such cases under antibiotic therapy, any tenderness or softening over the mastoid process should be regarded with suspicion. A profuse and persistent aural discharge is virtually pathognomonic of the spread of the infection to the mastoid cells. If a child develops such signs while under antibiotic treatment it would seem that immediate cortical mastoidectomy is indicated.

Perhaps the most striking characteristic of these children has been the similarity of the operative findings. In almost all cases there was evidence of infection spreading extensively through the mastoid cells. The cell system was occupied by a haemorrhagic granular process with frank granulations growing in many cases. Several showed a marked osteolytic character to the infection with dissolution of the mastoid cortex leaving a cavity occupied by indolent granulations. It was generally a simple matter to curette the soft chronically infected bone clear of disease.

The next point in the analysis of this series is the satisfactory result obtained. These children were discharged from hospital on an average of 12 to 18 days after operation. I have seen them all, except one recent case still in hospital at the time of writing, for follow-up two months after operation. They all have normal hearing and the tympanic membranes on the affected side are dry and clean.

Discussion

It should be stressed that all these patients were children. There would seem to be a strong case for referring all children with acute otitis media which has not resolved after antibiotic therapy for assessment with the view to surgery. Radiological investigation of the mastoid process is often helpful in those cases presenting minimal symptoms and signs of acute mastoiditis. When the infection has persisted for over 10 days there is almost always positive radiological evidence of its spread to the mastoid process.

The main interest in these cases has been the demonstration of this new variety of subacute mastoiditis arising out of unsatisfactory resolution of an acute mastoid infection. These cases may become increasingly common, and one should have this in mind where an acute middle-ear infection fails to respond adequately to antibiotics.

Surgery is highly advisable if these cases are to be treated successfully and their morbidity is to be minimized. It would seem that the persistence of such an infection may lead to chronic mastoiditis and eventually chronic suppuration in the middle ear, as well as to possible intracranial complications. This path of events should be avoided at all costs. As the Schwartze type of operation is a relatively simple procedure, its value in avoiding such a sequence of events is enormous.

The particular interest for the general practitioner should be an awareness of this problem. He should refer all acute middle-ear infections which have failed to respond after 10 days of adequate antibiotic therapy for consultant opinion. If the consultant is conscious of this problem, a timely cortical mastoidectomy will prevent a prolonged stay in hospital and the possibility of chronic middle-ear infection and deafness in the patient is diminished.

Summary

A series of 13 children in whom there was an inadequate response of acute mastoid infections to antibiotics is presented. A widespread subacute infection

was seen in nine of these cases. The uniformly satisfactory progress of these children after cortical mastoidectomy is shown. The necessity for careful assessment from a surgical viewpoint is made where acute otitis media in a child does not respond satisfactorily to antibiotic therapy.

I am indebted to Mr. Charles Gledhill for permission to do this work and for his encouragement and help in treating these cases.

MECHANISM AND SIGNIFICANCE OF ERYTHROCYTE SEDIMENTATION RATE

BY

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The earlier hypotheses on the causes of raised erythrocyte sedimentation rate require re-examination. The negative surface charge of the erythrocytes is not altered in bloods with a high sedimentation rate, nor are there always definite quantitative alterations in the distribution of the plasma protein fractions, and we have seen human plasmas with a normal distribution of the proteins which were associated with a raised sedimentation rate. Riva (1957) has already noted that a number of plasmas with a normal albumin/globulin ratio are associated with a high sedimentation rate, and vice versa. Thus an increase in fibrinogen or γ -globulin is only coincidental to a high sedimentation rate and not its cause. Fractionation of normal and high-sedimenting plasmas by means of ammonium sulphate precipitation or preparative paper electrophoresis has shown that the phenomenon is caused by specific proteins (Ruhensroth-Bauer, 1957, 1959; Ruhensroth-Bauer, Brittinger, Granzer, and Nass, 1960) (see Table).

By both methods protein fractions could be obtained which at a concentration of 1–2% caused a high sedimentation rate provided supplements such as 0.6% dextran had been added. The supplements by themselves had no effect, and the proteins which produce the increase in sedimentation rate behave, therefore, like incomplete antibodies. Except for fibrinogen, normal plasma contains no fractions which increase the sedimentation rate, and fibrinogen by itself is effective only at concentrations that are rarely seen even in pathological conditions. Investigations of the role of fibrinogen indicated in all cases that its contribution to the sedimentation rate was small. Thus serum from a blood with a high sedimentation rate had a diminished effect compared with that of the analogous plasma (Ruhensroth-Bauer *et al.*, 1960), and a high sedimentation rate is therefore due to specific serum proteins whose action is merely added to by the fibrinogen. It appears that the relationship between the variable levels of fibrinogen and the other factors may have some diagnostic significance.

