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INTRAVENOUS ARSENIC IN TREATMENT OF ANGINOUS FORMS OF GLANDULAR FEVER

WITH NOTES ON CLINICAL AND LABORATORY DIAGNOSIS

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Severe inflammation of the tonsils and fauces in glandular fever may cause serious illness which may even threaten life. It is the purpose of this paper to report the remarkably beneficial effect produced by intravenous injection of arsenic in six examples of this anginous form of glandular fever which have been met with at intervals over a period of 18 months. In general, the treatment of glandular fever is solely palliative, but for this special anginous group arsenic not only produces conspicuous and rapid improvement but may on occasion appear to be life-saving. Case histories illustrating the results of such treatment are recounted, and discussions on other methods of treatment and on the diagnosis and aetiology of the condition follow. For purposes of illustration reference is made to further cases of glandular fever seen during the same period, though not treated with arsenic.

Case I

An officer, aged 21, noticed between June 4 and 8, 1942, that he was sweating at night. This increased during the following week, but he still felt well during the daytime. On June 10 he complained

TABLE I.—The Haematological Findings in the Anginous Cases I-VIII

Case	Date	Days from Onset of First Symptoms	Paul-Bunnell Titre	White Cells per c.mm.					
				Total W.B.C.	Neutrophils	Eosinophils	Basophils	Lymphocytes	Mono-cytes
I	16/6/42	10	—	24,600	9,550	40	50	13,100	1,850
	17/6/42	11	10,240	25,800	12,800	200	200	10,300	2,300
	9/7/42	33	10,240	7,400	3,200	—	—	3,700	500
	1/9/42	87	nil	7,500	3,800	70	40	3,350	240
II	26/8/42	9	80	5,200	2,420	20	40	2,100	620
	27/8/42	10	1,280	15,500	6,400	—	100	8,200	800
	26/9/42	40	320	7,500	2,200	20	80	4,600	700
III	2/9/42	78	640	20,600	6,600	50	50	11,350	2,550
IV	20/3/43	9	—	16,000	2,900	150	150	12,800	—
	22/3/43	11	640	12,200	1,200	—	—	4,050	6,950
	28/3/43	17	1,280	6,200	1,050	310	250	4,160	430
V	17/3/43	14	80	5,300	2,760	—	—	1,060	1,480
	23/3/43	22	160	—	—	—	—	—	—
VI	2/6/43	15	640	10,800	3,560	—	108	4,968	2,160
VII	—	12	640	38,000	8,360	100	90	27,550	1,900
	—	33	1,280	4,600	1,290	20	—	3,100	180
VIII	—	19	5,120	21,500	3,750	400	170	16,450	730

NOTES.—The Paul-Bunnell tests were done by the method of Barrett (1941). For the most part, lymphocytes and monocytes appeared to be fully mature. In some films a small proportion of the lymphocytes showed evidence of immaturity of the slight degree quite commonly seen in lymphocytosis of varied origin. Occasional immature monocytes were also seen. Cells with vacuolated cytoplasm or with irregular or deeply indented nuclei were not seen. The majority of the lymphocytes were of the small or medium-sized variety.

of sore throat for the first time, and during the next 4 days his neck became swollen and stiff. Dysphagia developed, and became so severe that he could swallow liquids only. On June 15 he was admitted to a military hospital. On examination he looked ill and toxic. Cervical glands of the anterior and posterior triangles on both sides were grossly enlarged, giving a bull-neck appearance. Both tonsils were enlarged and inflamed and covered with purulent-looking exudate. A throat swab at this time showed only a few spirochaetes, but no fusiform bacilli or pus cells; culture for *C. diphtheriae* was negative, but there was a moderate growth of a haemolytic streptococcus. 48,000 units of diphtheria antitoxin were given on admission. During the next 48 hours the condition of the patient became grave. There was considerable bleeding from the tonsils. The spleen and axillary glands became palpable. All local and symptomatic treatment was without avail. The result of blood counts on June 16 and 17 are shown in Table I, and the Paul-Bunnell titres on the latter day confirmed the diagnosis. The Kahn test and aerobic blood culture were negative. On June 17 administration of sulphapyridine (10 g. in the first 24 hours) was begun, and at the same time novarsenobillon (M. and B.) 0.45 g. was given intravenously. In 12 hours dramatic improvement was evident, with cessation of tonsillar bleeding and an abrupt fall in temperature and pulse. Everyone who saw the patient was impressed by the rapid transition from an exceedingly grave state to commencing convalescence. Uneventful complete recovery followed.

