of a low grade bacteraemia in the rabbit after a rapid initial clearing from the bloodstream. Goodman and Moore (1956) showed
that these intracellular staphylococci are destroyed if they are coagulase-negative, but destruction of the polymorph itself occurs if they are coagulase-positive. Dubos (1954) suggested that the intraleucocytic bactericidal function is due to the acid pH attained. Smith and Dubos (1956), have made detailed bacterial counts in the course of experimental staphylococcal septicaemia. They confirmed the rapid initial clearing of organisms from the bloodstream but laid especial emphasis on the importance of the later development of extensive renal suppuration. Smith (1956) followed this up with a suggestion that renal suppuration was a significant factor in a fatal outcome in septicaemia in man.

The ease with which the liver and spleen (and the lung in the experimental animal) deal with large numbers of staphylococci may well provide a clue to some naturally-occurring chemical factor having a selective and highly effective action on Staph. aureus in vivo. Even if the destruction of staphylococci occurs in the phagocytic cells there still must be a final chemical or enzymic process involved. Lyons (1937) claimed that young staphylococci possessed a capsule which prevented their phagocytosis but this could not be confirmed by Spink (1939) or Kleineberger - Nobel (1948), although recent work has suggested that "bound coagulase" behaves like a capsular substance (Duthie 1954, Duthie and Houghton 1958).

The central nervous system was not studied in any detail in this investigation, but it is obviously comparable with the lungs, in that in man its involvement by suppurative lesions is quite common in the course of
staphylococcal septicaemia, whereas in the rabbit it is distinctly rare following the intravenous injection of Staph. aureus.

The Suppurative Renal Lesions.

The principal varieties of suppurative lesions were observed in the human and animal series - circumscribed pyaemic abscesses, pyelitis, a more diffuse interstitial suppurative process histologically identical with pyelonephritis, and papillitis necroticans.

The passage of Staph. aureus through the kidney of the experimental animal has been the subject of considerable investigation. Wyssokowitsch (1886) first studied the renal excretion of Staph. aureus in the rabbit, taking samples both from the living animal and at autopsy. He found that staphylococci appear in the urine about six hours after intravenous injection. Sherrington (1893), however, concluded that "at a time when the blood is teeming with micro-organisms there may not be the slightest transit of them into the urinary fluid then secreted." The problem as to whether the healthy kidney can excrete pathogenic staphylococci remained a subject of dispute until Dyke (1923) investigated it in a series of careful experiments. He cultured samples of urine at intervals following intravenous injection of Staph. aureus suspensions. Positive cultures were obtained 5-6 hours after intravenous injection and once staphylococci appeared they could be constantly isolated until the death of the animal. As cocci are difficult to find histologically when no abscesses are present, Dyke used the ingenious method of incubating kidneys removed aseptically. In kidneys removed 5 minutes after injection, staphylococci were
found (after incubation) in the vessels - intralobular arteries and afferent arterioles. No cocci were found in either the glomeruli or branches of the renal vein. Cocci were demonstrated in glomerular capillaries within 15 minutes of injection. After one hour thrombosis of the intralobular arteries of the cortex was observed. The passage of cocci out of the vascular system into the interstitial system occurred after 8 hours. Within 18 hours minute subcapsular abscesses first became visible and vascular thrombosis was marked. Medullary abscesses are secondary to the cortical abscesses, and are due to lodgement of cocci in the distal portion of the nephron. Thus, the sequence of events in the development of renal abscesses may be reconstructed. Coccal emboli lodge in the smaller afferent cortical vessels. The vessels become filled with polymorphs and the rapidly multiplying cocci. The surrounding kidney substance shows toxic changes, whilst outside the necrotic or damaged zone, congestion is marked. Finally, the walls of the blood vessels break down. Dyke only observed one example of suppuration in a glomerulus. His main conclusion was that urinary excretion of cocci is evidence of the presence of diseased kidneys. Dyke's findings are given in some detail because little of significance has since been added on this subject. Grey et al (1957) examined the kidneys in experimental staphylococcal septicaemia in the mouse. The findings they describe, which are of interest in this thesis, are their confirmation of the presence of tubular necrosis; the necrotic cone-shaped areas; vascular thrombosis of the larger vessels; papillitis necroticans, and foci of perivascular
lymphocytes. Gorrill (1951 and 1958) also studied renal abscesses in the mouse. He found that mice surviving with renal abscesses were able to cope with subsequent large inocula, and healing with scarring occurred. Unfortunately his papers contain no histological details.

It is doubtful whether there is any point in differentiating between metastatic abscess formation and pyelonephritis. The cone-shaped areas of suppuration studied in this series are obviously the same lesions as those described under the heading of "experimental pyelonephritis" by Mallory et al (1940), and De Navasquez (1950). The latter using a suspension of Staph. aureus in a dose of 50 million organisms per ml. for each Kg. body weight, produced a suppurative pyelonephritis with survival for several weeks or even months. He showed that infection is of the "descending type", thereby confirming Dyke's work (1923). He postulated that coagulase has an important in vivo effect being responsible, by agglutination of organisms and red cells, for localisation of infection. This possibility is similar to that envisaged by Gorrill (1951), who said that animals deficient in coagulase-activating factor in the plasma were the ones relatively insusceptible to staphylococcal infections. The possible in vivo effects of coagulase are referred to later.

Papillitis necroticans, which was observed in both human and animal series, is a hazard of staphylococcal septicaemia which deserves to be more widely recognised. It has also been noticed experimentally in mice given intravenous injections of Staph. aureus (Gray et al 1957). All the cases seen had masses of
cocci in the collecting tubules. The other invariable finding was that of capillary thrombosis. These two findings could be reasonably linked by De Navasquez's hypothesis (1950), of a diffusion of coagulase from a clump of cocci with resulting thrombosis of neighbouring blood vessels. The pyramids are particularly vulnerable because they are the sites of a maximal accumulation of cocci, and their blood supply is purely by means of capillaries. Alternatively, capillary thrombosis may be symptomatic of a hypersensitivity reaction. Heppleston's case (1955) is of interest in this connection. He reported a case of papillitis necroticans where there was no evidence of infection, urinary tract obstruction, or diabetes mellitus. The necrosis was due to a hypersensitivity angiitis - an explanation which this thesis argues may be just as applicable in the presence of infection. In fact, although Heppleston did not find organisms in the kidneys, his patient's illness commenced with a febrile disorder of two weeks' duration, four months before death. This case also showed acute tubular necrosis of the type described by Bywaters and Dible (1942) - another lesion which, when associated with septicaemia, as in this series, is being attributed to a hypersensitivity reaction.

The Importance of Non-Specific Factors in Host Resistance.

It may appear almost a platitude to emphasise the importance of host resistance when dealing with staphylococcal septicaemia in man or the experimental animal. Specific antibodies to the staphylococcus, or its products, almost certainly play a part in host resistance to infection. Nevertheless, I believe that
non-specific factors are probably of practical importance in this infection. The changing pattern of staphylococcal disease which has been observed, and the type of case studied in this clinical series, serve to show that there are several procedures in modern medical practice which can render the patient susceptible to blood stream invasion by Staph. aureus.

"Host Resistance" is a completely non-specific term, and there is a danger of using it under circumstances which beg the question. A consideration of the rôle of "host resistance" in the behaviour of a healthy individual, given a poison such as carbon monoxide, is merely a way of saying that a lethal dose may vary with each individual. If, however, the individual is severely anaemic then that person is particularly susceptible to the action of carbon monoxide. "Host Resistance" in the present context is used partly in this sense — namely a factor or group of factors, recognised or unrecognised, which render the host peculiarly liable to serious staphylococcal infection. The term is also used to include the importance of the type of reaction on the part of the host to the presence of staphylococcal infection. These two aspects of host resistance, it is suggested, are important factors in human cases of staphylococcal septicaemia. The human series, already considered, showed how frequently other major insults to the body or other disease processes were associated with septicaemia. Staphylococcal septicaemia, when unassociated with any recognisable complicating or predisposing factor, usually behaved in a fulminating fashion. It is in this latter type of patient
that a hypersensitivity reaction on the part of the host may be the explanation for the unusual course and outcome of exposure to *Staph. aureus*.

