times present as a contaminant in P.A.S., need not be invoked as the guilty agent. Thus the use of freshly prepared solutions only, while desirable, will not necessarily prevent the development of P.A.S. sensitivity. For the patient's future safety we advocate patch testing in every known instance of P.A.S. sensitivity, at least against the drugs mentioned. These substances are commonly used in medicine to-day, and the list of drugs containing an aminophenol group is very long, including, among others, sulphadiazine, sulphaguanidine, and picric acid. Testing against the sulphonamide group of drugs is of special importance because of their wide general application. Procaine may be equally important, but we have used it as an anaesthetic agent in several P.A.S.-sensitive patients without apparent ill effect.

With regard to the more specifically tuberculous aspects of streptomycin-P.A.S. sensitivity, the possibility of this development can no longer be ignored when considering the application of chemotherapy in a patient suffering from tuberculosis. Besides the risk of damage to the liver, kidney, skin, and other organs (including possibly the central nervous system) further treatment may be prejudiced—particularly resection, should this be required. P.A.S., because of its alleged harmlessness, has perhaps been employed rather more freely than would otherwise have been the case, but present knowledge of the profound bodily disturbance it may cause emphasizes the need to avoid indiscriminate chemotherapy.

It should be mentioned that our patient had no previous history of allergic phenomena other than a mild upset, possibly due to food, during childhood. The hypersensitivity appeared to develop purely as a result of drug administration. The severity of the reaction which occurred is all the more disturbing because there is no direct clue regarding which patients are likely to prove susceptible. When administration of the drug has begun, however, *particular attention should be paid to any unexpected rise of temperature, especially during the period two to four weeks after the beginning of treatment*, which appears to be the usual time for reactions to develop. In patients who have had P.A.S. previously, hypersensitivity may of course occur much earlier.

Finally, the possibility that P.A.S.-sensitive patients may develop local sensitization phenomena must be remembered. Our patient had a severe effusion into her Semm space following thoracoplasty, and, in retrospect, the possibility of its being due to the sulphathiazole-penicillin powder dusted into the space at operation has to be considered, although no generalized rash developed at the time. It is, on the whole, perhaps advisable to avoid using sulphathiazole powder or tablets in this way in P.A.S.-sensitive patients.

Treatment of the condition with A.C.T.H. was considered, but at the time it was felt that the danger of producing spread of the tuberculous lesion was best avoided. If A.C.T.H. had been administered it would have been difficult to avoid the charge that it was responsible for the spread of disease in the right lung, which did, in fact, occur after the acute reaction had settled down. Even so, the employment of A.C.T.H. in carefully graded doses remains a possibility in patients with tuberculosis who have developed acute drug-sensitivity.

Summary

The case history is given of a patient who suffered from a severe general toxic reaction to combined P.A.S.-streptomycin. Skin, alimentary tract, liver, kidney, and bone marrow all gave evidence of considerable damage, and the central nervous system may also have been affected. The patient later developed hypersensitivity towards penicillin.

Treatment adopted is outlined. Particular attention should be given to the mouth and to the protection of the liver by the administration of glucose in the early stages. The patient's skin should be protected from direct sunlight.

As a preventive measure it is important to stop P.A.S. as soon as any unexpected rise of temperature occurs; in susceptible patients this usually occurs two to four weeks after the beginning of treatment.

If sensitivity to P.A.S. has already developed it would seem that reaction to other drugs may more readily occur, particularly those containing an aminophenol group in the *para* position—for example, certain sulphonamides, picric acid, hair dye. The routine patch testing of P.A.S.-sensitive patients towards such drugs is advocated; it is preferable to begin with a 1% solution of each. The patient should be told what drugs to avoid.

The mechanism whereby hypersensitivity to a heterogeneous group of drugs becomes established is not properly understood and requires further elucidation. The mechanism of desensitization would also repay fuller investigation.

The development of drug hypersensitivity imposes limitations as regards future treatment; this aspect further emphasizes the need to avoid indiscriminate chemotherapy.

A description of this case from the nursing point of view, by Sister J. Kenshole, appeared in the *Nursing Mirror* of November 16, 1951, p. 151.

