circulation is usually so good. However, on four occasions we have reconstructed such vessels (subclavian and axillary) in patients who were unable to work because of the symptoms of ischaemia, and the results have been worth while.

Type of Reconstruction Operation

Table II gives our results with the various arterial reconstruction operations in all our patients over the last six years irrespective of the reason for the operation, and Table III lists the disease for which the artery was reconstructed.

For patients with obliterative arterial disease it is only occasionally possible to resect the occluded segment and restore continuity by a direct end-to-end anastomosis, but when this can be done it is the best procedure. In my view the next most satisfactory operation is thrombo-endarterectomy. This is of particular value in localized occlusions of the aorta and iliac arteries, but it is sometimes of value in vessels as small as the popliteal. Two important

TABLE II.—*Method Used in* 228 *Arterial Reconstruction Operations*

Operation	No. of Patients	Thrombosed Early and Late	Dead (including Operation Deaths)	Now Patent
Direct suture	25	1	3	21
Thrombo-endarterectomy ..	24	5	1	18
Autogenous vein ..	25	15	4	6
Homologous artery ..	109	34	10	65
Plastic cloth	19	0	5	14
Polyvinyl alcohol ..	26	9	5	12

TABLE III.—*Reason for Operation in the* 228 *Patients Listed in Table II*

Reason	No. of Patients	Thrombosed Early and Late	Dead (including Operation Deaths)	Now Patent
Injury	17	5	4	8
Congenital abnormality	12	0	0	12
Aneurysm or A-V fistula	85	19	16	50
Obliterative disease ..	109	39	6	64
Malignancy	5	1	2	2

points in choosing patients for this procedure are the size of the thrombosed segment and the state of the vessel wall proximal and distal to the occlusion, but, as the tables show, with careful selection the results have been very good. In our hands autogenous vein grafts have given disappointing results in patients with atherosclerosis. The tables show that homologous arteries have been satisfactory, and most of the thromboses in this group have been in patients with obliterative disease of the femoral and popliteal arteries; but the maintenance of an artery bank is by no means easy, and so we use a plastic prosthesis, either of plastic cloth or of polyvinyl alcohol sponge, for the reconstruction of the aorta and iliac arteries.

Anticoagulants

We use anticoagulants locally during the operation, and then from the third or fourth post-operative day as a long-term measure in patients with obliterative arterial disease. The idea is that these patients are likely to thrombose their arteries, either the one which has been reconstructed or another such as the coronary. Long-term anticoagulant therapy possibly reduces the incidence of this. Since 1952 we have kept many of our patients on phenindione (" dindevan ") in sufficient dosage to prolong the prothrombin time to just less than twice the patient's control level. It has caused little trouble beyond the need for regular control, and we now do not even stop the drug for such procedures as another surgical operation. With the prothrombin time at this level one can operate and fail to notice any change in the patient's bleeding. The value of this measure is still unproved.

Conclusion

Our follow-up shows that with careful selection the results of direct surgery in the treatment of obliterative arterial disease can be good. They are best in patients with occlusions of the aorta and iliac arteries and they are most gratifying in patients with gangrene of the toes and feet, cerebral symptoms due to partial internal carotid occlusion, or hypertension. Good results also follow the reconstruction of the femoro-popliteal artery in patients with intermittent claudication, but here selection is particularly important. In my view the by-pass type of operation is the best procedure for occlusions of this vessel, but its reintroduction has not widened the indications for surgery in patients with this general disease, unless the reason for operating is gangrene or rest pain.

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SOME DELAYED COMPLICATIONS OF INOCULATION

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For several years we have been aware of a number of curious disturbances which may occur during the first or second week after inoculation or vaccination. This paper is based upon a large number of clinical observations; no attempt is made to offer a detailed explanation of these disturbances, but rather to consider in what way they fit into the disease pattern of other syndromes and what is their long-term significance.

It has long been known that reactions could follow various inoculation procedures, and such reactions have usually been considered under " immediate reactions," as the delayed " serum sickness " type of reaction, or as anaphylactic reactions. We have not been particularly concerned with immediate reactions and have not met with any true anaphylactic reactions, but in the group of conditions related to serum sickness we have found the greatest variety of disease syndromes.

Present Investigation

With few exceptions, our observations were made upon young healthy adult recruits between the ages of 18 and 20. Within the first few weeks in the Service these recruits received various inoculations and all were vaccinated. As a rule, the first T.A.B.T. injection was given at the same time as the vaccination, and most of our observations were made in the period one to two weeks after this double procedure. A second T.A.B.T. injection was given six weeks after the first, following which only occasional reactions were seen. This can be attributed to various factors, but chiefly to the fact that those who reacted to the first injection were not usually subjected to a second, while those who did

not react to a first injection rarely experienced trouble with injections given subsequently. Isolated cases have occurred after other procedures, and are mentioned later.