Case II

An officer, aged 22, noticed stiffness of the neck and shoulders on Aug. 17, 1942, followed by sore throat and shivering on Aug. 21. He was admitted to a military hospital on Aug. 22. On examination there were glandular enlargements in both posterior triangles of the neck and in the right axilla. Temperature 101.4° F. The tonsils were greatly enlarged and acutely inflamed. A throat swab showed no Vincent's organisms; culture for *C. diphtheriae* was negative and there was an almost pure growth of a haemolytic streptococcus. During the following week intermittent pyrexia to 104° continued, the tonsillar swelling with ulceration and exudate increased, further glandular swellings appeared, and on Aug. 29 the spleen was palpable for the first time. Sulphanilamide therapy was started on Aug. 25, a total of 20 g. being given in 72 hours. A blood count on Aug. 26 showed only an absolute neutropenia; but a Paul-Bunnell titre of 1 in 80 was suggestive, and prompted repeat examinations on the following day, when the count and a titre of 1 in 1,280 established the diagnosis of glandular fever. The Kahn test was negative on Aug. 26. Slight albuminuria was present throughout, and for this reason the administration of arsenic was not at first considered advisable. During the next 10 days the temperature tended to fall and there was a slight improvement in the general condition, but the appearance of the tonsils and the glandular and splenic enlargements were unchanged. On Sept. 6 novarsenobillon 0.15 g. was given intravenously. The small dose was chosen on account of the albuminuria. On the next day the temperature and pulse rate had fallen to normal, the albuminuria ceased, and there was conspicuous subjective improvement. Uneventful and rapid full recovery followed without further injections or local treatment.

Case III

An officer, aged 20, was admitted to a civilian hospital in mid-June, 1942, with "septic throat." A blood count at that time showed W.B.C. 10,000 per c.mm., with neutrophils 19%, lymphocytes 66%, monocytes 15%. A Paul-Bunnell test was not done, and we have no information regarding enlargement of lymph glands or spleen, but the subsequent history suggests that this initial illness was glandular fever. The patient returned to duty at the end of July, though not feeling really well. In mid-August he again complained of sore throat with dysphagia and of neck stiffness and sweating. He came under our observation on Aug. 31, when he was admitted to a military hospital. On examination he did not appear acutely ill. Temperature 100° F. There were groups of enlarged discrete glands in the anterior and posterior triangles of the neck on both sides and in the axillae and groins. The spleen was not palpable at any time. The right tonsil was greatly enlarged and ulcerated, with blood and mucus on its surface. This swelling was so pronounced as to immobilize the soft palate on that side, and swallowing provoked nasal regurgitation of fluids and tonsillar bleeding. A throat swab showed no Vincent's organisms; culture for *C. diphtheriae* was negative and there was only a scanty growth of a haemolytic streptococcus. During the next few days the ulceration of the tonsil developed and deepened and the pyrexia continued though the general condition remained much the same. A blood count and a Paul-Bunnell test on Sept. 3 established the diagnosis of glandular fever. No benefit had followed local and symptomatic remedies, and on Sept. 4 novarsenobillon 0.15 g. was given intravenously. On the following day the temperature had fallen to normal and the tonsillar swelling had diminished. After a further 24 hours the tonsillar swelling and exudate had completely disappeared, and rapid convalescence with full recovery followed. No sulphonamide drug was given in this case.

Case IV

A gunner, aged 22, developed sore throat and swelling in the neck on March 12, 1943. He was admitted to a military hospital on the same day. On examination the tonsils were considerably enlarged and the fauces swollen and red. There was no exudate. Large glands were palpable below the left angle of the jaw. The next day there was a membrane on the left tonsil. 32,000 units of diphtheria antitoxin were given and at the same time administration of sulphapyridine was started, a total of 19 g. being given during the next few days, during which the local throat condition remained unchanged and there was continued pyrexia. On admission a throat swab showed large numbers of Vincent's organisms; culture for *C. diphtheriae* was negative. On March 17, when sulphapyridine was discontinued, sulpharsphenamine 0.45 g. was given intravenously. On the following day the temperature was normal and it remained so, rapid subsidence of the throat condition taking place. On March 19 the spleen was palpable and there was an enlargement of axillary, inguinal, and epitrochlear glands. Facilities for further laboratory investigations now became available, and blood examinations on March 20 and 22, together with a Paul-Bunnell test on the latter day, confirmed the diagnosis of glandular fever.