We proposed the term "agglomin" for all plasma proteins which on the addition of supplement cause an increase in sedimentation rate. In this respect fibrinogen is an agglomin which is always present in blood. Besides dextran, collodion, and similar supplements, plasma proteins without agglomin activity may also act as supplements. This can be shown by dividing a

high-sedimenting plasma into two parts, one of which is then diluted with physiological saline, and the other with an AB-serum-citrate mixture (1:5 with 3.8% sodium citrate). In the first case both the agglomerins and supplement are diluted, in the second only the agglomerins. Differences between the two dilutions will then depend on their supplement. Typical results are shown in Fig. 1.

FIG. 1.—Sedimenting activity of a high-sedimenting plasma after dilution with saline or normal serum.

Our investigations have shown that the agglomerins of different patients are not always found in the same electrophoretic fraction. Activity may also be present in two different protein fractions, but serum albumin is always negative (see Table).

Differences in agglomerins can also be shown in another way. There are numerous substances which in a concentration from 0.05 to 0.2% inhibit the sedimentation rate. Although they may be quite different chemically, they exert their effect through binding the agglomerins in a varying degree (Ruhensroth-Bauer, 1961). They may be classified as complete or partial blocking agents. An example of the former is lauric acid (Formijne, 1956) and of the latter antazolidine (Tange, 1955; Schultheiss *et al.*, 1958). A wide range of blocking activity has been noted for the partial blockers. Slight modification in the structure of salicylic acid leads to a marked change in its blocking activity (Ruhensroth-Bauer *et al.*, 1960). A given agglomerin is inhibited by partial blockers in a characteristic but variable manner. Typical sedimenta-

tion characteristics are noted, and they may be used for the identification of the agglomerin. It has not been determined whether variations in agglomerins are due to individual specificities or to organ specificities or pathologically induced differences.

Normal as well as pathological plasmas contain high molecular lipoproteins which act as pro-inhibitors of sedimentation and which are activated at 37° C. by a specific plasma lipolytic enzyme. The bond between the inhibitor and the red cells appears to be much stronger than that between the agglomerins and the red cells (Ruhensroth-Bauer, 1957, 1959).

A study by Gross *et al.* (in preparation) on 55 patients has confirmed our observation that the pro-inhibitor-lipolytic system has on the average a lower activity in malignant disease than in inflammatory conditions (Fig. 2).

The true lipases are enzymes which split emulsified fatty esters but not esters which are in true solution (Sarda and Desnuelle, 1958). Enzymes which split fatty esters that are in true solution belong to the esterases which are classified according to substrate and inhibitor specificity. According to its inactivators the

FIG. 2.—Activity of the pro-inhibitor-S-lipase system of different high sedimentation human plasmas (100% = no inhibitor activity).

Sedimenting Activity of Fractions of Proteins of Pathologically Sedimenting Human Plasmas

Plasma Fractions	Sedimentation after Half/1/2/18 Hours in 10 Experiments									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Albumin 5% ..	0.2 0.5 1/14	—	—	—	0.2 1/3/24	0.2 0.5/2/15	—	0.8/2.5 6.5/30	0.3 1/3/12	0.2 1/2/27
Albumin 1.5%	0.2 0.5/1/11	0.5/2 4/21	0.5 1/1 18	0.5/2 4/40	0.2 1/2 15	0.2 0.5/2/12	0.2 0.5/0.5/7	0.5 1.5 4/25	0.5 2/4 15	0.2 4/30
α_1 -Globulin 1.5%	0.5 1/3/37	0.2 1 3 18	0.5 1/2 11	0.2 0.8/2/20	0.0 0.2 4	5/10 20 80	0.2 0.5 1/19	60 85 112 120	0.5 1/2/24	2/6/15/69
α_2 -Globulin 1.5%	53 104/116/124	0.2 0.2/0.5/10	0.0 2 4	0.2 2 6/17	2/10/30/110	28/80/100 120	0.2 0.5 0.8/10	3 16 40 80	3 9/21/104	3 16/35/90
α_2 -Globulin 1%	17/38/70 116	—	—	—	—	—	—	—	—	—
β -Globulin 1.5%	0.2 0.5/0.5/5	0.0 1 19	0.0 1/3	0.2 0.2/0.8/5	3/6/15/73	0.2 0.2/0.5/4	0.2 0.8/8/19	0.0 0.5/3	10/20 34/98	0.2 1/2/19
γ -Globulin 2.5%	34 76 85 101	—	—	—	—	—	—	—	—	—
γ -Globulin 1.5%	2 8 24 69	1/2 6/25	10 35/53/87	8/25/45/101	20/52/83/100	2 10/30 53	0.5 1/21/42	0.2 0.5 3/27	0.2 0.5/3/27	0.2 0.5/1/6
Diagnosis	Broncho-pneumonia	Acute nephritis	Cholecystitis	Hodgkin	Pneumonia	Broncho-pneumonia	Pleuro-pneumonia	Acute polyarthrit	Pancreas Ca (?)	Paramyelo-blastic leukaemia

sedimentation-active lipase belongs to the so-called B group of esterases. One can prepare material from the microsomes of hog pancreas whose effect resembles this enzyme.