A large number of recruits pass through the region in which our group of four hospitals is situated, and approximately 200,000 have been inoculated and vaccinated during the past few years. We therefore had an excellent opportunity of studying a number of relatively rare occurrences in addition to the more frequent and minor disturbances. We have no accurate means of determining the actual incidence of major delayed reactions, but can give a rough estimate of some 0.25 to 0.3% of all those inoculated.

The delayed reactions usually occurred some seven to ten days after inoculation and, as already stated, corresponded approximately to the serum-sickness group. It is interesting to note that the great majority of delayed reactors experienced no immediate local reaction; and conversely, those who suffered immediate reaction did not have these delayed disturbances. The delayed reactions appear to affect chiefly the joints and the reticulo-endothelial system, though other tissues and systems may become involved.

No major neurological sequelae of the type described by Miller and Stanton (1954) were noted to follow inoculation. However, a number of patients developed headaches, meningism, and even stupor as a transitory symptom-complex, associated with the appearance of a few lymphocytes and a slight rise in protein in the cerebrospinal fluid. These cases were usually of too short duration (24–48 hours) to allow of detailed investigation, and none, so far as we know, has subsequently developed neurological trouble.

Very occasionally the reaction seems to have started off an irreversible cycle of events leading to the appearance of a syndrome resembling the collagen disorders.

Arthropathies

Such a wide variation in these joint manifestations occurred that to present a typical case would be misleading. A single large joint may be swollen and painful; a number of joints may be involved in succession; or there may be stiffness and pain only, without obvious swelling. Marked constitutional upset with high fever, sweating, tachycardia, and the like may be present or there may be little or no general upset.

Joint symptoms may subside rapidly and spontaneously or persist for long periods and respond to treatment with difficulty. In many cases it has proved difficult or impossible, on clinical grounds, to differentiate a delayed allergic arthropathy from a "rheumatic fever"; similarly, syndromes resembling acute rheumatoid arthritis and acute rheumatic carditis have followed an inoculation reaction. It would appear to be of great importance to establish a connexion between these artificially induced syndromes and those which occur spontaneously; for their differentiation is in some cases difficult because the disease process is identical.

So far as the arthropathies are concerned, the clinical differentiation is usually a matter of degree; thus, in typical "acute rheumatic fever" in this age group the E.S.R. is usually higher, the joint symptoms are more severe, and the constitutional disturbance is greater than in the allergic arthropathies. In many cases, however, these extremes are not present and there are no satisfactory criteria other than the history of recent inoculation. The early therapeutic trial of salicylates is not to be recommended. Whether they are used or not, the symptoms may subside rapidly; in the case of the allergic reactions because of spontaneous remission, and in the rheumatic fevers because of the specific therapeutic effect. Thus, if the patient be rendered symptomless at too early a date the whole picture becomes obscure and it is never entirely clear what the original disease was. This, of course, is of tremendous long-term significance to the patient, for a past history of rheumatic fever might be held against him medically for the rest of his life, whereas a transient allergic arthropathy would usually be entirely disregarded.

The picture is made more confusing by the apparent risk of precipitating a "true rheumatic fever" in patients who have a history of rheumatic fever in childhood or who give a strong family history of rheumatic disorders. We have in many cases noted a history of joint pains in childhood, but such a history must be accepted with caution, for it is quite possible that some of these patients were experiencing an allergic arthropathy from some other antigen. The risk of inducing an irreversible rheumatic syndrome following T.A.B.T. inoculation is greatly increased when there is a strong constitutional tendency to such trouble; therefore great care should be taken in the administration of any allergy-provoking substances in such cases.

We have seen several cases in which an apparently allergic syndrome followed ten days after inoculation and developed into a typical acute rheumatoid picture, although starting with just the same large-joint involvement as any rheumatic fever. In one such case, of great severity, spindling in the fingers and wasting of the small muscles of the hand developed, and nodules were noted in the limbs. Biopsy of the latter proved them to be recent rheumatic nodules. This patient responded only to cortisone, rapidly and dramatically improving to an apparently complete "cure," and did not relapse after treatment was stopped. He has remained well during the subsequent few months that we have seen him. In his case there had been no previous rheumatic trouble, but his mother had suffered from a severe rheumatoid arthritis.