Case V

An officer, aged 28, developed sore throat with swelling of glands on both sides of the neck on March 4, 1943. After 48 hours' treatment with sulphapyridine and local applications the condition appeared to subside completely. It recurred on March 15, and he was admitted to a military hospital on the 17th. On examination he looked ill. Temperature 100.5° F. There were discrete enlarged glands in both posterior triangles, especially in the suboccipital region, and also in the anterior triangles, axillae, and groins. The spleen was not felt. Both tonsils were greatly enlarged, almost meeting in the midline, and showed ulceration with yellow sloughs on their medial aspects. A throat swab showed no Vincent's organisms; cultures for *C. diphtheriae* and for haemolytic streptococci were negative. The blood picture was suggestive of glandular fever, but a Paul-Bunnell titre of 1 in 80 was inconclusive. Progressive deterioration in the general condition followed during the next few days, with remittent pyrexia to 103° F., severe dysphagia, and bleeding from the throat. On March 20 novarsenobillon 0.3 g. was given intravenously. By the same evening there was considerable subjective improvement, and after a further 24 hours the swelling of neck and throat and the tonsillar bleeding had greatly diminished. The spleen was palpable on March 21. During the next few days swelling of the throat further diminished and the patient was able to eat soft food. The sloughs on the tonsils persisted, with further profuse bleeding on March 23, and as remittent pyrexia also continued a further 0.3 g. of novarsenobillon was given intravenously on March 26. On March 30 the throat was completely normal in appearance and the spleen and glands in axillae and groins were no longer palpable, and only a few glands could be felt in the neck. The temperature fell by lysis after the second injection and remained normal after April 1. On March 23 a blood count

showed a pronounced mononucleosis and a Paul-Bunnell test a rise in titre to 1 in 160.

Case VI

An officer, aged 37, was admitted to a military hospital on June 1, 1943, complaining of weakness, general malaise, and sweating. About a fortnight previously he had had coryza, with left-sided sore throat and dysphagia. On examination he was febrile (temperature 99°-100° F.) and the throat showed an enlarged and inflamed left tonsil: there was an ulcer with a sloughy base. There were only one or two small glands in the posterior triangles, but enlarged groups of glands were present in both axillae. The spleen was easily felt, and was firm. A papular rash was present over the trunk and buttocks. A throat swab showed many Vincent's organisms. Cultures for *C. diphtheriae* and for haemolytic streptococci were negative. On June 2 the blood count and a Paul-Bunnell titre of 1 in 640 established the diagnosis of glandular fever. A blood count showed 4.5 million red cells, 100% Hb, and 10,800 white cells, of which 33% were polymorphs, 46% lymphocytes, 20% monocytes, and 1% basophils. The Paul-Bunnell test was positive at 1 in 640. On June 4 the glands in the neck were larger, fever was persisting, and the splenomegaly and the rash were unchanged. Intravenous novarsenobillon 0.3 g. was given at noon: within 6 hours there was a diminution of pain and dysphagia, and on the next day the temperature dropped to normal. During the succeeding days the throat healed, the rash faded, and the spleen became smaller. The patient was discharged from hospital on June 14.

Cases VII and VIII

These were mild anginous cases which were under observation concurrently with the first three. They presented no exceptional clinical features and did not receive treatment by arsenic. Accordingly no further description is given, but their haematological findings have been tabulated for purposes of illustration.

Local Treatment of Very Severe Throat Infections

The throat lesions of the anginous type of glandular fever may be among the most severe that can be encountered. Not only may there be massive oedema accompanying the acute inflammation of the tonsils and neighbouring structures, but these may become extensively ulcerated; considerable bleeding may ensue. Bronchopneumonia may develop and bring about a fatal issue. Severe dysphagia often occurs, militating against the full fluid intake so desirable in acute febrile illnesses. In addition, if the lesion is unilateral it may cause asymmetrical dysfunction of the soft palate with resulting regurgitation of fluids through the nose. In these circumstances local treatment becomes a matter of concern.