The host mechanisms which affect the ability of the body to cope with generalised infections must be extremely complex and integrated. They will involve local chemical, hormonal, tissue, and cellular reactions, some of which are known and probably many more unknown. Attention has already been drawn to the importance of the reticulo-endothelial system. Therefore, it might be surmised that conditions affecting the reticulo-endothelial system may also affect the course of a staphylococcal septicaemia. This has been tested in several ways experimentally. Antibody response can be modified by blocking the reticulo-endothelial system with particulate matter (Jaffe 1931). Nakahara (1925) injected mice intraperitoneally with olive oil and three days later gave them an injection of *Staph. aureus* suspension by the same route. The mice which were given preliminary olive oil showed an increased survival rate over control mice. Their increased resistance was attributed to the intraperitoneal accumulation of macrophages. Matracia (1954) claimed that excessive fatigue impaired the ability of the reticulo-endothelial system to deal with staphylococci.

Apitz (1934) studied staphylococcal septicaemia in rabbits previously rendered hypersensitive to horse serum. He was mainly interested in bacterial endocarditis, and said that this did not occur in the infected hypersensitive animals, although it was found frequently in the animals which only received *Staph. aureus*. He thought that resistance to infection was increased but the results are difficult to evaluate. True bacterial
endocarditis was not seen in any animal in this series. Apitz does not give the histological findings in any detail. The hypersensitive animals in this series did not show any qualitative difference from the controls, and although the numbers involved were small, the survival times of the two groups were closely comparable. Vascular lesions and glomerulonephritis were certainly more severe and widespread in the hypersensitive animals. These lesions are common to both states, namely hypersensitivity and staphylococcal septicaemia, so that it is only reasonable to assume that when septicaemia develops in a patient who has a non-related state of tissue hypersensitivity, there may be a summation process resulting in lesions of greater severity.

However, the experiments in this series, and others referred to in the text, are obviously only on the fringe of this problem. Other experimental methods of varying the course of infections include: X-irradiation (Perkins and Marcus 1957), nutritional disturbances (Smith and Dubos 1956), dinitrophenol and thyroxine (Smith and Dubos 1956) and adrenaline (Evans et al 1948). Fehr and Brunson (1957) sensitised rabbits to bovine gamma-globulin and then administered a single intravenous injection of Gram-negative endotoxin. Fibrinoid lesions in the heart, lungs, spleen, liver and kidneys were more frequent in the hypersensitive animals. Focal glomerular lesions and proliferative glomerulonephritis were also produced. This is referred to again later.

Selye (1950) has re-worded many of the older concepts of hypersensitivity states in his analysis of "stress disorders". He says that a
septicaemia is part of the "alarm reaction" of the "general adaptation syndrome", and is associated with hypocorticoïdism. The Waterhouse-Friderichsen syndrome is taken as a type of acute stress reaction and Selye lists many possible causes of the condition, but he does not include the staphylococcus. A study of his book on "Stress" did not shed any significant new light on the problem under discussion, but only seemed to add a new terminology.

Evaluation of the Lesions Attributed to a State of Hypersensitivity.

Elek (1959) after marshalling the evidence regarding immunity mechanisms in staphylococcal infections, reached the general conclusion that allergy is not important, but he admits the limitation of in vitro tests - "Allergy has been invoked in the explanation of staphylococcal lesions. In the limited environment of in vitro tests such changes would not be observable." The interpretation of tissue lesions may be debatable and they do not lend themselves to quantitative estimation, but at least they provided recognisable indices of an allergic response. Two organs, the lungs and kidneys, were selected as the main objects of study, and were used as indices of a state of generalised hypersensitivity. It is neither possible, nor important, at this juncture to decide what type of hypersensitivity state may be present - although the choice would appear to lie between either a manifestation of a generalised Shwartzman phenomenon, or a state of generalised hyperactivity of the tuberculin type. Suffice it to say, that evidence is presented, both in man and the rabbit, that there
is, in staphylococcal septicaemia, a state of altered tissue reactivity which gives rise to lesions of importance in the aetiology and course of the infection.

The present study is one in morbid anatomy, and it is realised that other avenues of approach might help to elucidate the importance of immune phenomena. The estimation of antibodies to the staphylococcus or its products is a case in point. Some of the work done in this field is discussed later in this chapter. Even though I have not done any serological investigations in this series, I feel that sufficient evidence of tissue damage of a hypersensitivity type is presented, to warrant a re-appraisal of the part played by immune phenomena in staphylococcal septicaemia. The selection of the best antigen, and the detection of the appropriate antibody, presents considerable difficulty. Even if any given serological investigate should prove negative, it would still not invalidate the finding of structural damage.

The principal lesions accepted as evincing a hypersensitivity reaction may be considered as vascular and parenchymal:

**Vascular lesions.**

- Fibrin thrombosis of capillaries, arterioles and venules.
- Fibrinoid change in vascular walls.
- Perivascular cellular reactions.
- Focal haemorrhages.
Parenchymal lesions.

Various types of renal necrosis.
Fibrinoid change in basement membranes.
Diffuse glomerulonephritis.
Focal embolic glomerulonephritis.
Infarcts in various organs due to thrombosis.

It should be re-emphasised that the non-suppurative lesions, which have been described, are not suggested as being in any way specific for staphylococcal septicaemia. They are common denominators to many infective processes, but their importance in staphylococcal septicaemia has been overlooked in the past. Identical lesions were seen in a variety of septicaemic conditions. A good example of acute renal tubular necrosis was observed in a case of R. burneti endocarditis. Similar lesions have been produced experimentally in a variety of infections - for example Ross (1955) described identical lesions in guinea-pigs given B. anthracis septicaemia. He also found small vessel thromboses.

The principal lesions observed in man and in the rabbit will now be considered

The Renal Lesions in Experimental Hypersensitivity.

Various agents have been used to produce hypersensitivity renal lesions. The rabbit is probably the most suitable animal for this purpose, although the not infrequent occurrence of spontaneous nephritis may be a source of experimental error (Bell and Hartzell 1919). A variety of antigens have been used in the production of hypersensitivity states for the study of the kidney changes - for example, egg-white (Longcope 1913), horse-serum (Longcope 1915, Rich and Gregory 1943, McLean et al 1951, and
Hamilton-Paterson and Henderson 1952), bovine albumin and gamma-globulin (Hawn and Janeway 1947, Heptinstall and Germuth 1957), and renal auto-antibodies (Masugi 1934, Cavelti and Cavelti 1945). Bacterial extracts have also been used to produce experimental glomerulonephritis, for example, Duval and Hibbard (1926) prepared an endotoxic principle from viable Strep. haemolyticus cultures through the medium of the peritoneal cavity of the rabbit which had been immunised against a homologous strain (Pfeiffer phenomenon). This lysate was potent in the production of diffuse glomerulonephritis. Schwentker and Comploier (1939) injected repeatedly, mixtures of rabbit kidney emulsion and staphylococcal toxin into rabbits. All animals developed positive complement fixation reactions, homologous kidney antibodies were formed and glomerulonephritis produced. Negligible reactions were produced when streptococcal toxin was used.

