may show small pockets at intervals where egg-laying probably occurs. When the track through the skin is located the cedarwood oil is wiped off with xylol and the parts cleaned with ether or spirit. Using the eye-spud, the track is then laid open to its terminus, taking care not to draw blood, which obscures visibility. The drops of clear fluid in the burrow are transferred to a slide and covered with a cover-slip for examination under an ordinary microscope. A drop of distilled water on a clean slide prepared with Mayer's egg albumen facilitates the procedure. In this way I was successful in obtaining what appear to be four stages in the development of a

Cross-section of "sandworm" track in human skin. Photomicrograph of Dr. F. G. Cawston's case (1928). The track lies entirely in the superficial layers of the epidermis and contains numerous lymphocytes. The stratum corneum has been separated by artefact. Serial sections of skin in two of my own cases revealed the track in an identical situation.

parasite hitherto undescribed as a cause of "creeping eruption."

The investigation was begun with the idea of looking for either a fly larva (*Gastrophilus* var. or *Hypoderma*) or a larval dog-hookworm (*Ankylostoma braziliense*), both of which are quoted in the textbooks as a cause. A cursory examination under the microscope made it obvious that from the size of the true track the causal organism was likely to be much smaller than expected. No sign of the above-mentioned larvae was evinced in any of about thirty tracks examined. A number of slides were prepared from droplets taken from various portions of tracks in the skin of a man infected with "sandworm" (Plate, Fig. 1), and examination of these revealed a mite about 300 μ in length and two developmental stages (Figs. 3 and 4). Tracks in a second case—that of "sandworm" of the hand (Fig. 6)—after a patient search produced a similar mite (female) (Fig. 5) and a number of eggs (Fig. 2). The minuteness of the parasite and its transparency when unstained make it very difficult to be seen in the skin. To realize the size, it should be noted that the mite could be dropped into a pinhole with room

to spare, and that its egg is little larger than a polymorphonuclear leucocyte.

Commentary

The attention of interested readers may be drawn to a note by Theobald which states: "It has been asserted by Haller that the Cape ailment (Port Natal sickness) is caused by mites, but this statement has been contested" (Fantham *et al.*, 1916). No mention is made of a "creeping eruption." The nearest resemblance, in the available literature, to the mite discussed in the present investigation is *Tetranychus molestissimus*, which is found in the Argentine and Uruguay on the under-surface of the leaves of *Xanthium macrocarpum*. It attacks mammals and men, producing severe itching, accompanied by fever in the latter (Fantham *et al.*, 1916).

The photographs of the various stages discovered must suffice for this article. Fuller details of the classification, life history, and occurrence are being prepared, and in a subsequent article the treatment will also be included.

Dr. J. Mackay, district surgeon, Durban, kindly referred suitable cases to me and provided the stimulus to investigate this common ailment. Mr. O. F. Gibbs, senior technical assistant, Government Laboratory, Durban, gave valuable advice in the photomicrography. I acknowledge my thanks for their assistance. I am also indebted to Dr. F. W. P. Cluver, deputy chief health officer, for permission to publish this report.

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OBSERVATIONS ON THE PERFORMANCE OF BLOOD-GROUP TESTS

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Compared with other parts of the world blood-group investigations in this country have been few. In a recent series of papers Taylor and Prior (1938a, 1938b, 1939) have given some account of what has been done, have described in detail their investigations of family and unrelated material in England, and have shown by statistical analyses that their results agree with current genetic theory.

Below is a description of the technique used in the Galton Laboratory for the diagnosis of the blood-group factors A₁, A₂, B, O, M, and N, followed by observations on technical points mostly concerned with the M-N factors, the detection of which, authorities are agreed, is difficult and full of pitfalls for the inexperienced. At the present time there may be interest in such a communication coming from a unit which for more than three years has been devoted, almost exclusively, to work on blood-group factors. It may appear that the difficulties are overstressed and that the technique is elaborate; the workers in this unit are of the opinion that anything less well-controlled and less careful would not be good enough.