Scrupulous attention to cleansing of the throat, teeth, and gums was the first essential. No benefit was to be obtained from the usual gargles, such as eusol 1 in 4 solution or Milton fluid, nor from Mandl's paint. It seemed that swabbing with hydrogen peroxide (10 vols.) was the most effective local treatment in the acute stage, while applications of hot cotton-wool or of kaolin eased the pain in the neck. After the very acute stage, and for residual ulceration of the tonsils, a paint made up of equal parts of liq. arsenicalis and tinct. ipecacuanhae was the most effective local application. In throat lesions of this severe order fluids had to be given neither hot nor very cold. In none of our cases was the reduction of fluid intake through dysphagia sufficiently prolonged to necessitate rectal or intravenous infusions. It was important to avoid any medicine containing piquant flavouring agents such as peppermint or ginger. Irritant solutions had to be avoided, and the well-known Army "three fifteens," containing sod. brom. 15 gr., chlor. hydras 15 gr., and tinct. opii 15 m., could not be employed. Morphine 1/4 gr. by injection had at times to be used to induce sleep.

The Use of Intravenous Arsenic

It is evident from the foregoing histories that arsenic was employed in Case I with the aim of countering a Vincent's infection which was believed to be complicating anginous glandular fever. The seeming beneficial effect of the drug in this case prompted its experimental use in Cases II and III even though no Vincent's organisms had been found in the throats. In both, rapid subjective and clinical improvement resulted, and substantially similar results followed the same therapy in the remaining cases. In view of the small number of cases treated in this way, and in the absence of any controlled

observations, impressions alone and not definite conclusions are the result. We are aware that in many instances a termination of the condition by crisis does occur, and that there is great variation in the severity and duration of illness in different cases. But in all the cases described here the immediate improvement in the patient's local and general condition, and the marked subjective improvement upon which all the patients themselves commented, do render it difficult to escape the conclusion that the arsenic was greatly beneficial. We find ourselves unable to offer any explanation of its mode of action, for the apparent effect did not extend to other manifestations—e.g., glands and spleen continued to enlarge in some cases, and it is interesting to note that in Case IV the Paul-Bunnell titre continued to rise.

Observations on the Diagnosis of the Condition

The diagnosis of glandular fever is usually not difficult. The disease is suspected more often than it exists, but, in general, strong clinical indications are followed by haematological confirmation. Certain relevant points emerge from consideration of these cases.

1. *History*.—In nearly all cases of glandular fever the history reveals some days of malaise before the onset of the acute illness. It is not uncommon for a patient to mention a recent feverish illness, with or without sore throat, from which an incomplete recovery has been made—e.g., Cases III, V, and VI. Sweating is usually a conspicuous symptom, and may even be the patient's principal complaint.

2. *Glandular Enlargements*.—Posterior triangle glandular enlargements are suggestive in association with sore throat, but if there are no other glandular enlargements the diagnosis is not likely to be established. The natural reluctance to examine the axillae thoroughly in feverish patients should be set aside, since with considerable glandular enlargement here the diagnosis becomes much more probable. The glands in the groin are rarely of diagnostic help unless they are enlarged to a very considerable degree.

3. *Throat Inflammations*.—The suspicion of glandular fever should be aroused in any severe inflammation or ulceration of the fauces in which the findings on microscopical and bacteriological examination of swabs are insufficient to account for the condition—e.g., Cases I and III. Conversely, in some cases the bacteriological findings appear at first adequately to account for the condition of the throat and so obscure the diagnosis—e.g., Case II, in which a pure growth of haemolytic streptococci was obtained, and Case IV, in which large numbers of Vincent's organisms were found.