We originally intended to regard any patient who developed a carditis as a case of true rheumatic fever, but we were forced to change our view up to a point, because several cases developed cardiac involvement, confirmed by E.C.G., in the course of a febrile rheumatic illness occurring in the second week after inoculation. In two such instances an aortic leak was heard during the course of the illness, though no clinical evidence of valvular damage remained after recovery. Cortisone was again found to be effective when salicylates had failed to control the illness. In three other cases originally regarded as simple allergic arthropathies a transient heart-block was noted, and two of them showed a Wenckebach phenomenon.

Those with monarticular lesions may be referred to hospital as suffering from a traumatic or other orthopaedic condition. It is interesting to note that trauma may, in fact, play a part in the appearance of a delayed joint reaction, just as it may in other rheumatic or gouty conditions, whether the trauma be old or recent.

Collagen Disorders

We have so far commented chiefly upon the arthropathies, these forming the group most often seen. However, at least one case developed a generalized "collagen disorder" strongly suggestive of periarteritis nodosa, though histological proof was lacking. This patient was admitted seven days after vaccination and T.A.B.T. inoculation; he had a gross purpuric eruption over the ankles and lower limbs, and there was swelling of the ankle- and knee-joints. He had a high swinging fever and appeared to be very ill; he developed a number of curious necrotic skin lesions, and later a perforation of the nasal septum about a quarter of an inch (6 mm.) in diameter. No evidence of septicaemia could be obtained from a blood culture or by other means, and none of the skin lesions became infected. There was marked albuminuria with microscopic haematuria and some elevation of the blood pressure. During the first few days no specific therapy was given, but when it became apparent that the condition would not spontaneously subside salicylates were administered in full dosage, and, as these had proved ineffective in doses of 240 gr. (16 g.) a day, cortisone was given, with immediate and lasting effect. There was no relapse, and the patient has remained well, though there was slight residual albuminuria.

Reticulo-endothelial Disturbances

Splenic enlargement was noted so often in subjects who had received T.A.B.T. and vaccination that it is now regarded as a common finding in the few weeks subsequent to inoculation. It may appear without any other evidence of a delayed reaction, and sometimes occurred in association with slight enlargement of the liver, and occasionally with a more generalized lymph-node enlargement. Two or three cases were seen with a mild transient jaundice occurring ten to fourteen days after inoculation, but there was no evidence of haemolysis to account for the jaundice. Another occasional finding was abdominal pain, particularly in the right iliac fossa, which may well be almost indistinguishable from acute appendicitis. A number of such patients were operated on, and the only findings were enlarged ileo-caecal lymph nodes which histologically showed a non-specific inflammatory reaction. These various findings in the spleen, liver, and abdominal glands all suggest a reticulo-endothelial disturbance, and one would therefore expect to find bone-marrow and probably peripheral blood changes in addition. This, in fact, is so. Many bone-marrow smears were examined, and frequently a slight preponderance of reticulum cells was present. In peripheral blood there was often an unexplained increase in abnormal mononuclear cells in the seven to ten days after inoculation, whether or not the patient had had a reaction.

Disturbances associated with purpura were a most important group. Twenty-two cases were studied in detail, and, in addition, large numbers of transient mild purpuric eruptions were seen. The connexion between these cases following inoculation and the syndrome of "idiopathic purpura" seems to us to be extremely close, and this clinical impression is substantiated by much previous published work on acute vascular purpura. Thus Whitby and Britton (1953) stated: "The aetiology [of acute vascular purpura] is ill-understood, but there is evidence to suggest that the acute vascular purpura may be the result of an immunological disturbance affecting the small blood vessels throughout the body."

In the anaphylactoid group of purpuras the process is regarded as immuno-allergic, affecting the epithelium of the blood vessels, joints, intestinal tract, and renal glomeruli; and relapse in the so-called essential thrombocytopenic purpura is thought by many to be of a similar nature.

Tocantins (1936) showed that platelets are antigenic and that they are antigenically similar to capillary endothelium. Clark and Jacobs (1950) prepared an antiserum from vascular endothelium, and after injection haemorrhages into the skin and internal organs were seen which did not cause any reduction in the platelets.

Whitby and Britton (1953) have summarized existing knowledge by suggesting that: "In principle, the antigen, an infection, a drug, or a toxin for example, may be regarded as forming a complex with capillary endothelium or platelets, thereby initiating active immunization. The resulting antibodies may have a potentiality for damaging endothelium or destroying platelets, or both. There is little doubt that many cases, at one time thought to be essential thrombocytopenia, have in fact been immuno-allergic vascular phenomena arising from the sensitization of some foreign or noxious substance."