Blood-group tests on 1,073 unrelated persons, a sample we believe to be representative of the population in England, are reported and analysed; of these 1,073 tests, 422 have already been reported by Taylor and Prior (*loc. cit.*). Our technique undergoes slight modification from time to time, as in the case of the strength of red-cell

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suspension, which has gradually increased to about 2 per cent.; the description below is of what we do at present.

Collection of Specimens

In most cases capillary blood, collected from finger or ear-lobe into 3.8 per cent. sodium citrate solution, is used for the tests; in other cases cells are recovered from blood clot, washed two or three times with saline solution, and resuspended. In all but a few instances cells are examined within thirty-six hours of being bled, and within a much shorter time if they have not to be sent from a distance. So far as possible samples are stored in the refrigerator; those which have been posted to the laboratory are washed in saline solution before being tested, although cells recently bled are not washed as a routine measure. The cell suspensions used are approximately 2 per cent., as judged by eye.

Performance of Tests

All tests are performed in small precipitin tubes, 2 in. $\times$ $\frac{1}{4}$ in. approximately. Equal volumes of reagents are used, measured by Pasteur pipettes graduated to deliver about 0.1 c.cm., and as diluent a 0.85 per cent. solution of sodium chloride in distilled water. In the tests for the A and B factors each tube contains one volume of the corresponding antiserum, one volume of cell suspension, and a further volume of saline; the saline is added to avoid pseudo-

only because they are of the type O, but because the particular cells we use tend sometimes to give a slight reaction—the OM with anti-N, the ON with anti-M, when the corresponding reactions of our A₁M and A₁N control cells are quite negative (see the OM control cells in Table I). A₁M and A₁N types are included to detect possible contamination with α . In addition, a volume of the cells from each person tested is mixed with an equal volume of saline and included as a control of the cell suspension. After receiving its reagents each tube is shaken sufficiently to yield an even suspension of cells, and covered with a small glass cap, which, it was thought, would prevent extraneous matter from falling into the tubes. The main usefulness of the caps, however, is in indicating, during the reading of the reactions, which tubes have been examined. The tubes are left undisturbed on the bench, at room temperature, for two hours, after which the readings are made.

Our system of scoring the strength of a reaction is very simple: ++ C (complete) is a reaction in which clumps of cells in a clear surrounding fluid are visible to the naked eye after the cell deposit at the bottom of the tube has been dispersed by tapping the tube sharply three or four times with the finger; ++ V (visual), a somewhat weaker reaction in which the surrounding fluid is not clear, but in which clumps are distinctly visible. No reaction is scored as negative until it is examined microscopically; for this purpose a small portion of the well-mixed contents of the tube is placed on a

TABLE I

Cells Tested	α	β	Anti-M's			Anti-N's			α_1	Saline Controls	Results of Tests
			1	2	3	1	2	3			
Control cells	C.V.H.	—	—	—	—	(+)	(+)w	?	—	—	OM
	R.T.	—	—	—	—	++V	++	++	—	—	ON
	E.W.I.	++C	?	—	—	++C	++V	++V	++V	—	A ₁ N
	G.L.T.	++C	++C	++C	++C	—	(+)w	—	++V	—	A ₁ M
	B.E.S.	—	++V	++C	++C	++C	++V	++C	—	—	BMN
	Sh.		Used only as A ₂ control cells						?	—	A ₂
Unknown cells	1	++C	—	—	—	++C	++V	++C	++V	—	A ₁ N
	2	—	++	++C	++C	++C	++	++C	—	—	OMN
	3	++V	++C	++C	++C	++C	++V	++C	(+)w	—	A ₂ MN
	4	—	++C	++C	++C	—	(+)w	—	—	—	OM
	5	++C	++C	++C	++C	++C	++V	++C	++	—	A ₁ MN
	*6	+	—	—	—	++C	++C	++C	—	—	A ₂ BN
	7	—	++C	++C	++C	?	(+)w	—	—	—	BM

* A₂B result confirmed by titration with α .