All the above-mentioned papers, and many others were consulted in an attempt to summarise the known histological features of glomerulonephritis produced in the course of experimental hypersensitivity. The salient features described and illustrated were:

**Glomerular Lesions.**

Enlargement of glomeruli, due to proliferation of the cellular component, is a constant feature of the kidneys in hypersensitivity states due to foreign protein. This, together with thickening of the basement membranes of the glomerular capillaries and capsules, results in obliteration of capillary loops, the entire glomerulus appearing ischaemic.
Necrosis affecting portions of capillary loops, causes widening of the intercapillary spaces. Frequently, the proliferative and necrotising changes may be focal, affecting only a portion of any single glomerulus. The capillary tufts may adhere to one another, or become partially adherent to the glomerular capsule giving a crescentic pattern. The other glomerular lesions observed have included exudation of cells and serum into the capsular spaces, also with organisation and crescent formation; dilatation of glomerular capillaries; vacuolation amongst the capillary tufts; hyaline thrombi and hyalinisation of the non-cellular components of the glomerular tufts.

The glomeruli may be surrounded by collars of lymphocytes and plasma cells, with a variable degree of periglomerular fibrosis.

**Tubular Changes.**

Various degenerative tubular changes have been reported. These include marked swelling of tubular epithelium, vacuolation, and foci of complete necrosis. casts are often present.

**Vascular Changes.**

The arteries show an acute periarteritis, with fibrinoid degeneration affecting the vessel walls. The vessel intima may proliferate. Necrotising renal arcuate arteritis is a characteristic finding.

All the above lesions have been produced repeatedly under the conditions of experimental hypersensitivity states. Recent confirmation of their allergic nature has been afforded by the use of the fluorescent antibody
techniques. Cruickshank and Hill (1953) immunised rabbits by intra-peritoneal injections of extracts of human glomeruli (amongst other antigens). The sera of these animals were conjugated with fluorescein isocyanate, and globulin fractions were used to treat human kidney tissue. When viewed under ultra-violet illumination, the basement membranes of the glomeruli were clearly outlined by their fluorescence. Mellors et al (1925) have used the same technique. They immunised rabbits to bovine gamma-globulin and then demonstrated localisation of antibodies in vivo. They observed most of the histological features described above and found that in the hypersensitive rabbits, antibodies were localised in the renal glomeruli, and particularly in the basement membranes. Therefore, the experimental evidence that the lesions described as those of diffuse glomerulonephritis are, in fact, due to a hypersensitivity state, is well-nigh irrefutable. These lesions were all observed in the human and animal series in the present investigation, indicating that the response of the host is of a hypersensitivity type.

The Varieties of Renal Necrosis.

The varieties of renal necrosis which were present in the human and/or animal series were:

1. Acute tubular necrosis.
2. Patchy necrotising glomerulitis.
3. Complete bilateral renal cortical necrosis.
4. Papillitis necroticans.

Complete bilateral renal cortical necrosis was not found in the animal series.
It is interesting that although staphylococcal exotoxin is frequently used as one of the most reliable methods of producing bilateral renal cortical necrosis experimentally, it should yet figure so very infrequently as a finding in either experimental or clinical staphylococcal infections. Dible (1953) drew a sharp distinction between the lesion of acute tubular necrosis and that of bilateral renal cortical necrosis, stating categorically that acute tubular necrosis is not a stage in the development of bilateral renal cortical necrosis. The latter is primarily a vascular lesion whose affinities lie rather with the lesions of acute glomerulonecrosis described by Dunn and Montgomery (1941). The present series does little to elucidate this question, partly because acute tubular necrosis and acute glomerulonecrosis were so frequently associated. Only one rabbit was given staphylococcal exotoxin, for a histological control, but this was enough to show that the toxin could kill a rabbit by producing a state of uraemia without finding complete or even extensive renal cortical necrosis. The patchy necrosis found could not easily be classified with Dible's acute tubular necrosis or with Dunn and Montgomery's acute glomerulonecrosis.

Neisser and Levaditi (1900) were the first to produce renal necrosis in the rabbit using intravenous staphylococcal toxins. After Parker et al (1925-26) had improved the technique of preparing staphylococcal exotoxin, further papers followed by Weld et al (1931), Forssmann (1932), Rigdon et al (1934), and Von Glahn and Weld (1935).
Considerable debate still centres around the role played by vascular occlusion in the aetiology of symmetrical necrosis. These diverse opinions have been referred to in connection with human material in Chapter 8. Rigdon et al (1934) stated that blood vessels are only rarely occluded by thrombi, although they did describe hyaline thrombi occluding capillary loops. They also emphasised that the principal damage was focal and tubular—a finding which suggests that Dible's rigid demarcation of cases of acute tubular necrosis may not be applicable in the assessment of lesions caused by the staphylococcus or its products. Von Glahn and Weld (1935), found that necrosis of renal arteries resulted within 4 hours of the intravenous injection of staphylococcal toxin in rabbits and cats. At 12 hours fibrin was demonstrated in capillary loops and arterioles. Tubular necrosis was also prominent within 12 hours. De Navasquez (1938) did not find thromboses, although he confirmed the presence of severe arterial damage. However, he attributed the ischaemia to obstruction of glomerular capillaries, and intralobular arteries and arterioles, by conglutinated masses of red blood cells. Dunn and Montgomery (1941) by the use of fibrin stains were able to demonstrate fibrin thrombi in their human cases of acute glomerulonecrosis. It might be thought that the presence or absence of vascular thrombosis would be an easily-ascertainable histological feature, but some cases undoubtedly present difficulty. This was found in the course of this study, and it was a difficulty which was not always resolved by consulting experienced histopathologists.
The incidence of thromboses in various types of renal necrosis may well be almost directly proportional to the care with which the histological examination is made. This is especially true with regard to the smaller arteries and capillaries. Certainly, a statement that thrombotic lesions were absent should not be made unless fibrin stains have been used. A note of caution must be sounded because the finding of thrombotic vascular occlusion does not necessarily mean that these are the cause of the ischaemic lesions. They may be secondary to the presence of surrounding necrotic tissue. Sometimes, however, an artery was occluded by thrombus at the apex of a cone-shaped area of necrosis. The artery itself might be in relatively healthy tissue and its wall quite normal. These lesions must be primarily those of arterial occlusion with subsequent necrosis in the tissues supplied by that artery.

It is generally agreed that symmetrical bilateral renal cortical necrosis is an ischaemic lesion – in those cases where no organic vascular obstruction can be demonstrated vascular spasm is invoked as the cause. Byrom (1937) produced renal necrosis following repeated injections of large doses of vasopressin in rats. He also found necrosis of the renal artery. His illustration of focal glomerular necrosis was not unlike that of focal embolic glomerulonephritis. Russell (1929) also found similar capillary loop dilatation; adhesions between tufts and capsules; intra-capsular haemorrhages; and proliferation of capsular epithelium at the margins of embolic arterial infarcts in man. A similar relationship of focal embolic lesions was striking in some of
the cases of the present clinical series. Classical wedge-shaped infarcts were found in humans and animals. As has been stated above, Dible emphasised that the conditions of bilateral renal cortical necrosis and acute glomerulonecrosis were examples of a primarily vascular obstructive condition. Yet, Scarff and Keele (1943) in their study of rabbits' kidneys after unilateral nephrectomy and clamping of the contralateral renal pedicle for up to 120 hours, produced gross degenerative changes of the first portion of the secreting tubules. This was followed by tubular dilatation and thinning of the epithelium. They likened their findings to those found in the kidneys of crush syndrome - one of the classical causes of Dible's acute tubular necrosis. Trueta et al (1947) administered intravenous staphylococcal exotoxin to rabbits and observed directly an exposed kidney. In susceptible rabbits the surface of the kidney blanched within a few minutes of the injection. Within 12 hours the kidney surface assumed a mottled appearance. This was the initial stage in the development of complete bilateral renal cortical necrosis, and they attributed it to a permanent diversion of blood through the medullary pathway. They also found histological evidence of vascular occlusion in the form of fibrin thrombi or conglutinated red blood cells. Thal (1955) also observed directly the sequence following intravenous injection of staphylococcal toxin and traced the vascularity of the viscera by injecting India ink. He stated that renal vein constriction with stagnation was the first event. He did not find thrombi in the ischaemic kidneys.
Glynn (1937) as a result of his experiments favours the theory that ischaemic and direct toxic effects play a part. Elek (1959) states that lesions such as renal necrosis are the result of the direct toxic effect of staphylococcal toxin. He does not accept Thal and Egner's observation of vasospasm in local lesions, because Lasfargues (1946) showed that staphylococcal toxin has a direct necrotising effect on guinea-pig spleen in tissue culture. Therefore, it can be seen that the findings of workers with human and experimental examples of renal necrosis are variable. However, there has been a remarkable lack of study of the renal lesions in cases of staphylococcal infection. The tendency has been to study the suppurative renal lesions in staphylococcal infections, or to study renal necroses following injections of staphylococcal exotoxin. The facts that emerge from the present study are that capillary and end-artery fibrin thrombi are often present in staphylococcal septicaemia, and these are almost invariably associated with various types of renal necrosis. Rarely, the necrosis is complete and symmetrical, but more usually it is either a patchy acute tubular necrosis; an acute glomerulonecrosis; or a patchy cortical necrosis possessing features of both. Whether a primary functional vasospasm initiates these lesions cannot be decided on morbid anatomical evidence, but it is felt that sufficient evidence is adduced to attribute the perpetuation, at least, of the state of ischaemia to the development of widespread vascular thrombosis.
The Renal Lesions in the Shwartzman Phenomenon.

