Its main use is in serial measurements to test the response to drugs and other antithyroid substances. Other possible uses are discussed.

I wish to thank my clinical colleagues at New End Hospital for permission to use their material and also Miss E. V. Webb for her technical assistance.

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OCCULT BLOOD IN FAECES AFTER ADMINISTRATION OF ASPIRIN

BY

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It is known that aspirin (acetylsalicylic acid) may occasionally cause a gastric haemorrhage due to gastritis or a peptic ulcer (Douthwaite and Lintott, 1938; Hurst and Lintott, 1939; Hurst, 1943; Douthwaite, 1954; Muir and Cossar, 1955; Kelly, 1956; Lange, 1957). Despite the frequent use of this drug such complications have been rare. Moreover, it is difficult if not impossible—certainly in individual cases—to establish a direct proof of an immediate causal connexion. This may be a reason why insufficient thought has been given to this possibility.

In some of our patients, who had been treated with aspirin for rheumatoid arthritis, unexplained occult blood in the stools occurred. This article describes an attempt to determine the possible role of aspirin as a cause of this blood loss. The only paper on this subject was published by Lange in November, 1957, concomitantly with my thesis which recorded the results of our own investigation. Lange came to the conclusion that, even when the most readily soluble salicylic acid preparations were used, irritation to the gastric mucosa, accompanied by an occult loss of blood, could not be avoided. He was of the opinion that this irritation was of a general nature and was not confined to ultrasensitive persons. According to him the frequency of the occult loss of blood could be reduced if the patient took the medicine after meals. He furthermore suggested that the frequency of this blood loss might also be reduced if the tablets were given a good coating.

As Lange himself points out, his tests are open to criticism. He did not ascertain in all his test cases whether the occult loss of blood could not be due to some other cause than the taking of aspirin preparations. Furthermore, he did not prescribe a meat-free diet for his patients, and consequently there was always a possibility of the benzidine reaction in the faeces being influenced by the quantity of meat consumed by the patients prior to the tests. Lange accordingly found a relatively large number of instances in which there were positive benzidine reactions in the cases of patients who had not been treated with aspirin, whereas they should have been negative, provided that there was nothing else to

cause bleeding. Moreover, he does not state the number of patients who had a positive benzidine reaction in the faeces, but only how many positive and negative specimens of faeces had been obtained from a group of patients during a certain period of time. It would have been more valuable if from each of the patients the same number of samples of faeces had been collected. During our tests we eliminated the above-mentioned drawbacks.

Method of Investigation

Since the results of tests for occult blood in the faeces are far from reliable in out-patients, the investigation was carried out only on patients who were hospitalized because of some rheumatic complaint. Those whose histories recorded stomach trouble were excluded from treatment with aspirin. Otherwise no selection was made.

The aspirin was administered in the form of tablets taken with milk or water shortly after a meal. As, according to the literature, a distribution of fine particles is less harmful than concentrated bulk, the patients included in this study were emphatically told not to swallow the tablets whole, but to permit them to disintegrate in the mouth or to chew them. It might have been better to administer the substance in the form of powder; but we gave up this idea, as patients generally object to taking it in this form and would seldom do so at home; it seemed to us that it would be better to carry out our experiments under conditions that were as near as possible to those generally prevailing in actual practice. We did, however, administer the drug in powder form to a small group of persons to determine whether results might be different.

The quantity of aspirin given as a medicine was not changed. In the main the quantity was 750 to 3,000 mg. a day, a few larger amounts being given as an exception. This moderate dosage may be taken as a criterion for the quantities generally administered in practice.

A meat-free diet was prescribed and the patient was not allowed to brush his teeth. In order to obviate possible disturbing factors, green vegetables and preparations containing iron were also forbidden; and, to preclude the possible influence of food consumed previously, no use was made of the first three lots of faeces produced after the diet had begun.

The benzidine reaction test was carried out as follows: Approximately 150 mg. of benzidine was dissolved in 7 ml. of ethyl alcohol 96%; to this was added 7 ml. of glacial acetic acid and 7 ml. of hydrogen peroxide. The strength of the resultant benzidine solution was therefore approximately 0.75%.