Many of our cases of purpuric eruptions following inoculation were severe and bleeding occurred into the skin, into the bowel, and into the genito-urinary tract.

Typical Cases

The findings in some typical cases are here briefly described.

A youth of 18 complained of swollen, painful ankles ten days after T.A.B.T. and vaccination. Both ankles were grossly swollen, tender, and painful, and a petechial rash was present over the lower limbs. Hess's test was strongly positive. Blood findings: haemoglobin, 12.4 g./100 ml.; P.C.V., 39%; E.S.R., 87 mm. in one hour; W.B.C., 10,200 per c.mm.; platelets, 350,000 per c.mm.; bleeding-time, clotting-time, blood films, and marrow films, normal. After four days the swelling and rash subsided and within four to five weeks the E.S.R. and haemoglobin had resumed normal levels and the patient was entirely symptomless.

In the following case an apparently pre-existent bleeding tendency was brought to light by inoculation and produced a severe episode.

A girl of 18 had a widespread and well-marked petechial rash ten days after T.A.B.T. inoculation; she gave a history of always bruising extremely easily and having had repeated small epistaxes. The skin rash became confluent in parts to form ecchymoses, and blood was found in the urine and stools. The liver and spleen were not palpable. Blood findings: bleeding-time, 30 minutes; clotting-time, 6 minutes; platelets, under 10,000 per c.mm. on several estimations; E.S.R., 18 mm. in one hour; W.B.C., 8,000 per c.mm. (polymorphs 56%, lymphocytes 40%, monocytes 2%, eosinophils 2%); sternal marrow, hyperplastic with considerable normoblastic hyperplasia; megakaryocytes, normal in appearance and number. After her admission the next menstrual period was excessive and persisted for ten days. There had been no previous menorrhagia. After six weeks the rash had partly subsided, but she continued to produce fresh crops of petechiae and the platelets were still under 10,000 per c.mm. In view of the age and sex of the patient, splenectomy was advised and undertaken by Mr. Simmons at the Manchester Royal Infirmary. The post-operative period was uneventful and there has been no relapse.

From time to time patients were seen with a symptom-complex closely resembling a Henoch–Schönlein syndrome. The following is an example.

A male patient was admitted with a well-marked purpuric rash limited to the legs below the knee-joints and associated with swollen and tender ankle-joints. On the second day he experienced colicky central abdominal pain, accompanied by the passage of bright-red blood in the stools and frank haematuria. The blood and marrow findings were completely normal. The condition resolved spontaneously, and within two to three weeks had entirely subsided.

Discussion

We have described a few examples of the types of purpura seen following T.A.B.T. injections. As a rule the petechial rash is limited to the lower limbs and there is swelling in or around the ankle-joint, but usually this is not very painful. The blood findings are often negative, except for a transitory fall in haemoglobin and a rise in the E.S.R., and these minimal blood findings are characteristic of the allergic purpura group.

In the case of the girl who had thrombocytopenia there seems little doubt that the acute relapse was related or entirely due to an immuno-allergic vascular phenomenon arising from sensitization to her inoculation. We believe that this case of thrombocytopenia provides some support to the contention that many of the so-called acute essential thrombocytopenias have, in fact, been immuno-allergic phenomena arising from sensitization to some foreign substance. In this respect we should compare that case with the production of an allergic arthritis in a patient who has previously had a rheumatic disorder and who therefore presumably has a rheumatic diathesis.

The question of the aetiology of rheumatic syndromes as a whole is obviously relevant to this discussion. We make no attempt to review accepted theories except to note that the most widely held view is that acute rheumatic fever is almost certainly due to an allergic reaction to streptococcal infection. We wonder whether exactly the same process, but on a much less severe scale, may not have occurred in the cases we saw. Obviously, where a streptococcal infection is present there is a constant source of antigen to provide a continuous allergic process, and this would be expected to be far more damaging than one isolated injection of antigen. It seems to us that in those cases where the patient has an extreme degree of sensitivity, or where there is a strong family background of rheumatism or a past history of rheumatic disorder, one isolated injection of antigen is

sufficient to set up a continuous clinical syndrome which is indistinguishable from that occurring "naturally."

The experimental work of Rich (1945) is of special interest. He demonstrated changes in cardiac muscle and skin tissues seemingly identical to those of rheumatic fever when repeated injections of antigenic horse serum were given. However, it has not been possible to reproduce the whole clinical syndrome of a self-perpetuating rheumatic fever syndrome by these or any other means (Holbrook, 1953). We believe that under certain circumstances such a syndrome very occasionally follows inoculation procedures.