Erythrocytes yield a glucolipid fraction which combines with the agglomerins. As little as 50 $\mu\text{g./ml.}$ of plasma of this partially purified material will cause a 50% inhibition of the sedimentation rate (Ruhensroth-Bauer *et al.*, 1960). Apparently the isolated receptor substances combine with the agglomerins and prevent them from combining with the erythrocytes. The blocking substances would then behave like these isolated receptor substances by competing with the erythrocytes for the agglomerins. Fig. 3 shows a scheme of the proposed mechanism of erythrocyte sedimentation.

A study of the blocking activity of numerous substances has shown that almost all of the anti-inflammatory substances are strong blockers of agglomerins. This applies to salicylic acid (Bendien, Neuberger, and Snapper, 1932), gentisic acid, phenylbutazone ("butazolidin"), "irgapyrin," and cinchophen ("atophan") (Martin and Scheidegger, 1952), polyphloretin phosphate (Fries, 1959), and the bioflavonoids (Menkin, 1959). Cortisone and resorcinol are partial blockers. Chemically similar substances without anti-inflammatory activity are poor blockers—for example, *o*-oxybenzoic acid shows a very good therapeutic effect and is a good blocker, *m*- and *p*-oxybenzoic acids are inactive in both respects (Formijne, 1955). This suggests that a decrease in agglomerin concentration will result in a decreased inflammatory response.

As regards the mechanism by which agglomerin production is stimulated, we have suggested that material from either homologous or heterologous (bacterial) cells

may be the effective agent. Intravenous administration to rabbits of certain fractions separated from different strains of *Escherichia coli* and other bacteria can produce a high sedimentation rate (Ruhensroth-Bauer *et al.*, 1960). As in the case of man, only a part of the activity is due to an increased fibrinogen level (Ruhensroth-Bauer *et al.*, 1961). The active fractions of *E. coli* are water-soluble, non-dialysable, and heat-stable (1 hour at 100° C.).

It is probable that with the breakdown of cells substances are liberated which can stimulate the formation of agglomerins by plasma cells (Fig. 4). These agglomerins would then be carried by the blood plasma to the damaged area, where their effect is manifested by an inflammatory response. The erythrocytes appear to possess receptors similar to the damaged cells and can therefore likewise combine with agglomerins. The release of different substances from the damaged cells would be expected to account for the different types of agglomerins.

Summary

A high sedimentation rate is caused by specific plasma proteins which are designated agglomerins. They resemble incomplete antibodies in that they require for their expression a high-molecular non-specific supplement. Every plasma contains a pro-inhibitor of sedimentation which is activated at body temperature by means of a specific lipase. A glucolipid fraction can be obtained from erythrocytes that contain the substance which combines with the agglomerins. A concentrate of this receptor substance added to whole blood (50 $\mu\text{g./ml.}$) decreased the sedimentation rate by 50%. A fraction from *E. coli* will on administration to rabbits produce a high sedimentation rate. Rabbits, like man, then produce agglomerins, of which fibrinogen is only a minor part. Almost all anti-inflammatory substances are inhibitors of agglomerin action. It is suggested that agglomerins are involved in the inflammatory response and that their action on the red cells is only coincidental.

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FIG. 3.—Scheme of mechanism of sedimentation of erythrocytes. On the erythrocyte surface are specific receptors for the agglomerins (A) of the plasma. S=Supplement. P=pro-inhibitor which is converted to inhibitor by a specific lipase. On conversion it can compete with the agglomerin for the red-cell surface.

FIG. 4.—Scheme of the biological significance of agglomerins.

The National Council of Social Service (Incorporated) has published a booklet on behalf of the National Old People's Council called *The Organization of a Visiting Service*, by an Old People's Welfare Committee. The booklet, recognizing the necessity for a planned visiting service for old people, gives recommendations for organizing such a service which are based on practical experience. There are appendices describing training courses for visitors, and examples of visiting services in various parts of the country; a useful list of publications is included. (From N.C.S.S. (Inc.), 26 Bedford Square, London W.C.1, price 4d.)