The types of renal necrosis discussed above, have been considered as manifestations of demonstratable lesions, in the form of vascular occlusion. The mechanism, or mechanisms, which may be responsible for these lesions must now be considered.

It has already been suggested that the lesions observed reflect a hypersensitive response on the part of the host. It would further appear that this response is of a specialised type resembling most closely that seen in the generalised Shwartzman phenomenon. Apitz (1934\textsuperscript{b}) observed the lesions in the localised and generalised Shwartzman phenomenon, and found that the type of tissue damage was similar in both types. Severe kidney damage resulted from the intravenous preparatory injection - "necrotizing nephrosis", and glomerular vascular damage, which in some led on to complete cortical necrosis. Subsequently Apitz (1935), analysed the renal lesions in greater detail using filtrates of \textit{E. typhosus}, \textit{E. paratyphosus B}, and \textit{N. meningitidis}. Fibrin thrombosis of the intralobular arteries was given as the cause of necrosis of the corresponding part of the renal cortex, and he described the cone-shaped areas of infarction such as were found in man and rabbits in the course of this work. Apitz made the interesting observation that the generalised Shwartzman reaction could be produced in the pregnant rabbit after only a single intravenous injection of bacterial filtrate. He, again in his 1935 paper, found a very close parallelism between the localised and generalised Shwartzman reaction, and compared
their relationship to the relation between the Arthus reaction and anaphylactic shock. Renal lesions which were almost identical with those described by Apitz, and found in the present study, were described by Gerber (1936). He produced the generalised Shwartzman phenomenon in rabbits, using filtrates of \textit{N. meningitidis} and \textit{E. typhosus}. His principal findings were - thrombosis of glomerular capillaries, focal tubular necrosis, cortical necrosis, and necrotising arteritis.

Brunson \textit{et al} (1950) in their study of the Shwartzman reaction produced by meningococcal filtrates described, and produced, illustrations of fibrin thrombi in glomerular capillaries and afferent renal arterioles which are identical with those illustrated in this work.

Black-Schaffer \textit{et al} (1947) have analysed the Shwartzman phenomenon and its relationship to the Waterhouse-Friderichsen syndrome and bilateral renal cortical necrosis, in detail. They used living and dead meningococci as well as meningococcal filtrates. The living organism produced lesions which were just as striking as those produced by dead organisms or bacterial filtrates. They stated that the lesions they produced were almost identical with those described by Apitz and Gerber, but they were less impressed with the importance of vascular occlusion, although their illustrations included a good example of thrombosis of an intralobular artery. They believed that the primary damage takes place in the walls of blood vessels. The frequency of haemorrhagic manifestations, and of adrenal necrosis and haemorrhage in the generalised Shwartzman reaction is additional evidence in favour of postulating
such a mechanism to be operative in staphylococcal septicaemia. Haemorrhagic manifestations were found frequently in the clinical series. The Waterhouse-Friderichsen syndrome also occurred.

Objection might be made to the postulate that the Shwartzman phenomenon is operative in staphylococcal septicaemia, however, on the ground that the Shwartzman reaction was nearly always produced by Gram-negative organisms or their products. Olitzki et al (1942) confirmed this but they also found that some strains of staphylococci produced hypothermic and adreno-haemorrhagic effects when two injections were given with a 24 hour interval between them. In any case, the problem is not what usually occurs in staphylococcal infection, but what occurs in the relatively rare examples of fulminating blood stream invasion. The human body has acquired nothing like the same degree of toleration to E. typhosus, for example, as it has to Staph. aureus. In any case it has been demonstrated that the Shwartzman reaction can be produced by chemical substances such as sodium polyanetholsulphonate, (Fehr and Brunson 1957). The technique used in reproducing the reaction has also varied considerably. It has already been noted how Apitz (1934), produced the generalised Shwartzman by a single intravenous injection of bacterial filtrate in pregnant rabbits. The reaction is also easier to produce after previous administration of thorotrast or trypan blue (Good and Thomas 1952); after previous administration of colloidal iron (Smith et al 1953); after cortisone therapy (Thomas and Good 1952); and after preliminary
sensitisation to bovine gamma-globulin (Fehr and Brunson 1957). Capillary thrombosis and renal parenchymal damage in the present experimental series were more striking in rabbits which had been previously sensitised to horse serum. It may well be that nonbacterial chemical factors are important preparatory agents in human disease. Brunson et al (1955) attributed the relatively rare event of renal cortical necrosis following a single intravenous injection of meningococcal toxin in the rabbit to a possible systemic infection at the time of the injection. This possibility is supported by the experiments of Thomas et al (1953), who found that a single intravenous injection of meningococcal toxin in rabbits previously infected with Group A haemolytic streptococci caused subendocardial fibrinoid lesions, and bilateral renal cortical necrosis in over half the animals.

Focal Embolic Glomerulonephritis.

No typical examples of focal embolic glomerulonephritis were encountered in the animal series. The various manifestations of glomerulonephritis, namely, proliferation of glomerular tufts and necrosis, sometimes affected only a portion of a single glomerulus, so that appearances somewhat similar to those of focal embolic glomerulonephritis were sometimes seen. Similar focal lesions have been noted in animals in hypersensitivity states. The illustrations of focal necrotising glomerulonephritis in hypersensitivity, in the papers of Heptinstall and Germuth (1957), and Fehr and Brunson (1957), resemble the lesions seen in this animal series. However, it is
difficult to understand why lesions identical with those of human focal embolic glomerulonephritis should not have been seen. The problem is put one step further back by stating that the answer is the absence of typical bacterial endocarditis in the animal series. Occasionally, infected intra-cardiac thrombi were seen, but no example of true valvular endocarditis was encountered. The staphylococcus is a poor organism with which to attempt to produce endocarditis in the experimental animal, although it had been hoped that preliminary sensitisation to horse serum would have facilitated the production of this lesion. Two examples of focal embolic glomerulonephritis were seen in patients who had no evidence of endocarditis, but the majority of cases do show this association. It may be that endocarditis can only become established when there is a very delicate balance, or rather a constantly changing im-balance between host and organism. The other fact to be remembered is that, contrary to what is often stated in textbooks, the staphylococcus can give rise to an endocarditis of a subacute clinical type, picking out heart valves previously damaged by rheumatism.