agglutination, as recommended by Landsteiner (1928, p. 905). In the tests for the factors M and N at least three anti-M and three anti-N testing fluids, prepared from the sera of different rabbits, are used, and it is the opinion of workers in this laboratory that the use of only one anti-M and one anti-N fluid would lead to errors in diagnosis: most authorities work with three of each type—for example, Wiener in America and Friedenreich in Denmark. As in the preparation of these testing fluids the original sera have been considerably diluted, the third volume of saline, used in the tests on the ABO system, is omitted; the tubes for the M and N tests contain only equal volumes of testing fluid and cell suspension. As controls, cells, the blood groups of which are well known, are included in each batch of tests, as it is essential to be certain that the reagents are reacting with appropriate cells, and only with appropriate cells. Among the controls there should always be cells of group O, cells containing the factors A and B, cells of the types homozygous M and homozygous N, and those of the heterozygote, MN. When the partition of the factor A into A₁ and A₂ is being made, control cells of the types A₁ and A₂ are needed. We always include controls of the following types, OM, ON, A₁M, A₁N, and BMN or A₁BMN, and are fortunate in being able to get them from colleagues in the laboratory. The OM and ON controls are included not

microscope slide and spread evenly thereon by means of the stem of the Pasteur pipette used for its transfer to the slide. No cover-slips are used. The film is viewed with a half-inch objective, and at least three fields are examined. A reaction showing very big clumps under the microscope is scored as ++, a reaction not quite so large as ++, still less reactions as (+), and (+)w (weak) in descending order of magnitude; (+)w indicating a definite reaction in which there is a uniform distribution of very small clumps containing about six to eight cells. A specimen in which the cells are not distributed quite evenly, but in which there are no very definite clumps, is scored as a ?.

As Table I is given the protocol of a batch of tests set up together. Actually there were twenty-four samples to be tested, the seven unknown ones in the table being chosen only because they show a great variety of groups. The very weak A reaction, which is found sometimes in cases of A₂B, is well illustrated.

Preparation of Antisera

ANTI-A (α) AND ANTI-B (β)

Anti-A and anti-B sera, obtained from suitable donors, are placed in amber-coloured glass ampoules and heated for twenty-five minutes at 56° C. on three successive days. The

ampoules are stored in the refrigerator at about 2°C. Before use the strength of the sera is determined by titration against cells containing the appropriate antigen, and for this purpose we use the precipitin tubes and the marked Pasteur pipettes previously described. The strength of the cell suspension is held constant, the serum dilutions being increased twofold at each stage. The reciprocal of the highest dilution of the serum giving a reaction of at least (+)w after two hours is taken as its titre, the fact that the dilution of the serum has been doubled by the addition of an equal volume of cell suspension being neglected. Sera of which the titres are less than 64 are not used. It should be noted that the titre of a serum varies quite markedly with the method of titration used. The cell suspensions used for titrating our α and β sera are in both cases always obtained from one of two donors of each type in this laboratory.

ANTI-M AND ANTI-N

For the preparation of these sera, rabbits are injected with cells of the types OM and ON respectively, bled into 3.8 per cent. sodium citrate solution. A course consists of the injection of suspensions containing the washed red cells from 1 c.cm. portions of blood on five successive days; sufficient cells for one course are stored in the refrigerator. Injections are made into an ear vein, except that the first dose of any further course is given intraperitoneally, as suggested by Wiener, Zinsher, and Selkove (1934), in order to minimize the risk of anaphylaxis. Rabbits are bled from the marginal ear vein eight to ten days from the last injection, and the sera are treated and stored as described for α and β .