4. *Blood Cytology*.—Table I illustrates well the wide range of variation which may be met with in the total and differential leucocyte counts, and it is evident that no one diagnostic picture can be described. Further to illustrate the variations which may occur, a case of "glandular" type (Case A, Table II) seen subsequently in an adult showed 3,000 per c.mm. of lymphoblasts and monoblasts out of a total white cell count of 32,000 per c.mm.: at a subsequent count a week later these cells had completely disappeared. While in general some fairly marked departure from the normal is encountered, the blood picture may at first fail to suggest the possibility of glandular fever. It is well for the clinician to bear this in mind in the interpretation of blood counts on cases which are clinically suggestive. In these anginous cases the important feature was a departure from normal in a direction other than the absolute neutrophilia which one would expect in a severe septic throat. Such a finding should certainly prompt repeat counts to determine the maximum mononuclear cell increase.

5. *Paul-Bunnell Tests*.—Whatever may be the significance of the agglutinins for sheep erythrocytes which are developed in this disease, demonstration of their presence in appreciable titre is still an essential factor in diagnosis. Attention is drawn to the following features: (1) In cases seen by the 12th day or earlier a diagnostic titre of agglutinations had already been reached. The very high level of 1 in 10,240 on the 11th day in Case I and its maintenance after a further 22 days is particularly noteworthy. (2) Case II, showing a titre of 1 in 80 on the 9th day and 1 in 1,280 on the following day, illustrates the rapid rise which may occur and emphasizes that repeated estimations of titre may be necessary. (3) In general there was no correlation between the titre attained and the severity of the illness; but the fact that a rapid increase may occur in a short time probably renders this observation invalid in the absence of serial daily determinations. (4) The importance of the absorption tests with guinea-pig kidney extract and autoclaved ox erythrocytes is well illustrated by Case I. In this the final test on the 87th day of the disease gave an unabsorbed titre of 1 in 320, but the agglutinations were completely absorbed by ox-cell suspension and are not to be regarded as of glandular fever type; the titre is accordingly recorded as *nil*.

6. *Response to Therapy*.—Any beneficial action of sulphonamides in glandular fever is exceedingly doubtful, as indeed might be expected if the disease is in fact due to a virus. In this series Cases II and IV received such therapy with no improvement, and Kilham and Steigman (1942) record the same lack of response in five anginous cases. In any acute throat condition treated by sulphonamides without response the possibility of glandular fever should be borne in mind, especially in cases in which a presumably sulphonamide-sensitive organism is present in large numbers (e.g., Case II). In the Army over-seas, the possibility of faucial diphtheria, often presenting atypical features, is of course ever in mind and carefully excluded. Our claims for the beneficial action of arsenic in these severe anginous manifestations of glandular fever may be contested on the ground that they were in effect examples of Vincent's angina superimposed upon glandular fever and that the favourable course was but a substantiation of the merits of the conventional treatment of Vincent's infection. But only three of the cases showed microscopical evidence of Vincent's infection, and the response in the other cases was similar in kind and degree. This prompts the reflection that many cases diagnosed as Vincent's angina might on further investigation be revealed as cases of anginous glandular fever.

Changes in Bone Marrow

The neutropenia present in many of these cases prompted inquiry into changes in the bone marrow. Sternal puncture was accordingly performed on two cases of mild glandular type. The blood changes in one of these has been previously referred to. The differential counts on the marrow cells are recorded in Table II together with the results of white blood counts taken at the same time. (The classification of the cells has been condensed for the sake of brevity.)

Both marrow smears showed an approximately normal degree of cellularity. It is noteworthy that the highly abnormal blood picture in Case A is not reflected in the marrow. The somewhat high myeloblast count in both suggests a disturbance of granulopoiesis. That this is probably a maturation defect at the myeloblast level is indicated in Case B by the diminution in numbers of more mature myeloid cells—an observation which coincides with the marked blood neutropenia. The normal erythropoiesis is in accord with the customary absence of anaemia usual in these cases.

It is regretted that circumstances were unfavourable to the carrying out of sternal puncture on some of the severe anginous cases. The determination of the degree and level of the marrow defect in such cases would have been of great interest in view of their similarity to agranulocytic angina in some points. It may be noted, however, that the neutropenia in Case B was as pronounced as any met with in our anginous cases.