**Pulmonary Changes in Experimental Hypersensitivity States.**

The literature concerning pulmonary changes in states of experimentally-induced hypersensitivity is confusing. Wissler et al (1949), and Germuth (1953), stated that no lung changes occur after single or repeated doses of intravenous foreign protein. However, the weight of evidence seems to be in favour of there being
lung changes in allergic states. Germuth himself, later in collaboration with Hepstínall (1957), described lung lesions following sensitisation to bovine gamma-globulin. Rich and Gregory (1943) found lung lesions in 10 out of 56 rabbits suffering from serum-sickness. The lesions consisted of focal capillary thrombi. Similar lesions in rabbits made hypersensitive to foreign protein, have been observed by Hawn and Janeway (1947) and Ehrich et al (1949). These characteristic focal capillary thrombi were found in man and rabbits suffering from staphylococcal septicaemia.

The lungs may also be involved in the generalised Shwartzman reaction. The lesions described have been similar to those found in hypersensitivity to foreign protein. (Brunson et al 1955). Haemorrhage, and haemorrhagic infarction may be associated with the occurrence of pulmonary arterial and capillary thrombosis. Ogasawara and Tanaka (1958) report some interesting experiments in this connection. They inoculated mice intranasally with Staph. aureus. These were gradually eliminated without abscess formation. If mice were inoculated intranasally with filtrate of Staph. aureus culture they died with extensive haemorrhagic consolidation in the lungs. When filtrate was given with staphylococci, extensive consolidation with abscess formation took place. This experiment provides support for the view advanced earlier with regard to the lung pathology in man, where thrombosis was adduced to be an important feature, and the factor which might determine the sites and extent of suppuration. Shwartzman (1929) reported venous thrombosis, haemorrhagic consolidation, and necrosis in the lungs of animals where the
reaction had been induced. These lesions have also been found in the generalised Shwartzman phenomenon by Apitz (1934) and Gerber (1936). A previously unrecognised factor which may complicate the interpretation of lung changes in staphylococcal septicaemia, is that of the "uraemic pneumonia" which may well be present. As in the various types of renal necrosis described, some of the lung changes in staphylococcal infections could be attributed to the direct effect of staphylococcal toxins. Jackson et al (1958) produced pulmonary haemorrhagic consolidation, with necrosis, by introducing staphylococcal toxin intratracheally in the rabbit. They attributed these changes to stagnation hyperaemia with functional ischaemia, but did not rule out a direct toxic effect. Guthrie and Montgomery (1947) drew attention to the severe haemorrhagic oedema which accompanies staphylococcal pneumonia in childhood. They described "groups of alveoli packed with red blood-cells", which are reminiscent of the focal vascular damage described in Chapter 7. It is, however, doubtful whether the lesions depicted by Guthrie and Montgomery, are the same as those I found in association with bacterial endocarditis. I have failed to find any previous description of a "focal pulmonary vasculitis" in association with bacterial endocarditis.

The Influence of Steroid Hormones on the Development of Lesions in Staphylococcal Septicaemia.

Before undue significance is attached to any modification of the host response under the influence of cortisone, it must be remembered that cortisone itself can produce a variety of
disorders and lesions in the human and animal body. The effect of cortisone upon the kidney is of particular relevance to this discussion. Rich et al (1951) studied the effect of cortisone on experimental glomerulonephritis and observed aneurysmal dilatation of glomerular capillaries, associated with the development of nodular lesions similar to those described in the human diabetic kidney (Kimmelstiel and Wilson 1936). Becker (1944), and Friedenwald (1950), produced similar lesions with cortisone. Bloodworth and Hamwi (1955) found that these cortisone-induced renal lesions were thrombi composed of mucopolysaccharide and lipid within dilated capillaries. These findings were confirmed by Bencosme et al (1958). The fatty nature of the intracapillary substance was also striking in the lesions described by Wilens and Stumpf (1955). Sommers and Haley (1956) demonstrated that the substance present in the glomeruli and arterioles of cortisone-treated non-diabetic humans and animals had ultra-violet absorptive properties identical with the nodules of human intercapillary glomerulosclerosis. Striking vacuolation of the glomerular tufts was seen in one human case, but there was no history of diabetes mellitus nor of steroid therapy. It was not possible to demonstrate whether the vacuolation was due to fat. No renal lesions definitely attributable to steroid therapy could be discerned in the human or animal series. The effects of steroids on the phenomena of hypersensitivity have been demonstrated repeatedly. Dews and Code (1951) stated that steroids did not appear to influence anaphylaxis in the guinea pig, although Humphrey (1951) denied this. In any case the guinea pig is an excessively susceptible
animal to use for experiments of this type. Nelson et al (1950) showed a definite protective effect of cortisone against anaphylaxis during sensitisation to horse serum in mice. Rich et al (1950) found that the lesions of hypersensitivity to horse serum in rabbits were much less frequently encountered when cortisone or A.C.T.H. was given. Cortisone and A.C.T.H. were found to inhibit, in particular, the proliferative glomerular lesions. The glomeruli were maintained in a normal state by A.C.T.H., but quite severe glomerular damage with haemorrhage was found in those animals given cortisone. The effect of cortisone and A.C.T.H. on the Arthus reaction and antibody formation in the rabbit has been observed by Germuth and Ottinger (1950), and Malkiel and Hargis (1952), amongst others. The conclusions are that cortisone and A.C.T.H. reduce the size and frequency of the Arthus reaction, although animals can still produce a normal Arthus reaction on passive transfer of antibody. There is a reduction of circulating antibody with A.C.T.H. and an almost complete suppression with cortisone. Powell and Gough (1959) have shown the opposing effects of cortisone and hypersensitivity on tissue reactions in an indirect way, by finding that the hypersensitive rabbit responds to intratracheal silica in a manner which is the converse of that found in the animal given cortisone.

Steroids have also been shown to influence the Shwartzman phenomenon. One of the earlier observations which is of interest from this point of view is that of Smith and Humphrey (1949), who found that sodium salicylate was
capable of inhibiting the phenomenon. There is evidence that the ameliorative effect of salicylates on hypersensitivity reactions may be mediated by the adrenal cortex (Humphrey 1951). Several publications have appeared reporting that steroid hormones can suppress the Shwartzman phenomenon – Soffer et al (1950), Shwartzman et al (1950), Humphrey (1951), and Marcus and Donaldson (1952).

The other aspect of steroid hormones, and their effects, which must be considered, is the influence they may have on the course of infective processes. It appears that one of the fundamental properties of steroid hormones which affects the ability of the host to cope with bacterial infections, is their depressing action upon the bactericidal function of phagocytes.

Marcus et al (1953) reported that cortisone actually increased phagocytic activity in the peritoneal cavities of mice against Staph. aureus. Unfortunately they did not observe the subsequent fate of the ingested organisms. Gell and Hinde (1953) confirmed these findings using Staph. albus and colloidal radio-active gold. Crabbé (1955) found reduced phagocytosis of staphylococci in cortisone-treated rabbits. Clawson and Nerenberg (1953), however, showed that although the ability to engulf bacteria may be normal during cortisone therapy, there was an impairment of the capacity to destroy these engulfed organisms. Apart from this possibility of an impaired state of "bactericidal function" on the part of the phagocytes, there is also evidence that cortisone does modify the cellular and tissue response to
established inflammatory processes. Gell and Hinde (1951) in a histological study of the tuberculin reaction as it is modified by cortisone therapy, found a reduction in the mononuclear component. Cortisone was found to delay or suppress all the morphological elements of turpentine-induced acute inflammation in mice, so that a diffuse tissue necrosis resulted (Spain et al 1952). Cortisone also delays fibroblastic proliferation in inflammatory processes (Hurley et al 1958).