No standard treatment can be used for the preparation of specific testing fluids for the factors M and N. Each raw serum has to be investigated and methods for the production from it of reliable fluids discovered. The crude serum is titrated against cells of types A₁M and A₁N, to show the general immunizing effect of the injections. Before preparing considerable amounts of testing fluid from an untried serum, exploratory absorptions of small quantities are made. For example, 2 c.cm. portions of the following dilutions of the serum—1/10, 1/20, and 1/40—are mixed with the packed washed cells from 2 c.cm. of whole blood. After gentle shaking the mixtures are left on the bench for an hour at room temperature, then centrifuged, and the supernatant fluids removed and titrated against cells of the two homozygous types M and N, and the heterozygous type MN. Reactions, especially with anti-N sera, tend to be definitely less with the heterozygote than with the homozygote.

A consideration of the results of the titrations may suggest a mixture of cells and diluted serum likely to yield a satisfactory fluid. Our aim is the production of a fluid which, after only one treatment, does not react at all with cells of the type used for absorption; but it may be necessary to reabsorb once or even twice. To avoid possible contamination with α , cells of the types A₁M and A₁N are used for absorbing. The possibility of similar contamination with β has to be considered, but, although we have not ready access to donors of the types BM and BN, we always satisfy ourselves from their behaviour with controls, and the results obtained, that our fluids do not contain β .

It is not easy to define the minimum strength required of a testing fluid. Those which do not give a reaction of at least + under the microscope, at a dilution of 1/4, when titrated with homozygous cells of the appropriate type, are rejected. Anti-M fluids tend to be much stronger than anti-N, and we have never been able to prepare an anti-N which approaches in strength the most powerful anti-M fluid. Complete sterility in the preparation of the fluids is not attempted, and they are stored frozen solid in small portions (for example, 2.5 c.cm.). After use the residue in a tube is at once refrozen. Preservative should not be added to fluids and sera it is intended shall be frozen solid, as it may result in complete loss of strength.

Sometimes a fluid which usually gives a negative reaction with control cells will on another occasion give a small reaction with the same cells. Such variations, however, occasion no uncertainties, as three fluids are used. If the slightest doubt arises as to the correct diagnosis it can be settled by titration of these cells and control cells with further antisera, and, if necessary, by re-examination with a fresh specimen of the cells.

Bipartition of the A Factor into A₁ and A₂

For the bipartition into A₁ and A₂ we do not use an "anti-A₂" serum (anti-O), but only α_1 prepared by absorbing anti-A serum, usually undiluted, with cells of the type A₂. To produce a satisfactory α_1 fluid the anti-A (α) serum must be of good strength. Our α_1 fluids have titres of at least 8 with the A₁ cells used as standard; they are stored frozen solid. Tests with α_1 receive the third volume of saline used with α and β . As with the anti-M and anti-N fluids, an α_1 will sometimes give a slight reaction with cells of the type used for absorption, in this case A₂ cells; and although there are quite definite variations in the strengths with which different A₁ cells react with α_1 , the diagnosis in cases of doubt can be settled by titration.

Thomsen (1929) and Thomsen, Friedenreich, and Worsaae (1930a) have shown that the A₁ in A₁B cells is sometimes obscured by the B factor, and Friedenreich and Zacho (1931) have suggested that, when A₂B is diagnosed, confirmation be obtained by titration of the cells with unabsorbed α_1 , with which the reactions of true A₂B cells are always markedly weaker than those of A₁B and A₂ cells (Taylor and Prior, 1938a, p. 349).

On Some Technical Points

The commonest source of error in determining the groups of the ABO system is the use of testing sera which are too weak; the A factor in A₂B cases is particularly liable to be missed, the B factor alone being recorded. Only a small proportion of persons of the groups A and B yield satisfactory β and α , and sera should be titrated before use; it should be remembered that they tend to weaken with age, sometimes with surprising rapidity. Probably the best way of storing α and β is frozen solid. False positive reactions, due to rouleaux formation, may be recorded, particularly with a slide technique. The reactions of the sera with well-known control cells should prevent most errors.

In this laboratory the diagnosis of the factors M and N has been found difficult and troublesome, and it was only after a great deal of preliminary work that satisfactory results were obtained; those for the first twelve months had to be discarded.