TABLE II.—*The Blood and Marrow Findings in Two Further Cases of Mild Glandular Type*

	Marrow		Blood		
	Case A	Case B		Per c.mm.	
				Case A	Case B
Segmented polymorphs	18.0	8.4	Total W.B.C. ..	32,000	17,000
Metamyelocytes ..	23.2	13.4	Neutrophils ..	5,250	1,200
Myelocytes ..	19.2	11.2	Lymphocytes ..	21,250	14,450
Premyelocytes ..	8.2	8.2	Monocytes ..	2,560	1,180
Myeloblasts ..	6.2	9.6	Lymphoblasts and monoblasts	2,940	170
Lymphocytes ..	13.0	15.2			
Monocytes ..	0.6	5.4			
Haemocytoblasts ..	0.4	2.2			
Erythroblasts ..	3.0	6.6			
Normoblasts ..	8.2	19.8			

Observations on the Aetiology of the Faucial Ulceration in These Cases

Glandular fever presents many diverse signs, and in general this may be ascribed to the great variation in the amount and situation of the lymphoid hyperplasia throughout the body. It is indeed remarkable that in a generalized septicæmic infection such as this, whose dominant feature is lymphoid hyperplasia, many areas of lymphoid tissue appear to escape relatively unaffected. There is a tendency to regard anginous glandular fever as a distinct type, whereas rather would it seem to be a fortuitous manifestation of a general infection depending upon the occurrence of a maximum degree of hyperplasia in the

lymphoid tissue of the fauces with subsequent ulceration of the overlying mucosa.

It has been seen that neutropenia of some degree was present in all our cases at some stage of the disease, and Kilham and Steigman (1942) report a similar finding. It has been suggested that this neutropenia bears a direct aetiological relationship to the occurrence of faucial ulceration—that the lesions are in fact of similar nature to those seen in agranulocytic angina. Against this view the following points may be mentioned: (1) The neutropenia is not confined to the anginous type of the disease. (2) In no case did it amount to the complete or nearly complete disappearance of neutrophils seen in agranulocytic angina. (3) Neutropenia of the same intensity as that seen in many of these cases—perhaps even a greater intensity—is observed in many conditions of which faucial ulceration is not a feature. (4) The stage of the disease at which it was observed in our cases varied greatly and in general could not be correlated with the condition of the throat: for example, Case I, one of the most severe, showed a neutrophilia during the worst phase, a moderate neutropenia appearing later; while in Case IV healing occurred despite the persistence of a severe neutropenia. (5) In agranulocytic angina there is evidence of long-continued neutropenia before the onset of faucial ulceration. The same may be the case in glandular fever, but in general the period of malaise before the faucial ulceration starts is relatively short, though it seems a more likely occurrence in the “double” or relapse type of illness seen in Cases II and V. If neutropenia does occur it no doubt facilitates the invasion of broken surfaces by secondary bacterial invaders, and so the initiation of a further degree of neutropenia by sulphonamides might adversely affect the outcome. Hence we consider that sulphonamide therapy is absolutely contraindicated in all cases of glandular fever, for a greater degree of neutropenia so induced may facilitate the development of the anginous form as the disease progresses. A possible example of this occurrence is Case V.

On the available evidence our conclusion is that neutropenia plays probably only a secondary part and is not in itself the cause of the ulceration. Further studies are needed for elucidation of this point. Blood and marrow studies during interim periods, such as were observed in Cases II and V, might yield information of interest.

Summary

Among patients with anginous forms of glandular fever are to be found some of the severest throat infections encountered in medical practice. Acute inflammation with purulent exudate, oedema, ulceration, haemorrhage, and mechanical interference with the action of the soft palate may severally be present.

Six patients suffering from anginous glandular fever were treated with intravenous arsenicals. Speedy and conspicuous benefit was obtained.

The haematological findings in these and other cases are tabulated and discussed. In cases seen before the 12th day a conclusive diagnostic titre of agglutinations had already been reached.

The general treatment and management of very severe throat infections are considered.

Diagnosis is reviewed briefly from the standpoints of history, glandular enlargement, throat inflammation, haematology, and response to drugs.

Neutropenia was present at some stage in each of our cases. Its significance is discussed. Since sulphonamides are apt to cause neutropenia they are contraindicated in this disease.

Our thanks are due to Major G. L. Robinson, R.A.M.C., for carrying out laboratory investigations in Cases IV, V, and VI.

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Kilham, L., and Steigman, A. J. (1942). *Lancet*, **2**, 452.
(It is regretted that the exigencies of overseas service have prevented fuller access to the literature.)