There is a large body of evidence supporting the belief that infections are enhanced and rendered more virulent to the host, by cortisone. This includes a wide variety of infective agents, for example, - Strep. pneumoniae, (Robinson 1951), M. tuberculosis (Spain and Molmut 1950), T. pallidum (Turner and Hollander 1950), Coxsackie virus (Kilbourne and Horsfall 1951), poliomyelitis virus (Shwartzman 1950), influenza and mumps viruses (Kilbourne and Horsfall 1951), B. abortus (Abernathy 1951), and Strep. haemolyticus (Mogabgab and Thomas 1952). The latter authors showed strikingly that after an intracutaneous injection of Group A streptococci, 6 of 86 control rabbits died, but of 76 cortisone-treated rabbits 71 developed a fatal septicaemia. They also found that physical well-being was marked in the cortisone-treated group until just before death, even though the blood culture was positive throughout. Immunisation of rabbits with preceding injections of living streptococci resulted in a state of resistance to the enhancing effect of cortisone.

Comparatively few experiments have been
performed to analyse the effect of steroid hormones on experimental staphylococcal infections. The literature on the subject reveals the paradox noted earlier in this thesis – namely, that steroids should on the one hand increase susceptibility to infection in man and the experimental animal, whilst on the other hand, if staphylococcal septicaemia exhibits features of a hypersensitivity state, then steroid hormones should exert an ameliorative effect. Some clinical reports indicating that there is in fact an enhancement of the infective process in man when steroids are administered, have already been mentioned. The paradox is emphasised when it is remembered that steroids are used therapeutically in fulminating infections. Their possible beneficial effect is said to be in avoiding vascular collapse in severe infections (J. Amer. med. Ass. 1958). Steroids are probably most useful (along with antibiotics) in infections caused by Gram-negative bacteria, (Spink 1957). Germuth et al (1952) found that cortisone-treated rabbits could successfully resist an intravenous injection of Staph. aureus which was fatal to approximately 50% of untreated controls. Higginbotham and Dougherty (1955) stated that adrenalectomy reduced resistance to an intravenous injection of Staph. aureus by at least a thousandfold. Adrenalectomy did not affect the ability to phagocytose, but only the animal’s susceptibility to the toxic action of the organism. They pose the interesting question whether the digestive processes of the reticulo-endothelial system liberate toxic substances from the bacterial cell into the circulation. Kleiger et al (1942) had previously suggested that the
early death of experimental animals after the intravenous injection of toxigenic staphylococci is due to an \textit{in vivo} production of toxin by bacteria. Part of the answer to this apparent paradox may be that whilst, theoretically, steroid hormones should exert a protective effect against any manifestations of hypersensitivity in a generalised infection, their first action is to facilitate the establishment of infection in the body. Antibacterial immunity responses may be impaired and the efficiency of the reticulo-endothelial system diminished. Once infection becomes established, especially in the case of an organism such as \textit{Staph. aureus}, which gives rise to suppurative lesions, then the suppurative foci provide repeated antigenic stimuli in high concentration which can give rise to hypersensitivity lesions either in the vicinity of the suppurative lesions or at a distance in other viscera.

The Antigenic Properties of Staphylococci.

No attempt will be made to discuss in detail the work done on the antigenic constituents of staphylococci. All that is suggested, is that there is a tendency to overlook the fact that the staphylococcus behaves as a complex system of antigens in the body, and that lesions are produced which are the result of antigen-antibody interaction.

Kolle and Otto (1902) studied staphylococci with agglutinating antisera, and differentiated between pathogenic and non-pathogenic strains. Hine (1922) confirmed their findings. He divided "\textit{Staph. pyogenes}" into
three serological types, and "Staph. epidermidis" into two serological types.

Zinsser and Tamiya (1925) found that bacteria do not contain any considerable amount of heat-coagulable albumin or globulin, although they may be present to a slight extent in bacterial extracts. Two main substances were obtained from bacteria - (1) A "residue substance", which is heat-stable; gives no protein reactions; is alcohol-precipitable; and is probably a complex carbohydrate. (2) A protein residue. This is a nucleoprotein precipitable by acids in the cold. In 1926, Zinsser and Tamiya claimed that in the case of bacterial hypersusceptibility, protein anaphylaxis plays a relatively important part. Goadby (1927 and 1932) isolated protein lipids and nucleoproteins from cell constituents. This has been confirmed repeatedly. It is interesting that bacteriophage contains a large proportion of nucleoprotein.

Julianelle and Weighard (1934 and 1935) made important contributions to the study of the antigenic properties of staphylococci. They found that agglutination was not a precise method for the demonstration of serological types amongst staphylococci. Precipitin tests were more reliable, and indicated at least two distinct immunological types - (a) the pathogenic, and (b) the non-pathogenic. When intravenous immunisation was carried out with heat-killed organisms, it always resulted in an increase of agglutinin production, and sometimes in increased precipitin production. Alcohol-ether washing did not affect the antigenicity or reactivity of the bacterial protein. The washings were ground until
the cocci were Gram-negative, and the powder taken up in N/100 NaOH. The protein thus extracted stimulated a specific antibody response, and caused in hypersensitive animals, a species-specific, delayed, inflammatory skin reaction. Unfortunately, they did not carry out any histological examination. However, there are many non-specific cross-reactions in precipitin tests with bacterial nucleoproteins, for example, Boor and Miller (1934) found a cross reaction between Staph. aureus and Type III antipneumococcus serum. Lancefield (1925) found that some protein antigens are common to haemolytic and non-haemolytic streptococci, and Strep. pneumoniae.

Cowan (1938, 1939) confirmed, and amplified the principal findings of Julianelle and Weighard. He also demonstrated a protective effect resulting from preceding immunisation. In addition, however, he made the significant observation that the mechanism of immunity appeared to be susceptible to non-specific enhancement, and vaccination with a Pasteurella vaccine induced as high a grade of resistance as specific vaccination.

Recently Stern and Elek (1951) have analysed the antigenic structure of Cowan's three types, using the technique of graduated absorption of antisera with heterologous strains. They have identified individual antigents a - h. Serological typing has also been correlated with biological characteristics (Thompson and Khorazo, 1937), and staphylophage, (Hobbs 1948).

In animal experiments where staphylococcal extracts are used as antigens, great care has to be taken lest the method of
preparation of the antigen has caused a fundamental change in its antigenic properties. Inoue (1942) heated and crushed staphylococci, and isolated an antigenic protein which was toxic for mice. However, heat-killed suspensions are not generally recommended (Kabat and Mayer 1948). Cutler (1929) showed that the immune response to native protein is quite different from that exhibited to denatured protein. Staph. aureus is easily disintegrated, for example, in a stone-ball mill, (Kabat and Mayer, 1948). Boor and Miller (1934) claimed a satisfactory extraction of nucleoproteins using N/100 NaOH. In view of the recognised dangers resulting from the extraction of bacterial antigens, I decided to make the process as simple as possible, as described in the previous chapter. Ideally, the only difference from the parent organism, required in a bacterial antigen is that it be dead. Any further degradation of the bacterial cell can proceed in vivo. Hypersensitivity lesions were produced by repeated injections of this crude extract. The extract was obviously relatively non-toxic, and was easily tolerated in high dosage. This is in contrast to the findings of Higginbotham and Dougherty (1955) who stated that, "bacteria formalinized and washed, heated to 58°C, exposed to boiling temperature, or incubated in distilled water, or with antibiotics, were not less toxic than control bacterial suspensions." Perhaps the observed toxicity is more a reflection of the modes of preparation, rather than due to any inherent antigenic toxicity. An attempt was made in the present study, using the bacterial
extract, to produce a local or generalised Shwartzman reaction, with doubtful results. The experimental use of staphylococcal bacterial extracts, provides a large field of research in which comparatively little has been done. Rich (1946) concludes that only intact M. tuberculosis, dead or alive, can establish a state of tuberculin-type hypersensitivity. When tuberculin is injected into a normal animal, there is no reaction. But when tuberculin is injected into a tuberculous animal, there is a vigorous reaction after a latent interval of several hours, (Rich 1946, and Kabat and Mayer 1948). When the converse is done, namely, introducing viable M. tuberculosis into an animal which has been sensitised to dead organisms, there is a marked intensification of the inflammatory response, (Olcott 1939). It is suggested that Staph. aureus can give rise to a state of hypersensitivity which has affinities with that of tuberculin hypersensitivity. This would explain the cases which remit and relapse. It would also emphasise the importance of previous exposure to infection.