Authorities are agreed that the diagnosis of these factors is far from easy, and that reliable results can only be expected from workers with considerable experience. In the Galton Laboratory, where on almost every working day M and N tests are performed, the most unremitting care and attention is necessary to ensure that there is always available a supply of reliable reagents, and the same is true of Scandinavian laboratories visited by one of us (G. L. T.).

Causes of Erroneous Diagnosis

Errors in diagnosis may be caused by false positive or false negative reactions.

False positive reactions are due to the presence in the testing fluid of a contaminating unwanted agglutinin, which may be α , β , possibly anti-O, some unknown and uncharted antibody, or species-specific antibody due to under-absorption. Both α and β may occur naturally in the uninjected rabbit, and although only cells of the type O

are injected for the production of anti-M and anti-N sera, considerable amounts of α , and occasionally of β , may be present in the immune serum. Any contamination by the known agglutinins should be disclosed by the reactions of a serum with control cells from persons whose blood groups are well known. Absorption with appropriate cells containing the corresponding antigen is necessary to remove the unwanted antibody. Contamination of a serum with an antibody other than those of the ABO and M-N systems must be rare, and the possibility of error remote if three fluids from different rabbits are used, for it is most unlikely that the contaminant would be present in all three. Danger from under-absorption is very real, for an absorbed fluid which no longer gives any reaction with the absorbing cells may give a small but definite reaction with certain other cells of the same group in the M-N system, and if such a fluid is the only one in use it may be impossible to interpret properly a small reaction, and a homozygote may be recorded as a heterozygote. An obvious remedy would seem to be further absorption, but very often, and particularly in the case of anti-N sera, this results in a testing fluid which is too weak, non-specific absorption having removed much of the antibody it is desired to retain.

False negative reactions are due to the use of testing fluids which are too weak, owing to their having been over-absorbed, or to their having lost strength during storage, or because it is impossible to prepare strong fluids from the sera used. Loss of sensitivity of the cells may also contribute to false negative results. The greatest difficulty met with in our work with the M-N system has been the avoidance of over-absorption of testing fluids, for not only do absorbing cells remove, specifically, unwanted antibodies, but they also, by non-specific absorption, take out some of the antibody it is desired to keep. Whilst non-specific absorption occurs with anti-M sera, it is much more marked and causes much more trouble with anti-N sera. Given an unabsorbed serum containing anti-M in good strength, we are able to prepare, with comparative ease, strong and satisfactory testing fluid. Far more troublesome is the preparation of good anti-N fluids, non-specific over-absorption with loss of strength being so difficult to avoid. Usually it is only after many trial absorptions with varying dilutions of serum and varying amounts of cells that a satisfactory prescription is found for an anti-N fluid, and a prescription which works well on one occasion is not always equally successful when repeated. Very often, after one absorption, an anti-N fluid is obtained which in titration reacts well with N cells, but also gives a small reaction with M cells. If the M reaction is not too big it is frequently better to avoid it by suitable dilution of the testing fluid, rather than risk weakening the anti-N by further absorption; often a small reaction with M cells will disappear after the fluid has been stored for a few days. It has already been said that anti-N fluids are more troublesome to prepare than anti-M fluids; they are also much more liable to decrease in strength, and unless they are stored frozen solid, anti-N fluids tend to lose much of their strength in a few days, even at refrigerator temperatures just above freezing-point. Frozen solid they weaken much more gradually.

Most of the rabbits injected in this laboratory have not yielded antisera from which we have been able to make good testing fluids, even after five or six courses of injections. It has been stated that about one rabbit in five yields a serum from which a satisfactory anti-M fluid can be made, and that from such a serum the preparation is not very difficult; our experience confirms this. It is

also said that from nearly every rabbit it is possible to get a serum from which satisfactory anti-N fluid can be made, but the making of it tends to be by no means so easy. With the first part of this latter statement our experience is not in agreement: the sera from about a quarter only of our anti-N rabbits have been good. Of the difficulty met with in the preparation of anti-N fluid there can be no doubt.