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TECHNIQUE OF JELLY (TUBERCULIN) TESTING

SOME FURTHER OBSERVATIONS

BY

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Recent correspondence in the medical journals shows that all physicians are not yet satisfied with this test. This may be due to technique, for it has been shown (Lendrum, 1951) that the test as described gives better results than the 10 T.U. (tuberculin units) Mantoux test, although fewer positive findings than the 100 T.U. test—perhaps an advantage when the non-specific element of the latter is taken into account (Long and Seibert, 1937; Furcolow *et al.*, 1941; Furcolow and Robinson, 1941; W.H.O., 1948).

When Dick (1950) described the technique, using flourpaper and P.P.D. jelly, he noted a discrepancy in results between P.P.D. and O.T. jellies which he was unable to explain and which I, having noted the same discrepancy independently, suggested was due to insufficient lapse of time before the test was read.

The investigations reported here are considered to be of importance, as they explain the discrepancies in results, as well as the dissatisfaction of some physicians.

Storage at Room Temperature

A number of tests were performed on schoolchildren aged 5 to 17, using (1) O.T. jelly kept in a refrigerator throughout, and (2) O.T. jelly of the same batch (A. & H. 371) stored for from 11 to 15 months at room temperature, results being read on the fifth day. The technique of the test is as follows: A firm rub with a plug of cotton-wool soaked in acetone is given to the interscapular area to be tested, followed by six light strokes with flourpaper. The minimum thickness of jelly is applied to the area in a recognizable shape (the letter T is used, as this gives a right-angle, as opposed to the acute angle of the V usually recommended) and covered with adhesive plaster, firmed as close into the T as possible. The plaster is kept dry and removed at 48 hours.

TABLE I.—*Effect of Storage at Room Temperature, Read on Fifth Day*

Results by O.T. jelly stored at room temperature	Positive Negative	Results by O.T. Jelly Stored in Refrigerator	
		Positive	Negative
		319 4	Nil 676

Table I shows that out of 999 individuals whose tests were read on the fifth day only four gave differing results, to the disadvantage of the R.T. jelly.

Serial Results Using O.T. and P.P.D. Jelly

A group of children aged 5 to 17 years were tested by both types of jelly at the same time, by the same described technique, the results being read serially. All who were absent for one reading are excluded. The group whose initial reading was on the fourth day were all aged 11 or more.

TABLE II.—*Serial Readings*
A. Third to sixth day, all age groups

Day 3		Day 4		Day 5		Day 6	
O.T.	P.P.D.	O.T.	P.P.D.	O.T.	P.P.D.	O.T.	P.P.D.
+ 211 - 424	+ 180 - 455	+ 223 - 412	+ 209 - 426	+ 230 - 405	+ 222 - 413	+ 232 - 403	+ 227 - 408
635		635		635		635	

B. Fourth to seventh day, aged 11 and over

Day 4		Day 5		Day 6		Day 7	
O.T.	P.P.D.	O.T.	P.P.D.	O.T.	P.P.D.	O.T.	P.P.D.
+ 76 - 73	+ 76 - 73	+ 84 - 65	+ 83 - 66	+ 84 - 65	+ 83 - 66	+ 83 - 66	+ 83 - 66
149		149		149		149	

Table IIA shows that the number positive on the third day was 211 with O.T. jelly and only 180 with P.P.D. jelly (a similar degree of difference to previous findings); by the fifth day the figures were 230 by O.T. jelly and 222 by P.P.D. The rise in positive results is 19 (3% of the total examined) with O.T. jelly and 42 (6.6%) with P.P.D. jelly. The further rise on the sixth day is slight, and greater for the P.P.D. group.

Table IIB shows little difference between the two groups, but again demonstrates that a rise in positive rates occurs between the fourth and fifth days (51% to 56.4%).

Serial Results with O.T. Jelly

Two groups of children were examined, all aged 5 to 17 years. The group initially read on the third day had a majority under 11 years; the other group had a majority of 11 years and over. Results were read towards the end

of the day shown; thus the third day's result was read between 66 and 72 hours after application of the jelly.