Flaum (1938) found that immunised rabbits can resist large doses of staphylococcal suspensions. Forssman (1935) emphasised this protective effect, and showed that it was possible to transfer immunity passively - this was not an antitoxic immunity (Forssman 1936 and 1937). Elek (1959), after reviewing the evidence, states that this protection against successively larger doses of cocci, which can be induced by bacterial immunisation, "is almost the only solid fact that is known about staphylococcal immunity." Panton and Valentine
(1929) also found that repeated intravenous infections of *Staph. aureus* in the rabbit gave rise to immunity, but they also showed hypersensitivity to smaller doses. Infected animals show an intensified reaction to intradermal injections of toxoid. Unfortunately, Panton and Valentine did not examine the visceral lesions in any detail. Brahic *et al* (1953), and Zironi (1938), believed that a hypersensitivity response might be involved. Domagk (1924) produced staphylococcal anaphylaxis in mice. Forney (1954) found that when guinea-pigs were sensitised to "wax" extracts of *M. tuberculosis* and *M. smegmatis* together with formalinised staphylococcal cells, cutaneous hypersensitivity was induced. This could not be caused by "wax" extracts or staphylococci alone. The guinea-pigs also exhibited corneal reactions.

Serological studies of circulating antibodies to the diffusible products of staphylococci (which are referred to briefly later), have been rather unhelpful and variable. Bacterial allergy, with its marked tissue responses, may well be a more important factor in generalised staphylococcal infections - "Bacterial allergy is the strong development of the early phase of the specific response to antigen, preceding the production of circulating antibodies," (Dienes, 1935).

The fact that staphylococci are found to be so widely distributed, and are such common commensals of the human body, does not invalidate the possible part played by immune mechanisms. In fact, it is precisely under such conditions that immunisation is most likely to occur, as stated by Rountree and Barbour (1952)
- "this type of symbiotic existence without tissue invasion is most likely to lead to immunisation, and the evidence in infarcts that there is no increase in the carbohydrate antibody bears this out."

The emphasis which is being placed on the rôle played by bacterial allergy in generalised staphylococcal infections, raises the question of prophylactic vaccination. Cannon and Pacheo (1930) stated that, "a scar from a furuncle is small price to pay for the prevention of pyaemia," - a statement more striking in its alliterative appeal, than a true reflection of clinical experience. Indeed, in their article prefaced by this remark, they proceed to demonstrate an improved local reaction to infection in the previously-immunised guinea-pig, but conclude by wondering whether non-specific factors may not be just as important in local tissue immunity. Mallory and Marble (1925), and Friedland and Toomey (1928), had previously shown that the application of plain broth to the skin, was just as efficient a protection as specific broth filtrate. However, the recognition of these non-specific factors does not entail a rejection of the rôle ascribed to bacterial allergy. It is, in fact, the argument of this thesis, that these are the two factors which are of prognostic import in staphylococcal infections. In any case, hesitancy must be exercised in labelling any influence as "non-specific", when the complexity of the basic structure of staphylococci and their associated bacteriophages is becoming increasingly recognised. This also provides a large technical problem if immunisation against
the staphylococcus is contemplated in clinical practice. An interesting recent paper, illustrating the protective effect of bacterial immunisation, is that of Brodie et al (1958). They experimented on Cowan's original serotype I staphylococcus, which after approximately 19 years of repeated sub-culture, had become attenuated for the rabbit. Intravenous injection of this organism gave complete protection to a recently isolated pathogenic serotype I. This protection did not obtain if the organism was formalinised or boiled.

The Exotoxins of Pathogenic Staphylococci.

An enormous literature has grown up around the exotoxins of Staph. aureus. Only a few aspects are considered briefly in this discussion.

Experiments on immunity were performed soon after the discovery of the staphylococcus. Hericourt and Richet (1888) demonstrated passive immunity, by giving blood from infected dogs intraperitoneally to the rabbit. Mosney and Marcano (1894), and Kraus and Pribram (1906), claimed to have demonstrated that the serum of a rabbit infected with Staph. aureus has an antitoxic effect. It is appreciated, of course, that the rabbits which died within 24 hours of intravenous injection of staphylococcal suspensions, did not die from infection, but from the effect of toxins.

The Rôle of Coagulase in Staphylococcal Infections.

Coagulase production is still the most commonly employed laboratory test, as an index of pathogenicity, (Cruickshank, 1937). Pathogenicity
is so constantly associated with coagulase production that it is difficult to avoid a teleological approach when considering whether coagulase has an in vivo function - this is still an undecided question.

Loeb (1903-04) first showed that Staph. aureus could cause clotting of goose plasma. Much (1908) correlated this property with pathogenicity, and Darányi (1925 and 1926) pointed out it might be a useful test clinically. This has since been confirmed repeatedly.

Delezenne (1898) suggested that the venous thrombosis which is so frequently seen near pyogenic lesions is due to the action of coagulase. Genpu (1935) found that coagulase agglutinates platelets, and staphylococcal toxin fuses them into a homogeneous mass.

Hale and Smith (1945), and Smith, Hale and Smith (1947), found that plasma which had been clotted by coagulase inhibited the phagocytosis of staphylococci. They took a strain of staphylococcus which was coagulase-positive to human plasma, but coagulase-negative to guinea-pig plasma. When this strain was injected subcutaneously into the guinea-pig, no abscess formation occurred, but if the injection was made into an area where human serum had previously been injected, multiple abscesses were produced. They also produced two type-specific anticoagulase- sera in the monkey. As a result of their work, an accessory factor was postulated. Animals which do not possess this factor are particularly resistant to intravenously injected Staph. aureus, for example, mice, fowls and rats. Gorrill (1951) found strains of mice whose plasma coagulated
with *Staph. aureus*. These strains were susceptible to *Staph. aureus* administered intravenously, but not when given by other routes. Hale and Smith concluded that an in vivo clotting function of coagulase might be an essential step in the establishment of staphyloococcal infection. Lominski and Roberts (1946), and Lominski (1949), demonstrated an anticoagulase factor in human serum. This factor was absent from patients who had had a recent major staphyloococcal infection, and it also could protect rabbits against experimental infection. Boake (1956) has shown that animals can be actively immunised against coagulase, and that this procedure confers a degree of immunity. Barber and Wildy (1958) have recently shown a close correlation between staphylophage and the antigenic specificity of the free coagulase produced by the corresponding strains. Coagulase from different strains differ serologically (Rammelkamp et al 1950). There is evidence that coagulase may act as a hapten (Becker, 1949).

Menkin and Walston (1935), and Fisher (1936), failed to demonstrate an in vivo clotting effect during the course of staphyloococcal infections, although Fisher did observe clotting in dead and dying animals.