Freshly shed cells tend to react better than older ones, and there is a definite loss of sensitivity with storage, which is less at low temperatures. The reactions of cells bled twenty-four or thirty-six hours and sent through the post are markedly weaker than those of cells recently shed, and even of cells of the same age stored in the refrigerator. The combination of a not very strong testing fluid and cells which have lost in sensitivity may lead to a reaction which is only slight, and a doubt as to its being negative or positive: when three sera are used results should give no cause for doubt.

We regard as one of the most important factors contributing to the successful diagnosis of the M-N groups a day-to-day familiarity with the actual reagents used. As it is much diluted before absorption, a supply of 20 to 25 c.cm. of raw serum permits of many batches of testing fluid being prepared and of a very large number of tests being performed with it. Thus a good serum serves for many months, and the worker becomes familiar with its characters and peculiarities, for sera differ much as regards the treatment needed to yield good testing fluid, and as regards the keeping properties and strength of fluids obtainable therefrom. If the testing fluids used are shown to be reliable by their correct behaviour on many occasions with well-known control cells, and by a statistical analysis of a goodly number of results yielded by them, and if new sera are tried out alongside those whose behaviour is well understood, a constant supply of well-tested and dependable sera should be obtained and correct diagnoses ensured.

The χ^2 Test

The agreement between the numbers of a random population observed and the numbers expected, according to the genetic theory of Landsteiner and Levine (1928), in each of the three M-N groups, can be readily tested for significance by means of the well-known χ^2 test (see Taylor and Prior, 1938b). If, of those examined, a, b, and c are the numbers observed in the groups M, MN, and N respectively, then it can be shown that

$$\chi^2 = \frac{(b^2 - 4ac)^2(a+b+c)}{(2a+b)^2(b+2c)^2},$$

there is but one degree of freedom. The value of χ^2 is a measure of how much the observed results differ from those expected, and can be used to indicate the probability of those differences being due to chance. Fisher (1938) has constructed tables of χ^2 values corresponding to various levels of probability and different numbers of degrees of freedom. By calculating the χ^2 value for a batch of M-N results, and by consulting the tables, the limits between which the probability of the observed result lies can be seen at once. The value of χ^2 , for one degree of freedom, corresponding to a probability of 0.05, the level usually taken as significant, is 3.841, and values greater than this are suggestive of errors in diagnosis. A beginner with the M-N system would do well, before resting satisfied with his technique and reagents, to submit a good number of his results, say 300 or more, to a statistical analysis such as that described below for the 1,073 cases we are here reporting.

The presence of contaminating agglutinins is likely to lead to homozygotes being mistaken for heterozygotes and a consequent excess of this latter type, while weak testing fluids will have the opposite effect—too few heterozygotes. Both sources of error may be present at the same time, their effects on the resulting data cancelling each other, so that what at first sight appear reasonable figures for the M-N groups may be obtained. Contamination of sera by the agglutinins of the ABO system should be disclosed by examining the frequencies of the M-N groups in the various groups of the ABO system; the presence of α , for example, in testing fluids for M and N would lead to a marked excess of the type AMN. In Table II are the

TABLE II

ABO Groups Number and Percentage	Number and Percentage in Groups of MN System			χ^2	Prob- ability
	M	MN	N		
O, 493 (45.946)	150 (30.426)	233 (47.262)	110 (22.312)	1.160	> 0.20
A, 451 (42.032)	128 (28.381)	230 (50.998)	93 (20.621)	0.308	> 0.50
B, 100 (9.320)	32 (32.000)	47 (47.000)	21 (21.000)	0.235	> 0.50
AB, 29 (2.703)	9 (31.034)	16 (55.172)	4 (13.793)	0.546	> 0.30
Total .. 1,073*	319 (29.730)	526 (49.021)	228 (21.249)	0.167	> 0.50

* Includes 422 already published by Taylor and Prior (loc. cit.).

details of such an analysis of our 1,073 cases. The probabilities given were obtained from Fisher's χ^2 tables previously mentioned. It is seen that the figures for the M-N groups as a whole, and in regard to the groups of the ABO system, are in excellent agreement with the expectations. That the heterozygotes, MN, are only in excess in the two groups containing the factor A might suggest contamination of testing fluids with α ; a statistical test, however, with a χ^2 value of 1.726 for one degree of freedom, shows that the excess is not significant.