H. H. Clemens (*J. Pediat.*, 1945, **26**, 66) records his observations on 80 cases of exanthema subitum (roseola infantum), of which 42 were in boys and 38 in girls. Most occurred in February, March, April, and October. The disease is characterized by an abrupt onset, malaise, and termination in an afebrile exanthem. Fever, irritability, and slight enlargement of the lymphatic glands are typical in the eruptive stage. Complications are very rare. The blood shows relative leucopenia and neutropenia with lymphocytosis by the third day of disease.

POTENT ANTI-Rh AGGLUTININS DEVELOPED IN AN Rh-NEGATIVE FEMALE AFTER MULTIPLE TRANSFUSIONS OF Rh-POSITIVE BLOOD*

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In the case here reported iso-immunization to the Rh factor followed repeated blood transfusions and resulted in haemolytic reactions of varying degree and in the development of anti-Rh agglutinins of exceptionally high titre in the serum of the recipient. The recipient was Group O, as were all the donors. All ABO blood-grouping and cross-matching tests were performed in tubes (5 cm. by 1 cm.). In the cross-matching tests equal volumes (0.4 c.cm.) were used of serum, citrate-saline, and citrated cell suspensions of 0.5% strength in terms of cell sediment. Mixtures were stood five minutes and then centrifuged at 1,500 revs. per min. for two minutes. Readings were made with the naked eye after adequate agitation of tubes. Blood groups were always tested on cells and serum. In cross-matching tests the recipient's serum was tested against the donor's cells, and the donor's plasma against the recipient's cells. In Rh investigations the tube technique described below (on p. 586) was used.

Case History

An unmarried woman aged 47 sought medical advice in April, 1943, because of increasing lassitude and pain in shoulders and elbows. She had recently had a “chill.” On April 29 she had a severe bout of melaena and pain in her abdomen, left side of chest, and knees. There was no fever. The Widal reaction was negative. On the 30th she had a haemoptysis. Purpura now appeared on the limbs and trunk. On May 1 the blood count was: red cells, 1,552,000; platelets, 144,000; leucocytes 19,800. Haemoglobin 36%; coagulation time, 2½ minutes; bleeding time, 12 minutes. Her last menstrual period began on May 3, and lasted 16 days; the loss was profuse. The spleen was not palpable. Her previous medical history was unimportant. The patient had never had a blood transfusion and had never been pregnant. In spite of the platelet count a very tentative diagnosis of thrombocytopenic purpura was made. It was decided to give blood transfusions to raise the haemoglobin to a level high enough to permit of splenectomy. At this time the Rh group of the patient was not ascertained. Concentrated red-cell suspensions only were used in the 10 transfusions reported below. All transfusions were given at very slow drip rates. Blood older than eight days was not used. The standard mixture of donors' blood from which concentrated red-cell suspensions were prepared was: whole blood, 400 c.cm.; glucose, 20 c.cm. of 15% solution; and sodium citrate, 120 c.cm. of 2.5% solution. The sequence of events was as follows, dating from the first transfusion given on May 1.

1st Day.—First transfusion. Given 450 c.cm. (two donors). No febrile reaction. Later, one donor was found to be Rh+, but the other was never traced.

2nd Day.—Second transfusion. Given 450 c.cm. (two donors). No febrile reaction. Both donors later found to be Rh+. Cross-matching tests for the first two transfusions showed compatibility. Marked improvement followed these transfusions.

3rd Day.—The patient had a severe vaginal haemorrhage, but, despite this, was much better. On the 4th day the R.B.C. was 3,720,000 and the Hb 66%; next day the Hb had fallen to 60%.

6th Day.—Third transfusion. Red cells were prepared from two donors, both subsequently found to be Rh+. When 200 c.cm. had been given the patient had a rigor. Transfusion was promptly stopped. The temperature rose from 99 to 103° F. No improvement. On the 8th day the Hb had dropped to 46% and the R.B.C. to 2,480,000. On the 9th day the patient suffered from retinal haemorrhages. On the 11th day multiple ecchymoses appeared on the trunk and there was a profuse epistaxis. A specimen of blood

* This article came into our hands when the untimely death of one of the authors—Dr. G. L. Taylor—was announced.