An essential step in the investigation of coagulase function is, of course, the purification of free staphyloococcal coagulase. This has been done by Duthie (1954), and Duthie and Haughton (1958). An in vivo clotting effect by purified coagulase has, as a result, been demonstrated by Smith and Johnstone (1958). The lungs were most severely affected, the
arterioles and capillaries being occluded by fibrin thrombi. No damage to the vessel walls was seen. Death appeared to be due to acute right heart failure, following multiple thromboses in the pulmonary blood vessels. These findings immediately raise the question whether the high incidence of fibrin thrombi, seen in the present human and animal series, could not be due to an in vivo action of coagulase. I do not think this can be the simple explanation. The distribution of lesions differed in the case of staphylococcal septicaemia. They were also invariably associated with damage to the vessel walls, and surrounding parenchymal necrosis. Haemorrhage was frequent because of the vessel wall necrosis. None of these features were noted in Smith and Johnstone's histological findings. Fisher's (1936) failure to produce this syndrome, by the intravenous injection of coagulase, is criticised on the grounds that his coagulase preparation was weak. But the intravenous injection of large quantities of highly concentrated coagulase can hardly be compared with what obtains in the course of human or experimental staphylococcal infections. One of the two coagulase preparations used by Smith and Johnstone, clotted human plasma diluted 1 in 10, at a dilution of 1 in 500,000 in vitro. The other preparation was four times more active. It is clear more work needs to be done on the clotting mechanisms in staphylococcal septicaemia, and in anaphylactic states. There is a close connection between anaphylactic shock and disorders of blood coagulation, (Arthus, 1909; Biedl 1909; Jaques and Waters 1941; Rocha e Silva, 1952). Robbins and Stetson (1959) have recently
shown that sensitisation of a rabbit to foreign protein, results in a marked shortening of the in vitro coagulation time of samples of whole blood kept in siliconised glassware. Addition of the specific antigen to the blood of actively immunised animals also produced this effect.

The effect observed by Smith and Johnstone may be part of the syndrome of anaphylactic, or anaphylactoid shock. Although these authors, and Tager (1954), observed a fall in fibrinogen levels after the injection of coagulase, it is noteworthy that detailed coagulation studies do not seem to have been performed in clinical or experimental staphylococcal septicaemia. This should be an interesting avenue of approach to the problem.

The morbid anatomy of the lesions in the present series only made one think of the possibility of an in vivo coagulase effect, when an unusual type of massive large-vessel, and cardiac obstruction, was found at autopsy in some rabbits. This was presumably agonal, but did not have the appearances of post-mortem clot.

Coagulase-positive staphylococci persist longer in the circulation after intravenous injection than coagulase-negative varieties (Seno 1939).

The latest research work on coagulase, concerns its bacterial surface action. Rogers and Spensley (1954), and Rogers, H.J. (1956), have shown that if staphylococci are coated with a layer of a highly negatively-charged, synthetic polymer, the formation of coagulase, hyaluronidase, and alpha-lysin, is almost completely inhibited, although growth proceeds unchanged. Rogers has named these negatively-charged polymers,
"macroanions". The possible clinical implications of these findings, and of Duthie's distinction between free and bound coagulase (or "clumping factor"), are not clear. It may be that an organism which shows coagulase activity in vitro may not be allowed to exert this effect in vivo. On the other hand, this teleological argument can be used in the opposite sense - namely, that if the "clumping factor" of bound coagulase is not able to act, then clumping of organisms (presumably a beneficial event from the host view-point) is impaired.

Other Diffusible Products of Staphylococci.

Duran-Reynals (1933) made the observation that organisms of low grade virulence, when injected along with testicular extract, gain considerably in virulence. Pure testicular extract seemed to lack antigenic properties. In a study of Staph. aureus, Duran-Reynals concluded that invasive strains possess this spreading factor. The factor (subsequently recognised as hyaluronidase by Chain and Duthie, 1939, 1940), also induced a generalised state of increased tissue permeability, so that infections elsewhere in the body, were enhanced. Hyaluronidase is produced by over 90% of coagulase-positive strains, but never by coagulase-negative organisms, (Schwabacher et al 1945). There is no clear evidence that hyaluronidase has a pathogenic rôle in the body. Málék and Málék (1948) claimed there was a correlation between hyaluronidase production and pathogenicity in puerperal breast abscess. Others deny that it has any bearing on
the virulence of staphylococci to man, (Ungar and Bacharach, 1942, and Kulonen, 1951). In any case it is doubtful whether "dilution by spread" facilitates invasion. It may rather ease the task of phagocytic destruction.

Other staphylococcal exotoxins which have been studied in detail are leucocidin (Valentine 1936); alpha-haemolysin (Burnet, 1929, 1930, Bryce and Burnet, 1932), and enterotoxin, (Dack et al 1930).

It is not necessary to consider these toxins in detail. The only interest which they have in the present context, is the part they may play in immunity mechanisms. A recent publication (Towers and Gladstone 1958), claims that the anti-alpha-haemolysin and anti-P.V.-leucocidin titres are of diagnostic value, particularly in deep-seated infections.

Staphylococcal leucocidin was shown to be heat-labile and antigenic by Denys and Van de Welde (1895). Valentine (1936) demonstrated that in chronic suppurative staphylococcal infections, the anti-leucocidin titre shows an increase, which is not shared by the anti-alpha-haemolytic titre. In deep-seated infections there is a rise in the anti-alpha-haemolytic titre, often accompanied by a relatively greater increase in anti-leucocidin. Leucocidin has been shown to be antigenic to rabbits (Flaum, 1938, Gladstone and Van Heyningen, 1957).

Burnet (1929) claimed that the haemolytic, skin-necrosing, and lethal manifestations of staphylococcal exotoxin, were due to an antigenically similar substance. Julianelle (1922), Parker (1924), and Burky (1937), have denied this. Burnet used small numbers of
rabbits with which to study the lethal effects, but he claimed that a subcutaneous staphylococcal infection in the rabbit, established a state of immunity, whereby the animal survived an intravenous dose of toxin which would otherwise have been lethal. Bryce and Burnet (1932) observed the changes associated with age, of the anti-haemolytic titre, in man. There is a high level after birth due to maternal transfer, but then a marked fall at two months. There is a steady rise from two to ten years, with a wide range in adults (2 - 650 units).

Skin testing in man has provided some evidence of hypersensitivity to staphylococci, although there have been conflicting reports. Afremow and Pilot (1929) found a higher proportion of positive reactions to filtrates and vaccines in patients with staphylococcal infections. Erlsbacher and Saxl (1932) demonstrated, however, that all adults reacted to filtrates, although antitoxin abolished the reaction. Remé (1930) injected dilute culture filtrates in children, and found an increasing proportion of positive reactors up to six years. After six years, the proportion approached 100%. In this respect the staphylococcal product behaved like tuberculin in the Mantoux reaction, and not like the pattern found on Shick and Dick testing. Turk (1941) failed to confirm these findings. Allergy to skin toxoid in man has been correlated with clinical infection (Wagner and Maly 1952, 1953), although no clinical details are given by these authors. It is of considerable interest to note that the Shwartzman phenomenon has been elicited in the rabbit, using staphylococcal filtrates,
(Alechinsky 1936, and Michelazzi 1935).

Therefore, in summary, there are three main groups of substances which must be taken into consideration in assessing both resistance to staphylococcal infections, and the lesions in the host, which may be produced as a result of antigen-antibody interaction. These are the bacterial protein; its diffusible products (alpha-haemolysin, hyaluronidase and leucocidin); and coagulase, which occupies a peculiar position. After examining some of the very numerous reports of the antigenic properties of a variety of staphylococcal products; the variability of the host immune response; the numerous specific and non-specific factors, which may influence this response; and finally, the non-suppurative lesions which form a significant feature of the morbid anatomical changes in staphylococcal septicaemia, the case made out for treating the problem of staphylococcal infections as an immunological one, is very strong. This would be a truism, were it not for the fact that I do not think this is the way in which the problem is usually approached. The staphylococcus is still frequently regarded as the one agent, more than any other, which may be recognised by its suppurative lesions. This attitude conditions the avenues of research on the problem, which are principally concerned either, with epidemiological problems, or with antibiotic resistance. The ultimate problem is the individual who shows his individuality in his peculiar, and often unfortunate, manner of dealing with generalised staphylococcal infections.
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