In the ABO and the extended A_1 , A_2 , B, O systems the agreement between results observed and expected, according to accepted genetic theory, can be examined as described by Taylor and Prior (1938b), and by Stevens (1938). That the 1,073 ABO results agree with the triple allelomorph theory of inheritance advanced by Bernstein (1924, 1925) is shown by a test giving a χ^2 value of 1.168 for one degree of freedom, which corresponds to a probability greater than 0.20. Only 996 of the 1,073 samples were tested during the time partition of the factor A into A_1 and A_2 was performed as a routine measure, the distribution among the six phenotypes being:

O	A_1	A_2	B	A_1B	A_2B
451	346	76	94	22	7

Agreement with the four-gene theory of Thomsen, Friedenreich, and Worsaae (1930b, 1930c), an extension of Bernstein's theory embracing the factors A_1 , A_2 , is demonstrated by a χ^2 value of 0.9311 for two degrees of freedom, indicating a probability greater than 0.50.

Summary

The technique for the diagnosis of the factors A_1 , A_2 , B, O, M, and N, used by a unit constantly engaged in work on blood groups, is described, and difficulties discussed.

The results of tests on the blood cells of 1,073 people in England are given, and shown by statistical analysis to be in agreement with genetic theory.

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Clinical Memoranda

Fatal Agranulocytosis after Sulphanilamide Treatment

The following case of fatal agranulocytosis occurring after a course of prontosil treatment is of interest because of the comparatively low dosage of the drug given and the fulminating nature of the final illness.

CASE RECORD

The patient, an obese married woman of 60, was receiving treatment from her doctor for recurrent frontal sinusitis, and prontosil administration had been started for this condition on July 25, 1938, the dose being 3 half-gramme tablets of prontosil album (*p*-aminophenylsulphonamide) daily. This was continued until August 18, when the drug was stopped owing to increased headache; aspirin, 10 grains thrice daily, was substituted. On August 24 she became acutely ill, with sore throat, headache, and rigors, and there was an increase of the purulent nasal discharge. On August 27 examination revealed severe inflammation of the fauces, pharynx, and nasal mucosa, with oedema and deep necrosis. The cervical glands were enlarged, and, with extensive periadenitis, presented a "bull-necked" appearance. The tongue was dry and covered with sordes. Circulatory collapse was marked, with slaty pallor and a thin running pulse.

A throat swab showed *Streptococcus viridans* and *Staphylococcus aureus* on culture, no diphtheria bacilli being seen, and the blood count gave the following result: red cells, 3,580,000 per c.mm.; haemoglobin, 56 per cent.; white cells, 600 per c.mm.—polymorphs 2 per cent., lymphocytes 94 per cent., monocytes 4 per cent. A transfusion of 300 c.cm. of citrated blood was given from a donor suffering from myeloid leukaemia whose total white cell count was 120,000 per c.mm., but the patient never rallied, and she died early the next morning.

A post-mortem examination was made by Dr. T. Skene Keith, who reports as follows.

"Mouth edentulous. Oedema and ulceration of gums and of pharynx; the posterior nasopharynx blocked by oedematous mucous membrane. Larynx and trachea not ulcerated, but full of blood-tinged sputum. The pleural cavities contain a few old adhesions. Both lungs show a medium degree of bronchopneumonia. The heart and other viscera are normal. A film from the sternal bone marrow reveals many mononuclear cells, but no polymorphonuclear leucocytes. Immature and developing erythrocytes found. Cause of death, agranulocytosis."

COMMENTARY

In view of similar cases that have been reported it is reasonable to assume that the agranulocytosis in this instance is attributable to the occasional depressant action of the sulphanilamide group of drugs on the leucopoietic