Whilst it is noted that the majority of delayed reactions of all types have followed a combined T.A.B.T. and vaccination procedure, similar disturbances have often been seen after either has been given separately. The reactions to vaccination are too well known to require description, but as these generally occur after about the same time interval—that is, seven to ten days—many of the cases have presented a rather confused pattern owing to the fever and malaise from the vaccination becoming superimposed upon the allergic reaction. In point of fact, it is quite possible that many of the delayed symptoms from vaccination are actually allergic.

A further clinical observation, though not statistically substantiated, is that infective conditions of all kinds, including upper respiratory infections, segmental pneumonias, and skin and tissue infections, are more common during the seven to ten days following inoculation, and this may help to make recognition of an underlying cause rather difficult. A possible explanation of this observation is that all the immunological processes are disturbed at this time, giving rise to a general lowering of resistance to infection.

We have, so far, mentioned only T.A.B.T. and vaccination reactions, but we do not believe that these are in any way due to specific antigens; it is merely that we have been able to observe so many delayed reactions because of the enormous scale of the procedures. We have seen occasional rheumatic syndromes after Mantoux-testing and also during the course of a delayed pulmonary reaction to lipiodol bronchography. It is interesting to note, in this connexion, that one of us has, in fact, suffered both a delayed pulmonary reaction to lipiodol (Roberston and Morle, 1951) and also a delayed allergic arthropathy to a Mantoux test.

Summary

Clinical observations have been made upon the reactions occurring one to two weeks after T.A.B.T. injection and vaccination and certain other procedures. These may involve the joints, closely resembling acute rheumatic fever or acute rheumatoid arthritis. There may actually be an apparent rheumatic carditis. A syndrome resembling periarteritis nodosa following inoculation is described. Various purpuric manifestations, identical with the so-called immuno-allergic vascular purpuras, are discussed. Changes in the reticulo-endothelial system, including spleen, liver, lymph nodes, and bone marrow, are described.

The significance of these delayed reactions is discussed, especially in connexion with the aetiology of the rheumatic and purpuric disorders.

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QUANTITATIVE EXAMINATION OF BONE MARROW IN GUINEA-PIGS AFTER GAMMA IRRADIATION

A PRELIMINARY NOTE

BY

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Previous work on the quantitative study of the bone marrow of the guinea-pig has shown that there are three main cell groups—myeloid, erythroid, and lymphocytic. The lymphocytes were found to constitute an unexpectedly high proportion of the total nucleated cells (Harris *et al.*, 1954). In a recent series of 10 normal animals (Harris and Harris, 1956), out of a total nucleated count of 1,814,000 (±86,000) per c.mm. marrow there were about 430,000 (±42,000) lymphocytes, or just under 25%, a figure which agrees closely with that of Sawitsky and Meyer (1948). So large a number of lymphocytes cannot possibly be due to contamination of the marrow with blood (Yoffey, 1954).

The question at once arises whether the presence of all these lymphocytes in the marrow is a purely incidental phenomenon, or whether they may function as stem cells for the myeloid and erythroid series. On this, perhaps the most controversial of all problems in haematology, it was felt that a quantitative analysis of marrow changes in conditions of severe marrow damage and subsequent regeneration should yield more precise information than has hitherto been available. If lymphocytes really can function as stem cells, then under these circumstances the course of the recovery should be associated with significant changes in the marrow lymphocytes.

Despite the very extensive investigations which have already been made upon the effect of irradiation on the haemopoietic system, some initial experiments indicated that a quantitative technique would make possible a much more precise analysis of the changes occurring. This communication presents the results of further investigations along these lines.

Material and Method

The dose of irradiation chosen was such that it produced marked changes in the haemopoietic organs, but at the same time involved as small a mortality rate as possible. For the guinea-pig, the minimum lethal dose for 50% of animals within 30 days of irradiation is said to be approximately 200–250 r (Ellinger, 1945). A dose of 150–170 r was ultimately selected as the dose that best fulfilled the above requirements. Marked changes in the bone marrow have occurred when using this dose, and in addition distinct cellular simplification has been achieved at a certain stage in recovery.

All animals used were males of a standard strain (Dunklin-Hartley) and about 400 g. in weight at the time of irradiation. A preliminary blood count was made, using blood obtained from an ear vein. Total R.B.C., W.B.C., and reticulocyte counts were made, together with a differential white cell count and haemoglobin estimation. An interval of about 10 days then elapsed, after which the animal was irradiated. Total-body irradiation was given, a cobalt-60 unit being the source of irradiation. It was performed under general anaesthesia (intraperitoneal pentobarbitone sodium) to ensure uniform dosage.