TABLE III.—*Serial Readings, Using O.T. Jelly*

A. Third to sixth days

Day 3		Day 4		Day 5		Day 6	
+	-	+	-	+	-	+	-
243	503	258	488	269	477	273	473*
746		746		746		746	

B. Fourth to seventh days

Day 4		Day 5		Day 6		Day 7	
+	-	+	-	+	-	+	-
249	261	269	241	273	237	261	249†
510		510		510		510	

* Includes 63 negative on the first three days and assumed negative on the sixth day.

† Includes 162 negative on the first three days and assumed negative on the seventh day.

In one school the authorities did not wish those children who had had three negative readings to leave for a fourth time; some of these might have become positive on the fourth reading, and thus have stressed the tendency of the number of positive results to increase with time.

Table IIIA shows that the 243 tests positive to O.T. jelly on the third day had risen to 269 by the fifth day and to 273 by the sixth, or from 32.6% on the third day to 36.1% on the fifth day, a rise of 3.5%.

Table IIIB shows, again, a considerable rise between the fourth and fifth days, from 249 to 269, or from 48.8% of those examined to 52.7%, a rise in this group of 3.9%.

Discussion

Storage of Jelly.—The results in Table I show that no significant loss of potency occurs in O.T. jelly resulting from storage at room temperature. The usefulness of the test material, by the prevention of waste and by making refrigeration facilities unnecessary, is thus confirmed. Its other advantages have been discussed previously.

Effect of Time on Results.—The importance of the time factor was seen during the previously reported work on skin testing, when it was observed that, in a school where 312 boys were tested, 14 showed a change from negative to positive with the passage of time using P.P.D. jelly, and four with O.T. jelly. The serial results in Table II show that there is a progressive rise in the number of positive results with both types of jelly from the third to the sixth days; they also show that the increase is greater for P.P.D. jelly than for O.T. jelly. Dick (1950) was unable to give an explanation of the discrepancy in results from the two jellies; as his results were read at 72 hours, the time factor is seen to be the explanation. In the present series, 6.6% of those examined (Table IIA) would have given false negative results with P.P.D. jelly as judged by the findings on the fifth day. These findings and those in Table III also show why some physicians are dissatisfied with results. Most seem to read their results on the third day (Lendrum, 1951), but Table IIIA shows that there is a rise of 3% in positive results with O.T. jelly between the third and fifth days, and a higher percentage in the older age groups. Table IV shows this rise as a percentage of the total examined in each group, serially.

TABLE IV.—*Rise in Percentage of Positive Results with O.T. Jelly*

Source	Between Days			
	3 and 4	4 and 5	5 and 6	6 and 7
Table IIA	1.9%	1.1%	0.3%	
" IIA	2.0%	1.5%	0.5%	
" IIB		5.4%	Nil	Fall
" IIIB		3.9%	0.8%	"

It is apparent from the serial results that in some cases fading was taking place on the sixth day; and there was a fall on the seventh day in the number which, seen for the first time, could be called positive.

The fifth day would therefore seem to be the optimum for reading O.T. jelly tests. The few who may be missed will not be of significance from the clinical point of view, as those with active disease are likely to become positive before this day. It may be a minor disadvantage in the field to test prior to B.C.G. inoculation, but this must be offset against the disadvantage of the non-specific reaction to the 100 T.U. Mantoux test. A considerable number of false-negative results will be obtained if readings are made only on the third day.

Consistency of Serial Positive Tests with O.T. Jelly.—It is of importance that the increasing number of positive results up to the sixth day should include *all* those previously positive in the serial readings. Among the 746 individuals whose tests were read from the third to sixth days (Table IIIA) there was, in fact, one discrepant result—a negative on the fourth day, the remaining three readings being positive; this is interpreted as a false positive on the third day. One case positive on days three, four, and five was negative on the sixth day. Of the 510 persons tested from the fourth to seventh days (Table IIIB) only one who was positive on the fourth day became negative before the seventh day, although 13 who were previously positive were negative on that day. This one case was positive on the fourth and seventh days and was recorded as negative on the fifth and sixth, and does demonstrate an error in technique—of testing, reading, or recording. In referring to false positive results, Dick's advice that a control be used until one is thoroughly conversant with the method is very sound. It is not only plaster reactions which may cause doubtful results (although these are avoided by reading on the fifth day); I have heard of some physicians who accept the mother's word for the result. With regard to false-negative results, it is important that the same piece of flourpaper shall not be used on more than one individual.

Summary and Conclusions

Simultaneous tests on 999 children using O.T. jelly stored in a refrigerator and at room temperature for a period of from 11 to 15 months show only four differences in results on the fifth day. The jelly may therefore be kept at room temperature without loss of potency.

A series of tests using O.T. jelly and P.P.D. jelly simultaneously and read serially confirms the previously reported findings that O.T. jelly gives a higher proportion of positive results on the third day than does P.P.D. jelly, the differences between the two being 3.6% on the third day, 1.3% on the fifth day, and 0.8% on the sixth day. Thus the previously unsatisfactory results with P.P.D. jelly are seen to be due to the fact that it is later in giving positive reactions.

A series of tests using O.T. jelly only and read serially shows a progressive rise in positive results up to the sixth day; on the sixth day one test previously three times positive became negative and reactions tended to fade. On the seventh day 13 reactions previously positive on three occasions had become negative. The optimum day for the reading of O.T. jelly tests is therefore the fifth day, but this may be extended to early on the sixth day. Tests should not be read as early as the third day, as there may be a significant number of so-called false-positive tests due to plaster reaction and other factors, and as there will be an appreciable proportion of false-negative reactions. The seventh day shows a fall in the number of positive reactions.

Serial readings in a series of 746 individuals show that only once did a positive result become negative before the sixth day; this is regarded as a false-positive result on the third day, which should not be used for reading. In another series of 510 individuals one case was recorded as positive on the fourth and seventh days and negative on the fifth and sixth. This is admitted to be an error of technique, and stresses the need for controls. Thus, in a total of 1,256 individuals, only one case read on the fifth day gave a result possibly inconsistent with the true tuberculin state as shown by other serial readings; these have been shown previously to give results between those found with the 10 T.U. and the 100 T.U. Mantoux test.

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Medical Memorandum

Ununited Fractures of the Clavicle

There are few reports of ununited fractures of the clavicle in the literature. The two largest series are those of Berkheiser (1937) (nine cases) and Ghormley *et al.* (1941) (20 cases). These latter were collected from the records of the Mayo Clinic between 1913 and 1939, and the authors could find no previous references in the literature other than that of Berkheiser. Amongst their 20 cases 3 were classified as possibly being congenital pseudoarthroses. One was in a female child of 2 years with a fracture of the outer third of the left clavicle in whom no previous treatment had been given. There were no symptoms, no operation was carried out, and there was excellent function. The second case was that of a man aged 33 in whom a fracture was apparently detected in infancy; a congenital origin was suggested but not proved. The fracture was in the middle third of the left clavicle and there had been no previous treatment. The only symptom was mobility at the fracture site. A bone graft was inserted and union resulted. The third case was that of a girl of 18 months; again a congenital origin was suggested but not proved. The fracture was in the middle third of the right clavicle. No previous treatment had been given, and again the only symptom was mobility at the site of fracture. Despite the youthful age of the patient a bone graft was inserted and union resulted.

The fourth case in their series was that of a girl aged 8 years who fell in her bath when 2½ years old. The right clavicle was fractured in the middle third. No record of any previous treatment was obtained. Once again the only symptom was the movement at the fracture site. Open reduction was carried out with the insertion of catgut sutures, but the follow-up was insufficient for observation of the final result. All the other cases recorded in the papers consulted were in adults. The case here recorded occurred in a young child.

CASE REPORT

A female child aged 20 months was first seen in the out-patient department on April 23, 1951. She was referred from a welfare clinic because of deformity of the right clavicle (? as a result of birth injury or as a case of cleidocranial dysostosis). The patient was a healthy child, the firstborn, and her mother was in her twenties. There were no