Gregersen (1919) showed that the benzidine reaction becomes more rapid in proportion to the concentration of the benzidine solution. He therefore recommended a solution with a strength of 0.5%, while Hulst (1933) obtained good results with a solution of 1%. We therefore certainly did not use too high a concentration of the solution in our experiment. This is proved by the fact that the reaction was always negative in the periods when no aspirin was taken. After the benzidine solution had been prepared we waited a while to make sure that it did not become coloured through the presence of impurities before the faeces were added. Then, using a glass rod, we took a small quantity of faeces from the centre of the mass and mixed it well with the benzidine solution. The following criteria were established:

Strongly positive ..	Deep blue colouring within 20 seconds
Positive ..	Deep blue colouring within 60 seconds
Slightly positive ..	Greenish blue colouring within 60 seconds
A trace positive ..	Green colouring within 60 seconds
Negative ..	No colouring within 60 seconds

In order to ensure the greatest possible uniformity in these observations all benzidine tests were carried out by the same technician.

Only after a positive or a negative reaction had been found in three successive specimens of faeces was the result

recorded as such. A benzidine reaction which showed only a trace (green colouring within 60 seconds) after aspirin had been taken was regarded as negative. As a rule the benzidine diet was prescribed after the patient had been taking aspirin for 14 days. In some cases, however, the diet was prescribed after the patients had been taking the medicine for a much longer period. A patient was said to react to aspirin *negatively* when the benzidine reaction was still not positive after aspirin had been taken for 20 days or longer (the last six days of the period with a diet).

A patient was said to react to aspirin *positively* when the benzidine reaction was positive during the taking of aspirin and became negative when he stopped taking it. The following scheme illustrates this classification.

Aspirin given	{ Benzidine - Benzidine - Benzidine - }	Patient reacting negatively to aspirin.
Aspirin given	{ Benzidine + Benzidine + Benzidine + }	Aspirin stopped
	{ Benzidine - Benzidine - Benzidine - }	patient reacting positively to aspirin.

As it was found that "entrosalyl" (coated sodium salicylate) never caused a positive benzidine reaction, those patients for whom salicyl therapy was desirable were given this medicine after they had stopped taking aspirin.

The results obtained when aspirin was taken were checked in two ways: (1) By determining the possibility of reproducing the phenomenon during alternating periods with and without administration of aspirin. Here the patient himself serves as a control. (2) By bringing groups of healthy volunteers into the scheme. With these control groups of healthy men and women we followed the same method of testing.

Results

Altogether 144 patients were examined. In four cases an alternating positive and negative benzidine reaction was observed after the patients had taken aspirin, and they could therefore not be designated as reacting positively or negatively. These four cases are left out of further consideration. Of the remaining 140, 95 showed a positive reaction to aspirin. These 140 patients comprised 38 males and 102 females; 23 and 72 respectively showed a positive reaction to aspirin (Table I).

TABLE I

	No.	Positively Reacting
Males	38	23 (60.5%)
Females	102	72 (70.6%)
Total	140	95 (67.9%)

Out of the 95 patients who had reacted positively, 79 who needed further treatment with salicyl were given sodium salicylate instead of aspirin (10 patients were given ordinary tablets and 69 coated tablets). In all these cases the benzidine reaction became negative.

Reproduction of the Phenomenon.—In 27 of the 28 cases in which the possibility of reproducing the phenomenon was examined, we were able to cause a repetition of the positive or negative benzidine reactions by administering or not administering aspirin. Examples are given in the Graph in which it is shown how the benzidine reaction repeatedly became positive after the administration of aspirin and negative when the drug was discontinued. In one case it was not possible to reproduce this condition. After this patient had taken aspirin for 18 months the benzidine reaction was strongly positive. When entrosalyl was substituted the reaction became negative. When aspirin was administered again the benzidine reaction was still negative after 45 days. It was not possible to ascertain the reaction of this patient again at a later date.

Controls with Groups of Healthy Volunteers

The possibility that rheumatic patients would react to aspirin differently from healthy persons should be con-

sidered. For this reason the same method of testing was applied to a number of men and women who could be assumed to be healthy. If a person was found to have any sort of gastric complaint he was excluded from the experiment.

It was found impossible to take an absolutely random sample from the general population. We had to confine ourselves to persons who took their meals in groups. This made it easier to check whether the diet prescribed was being strictly observed and also whether the tablets were taken as directed.

The control groups consisted of 20 women and 20 men (Table II). The doses prescribed for the 20 women were: 8 women to take 3 g. a day (3×2 tablets); 12 women to take 1.5 g. a day (3×1 tablet). It was our intention to

TABLE II

Quantity of Aspirin (mg./day)	Negatively Reacting	Positively Reacting			
		Total	Slightly Positive	Positive	Strongly Positive
Females					
1,500	3	9	—	3	6
3,000	2	6	1	1	4
Total	5	15	1	4	10
Males					
1,500	4	16	1	7	8

split the group of men in the same way, but when a gastric ulcer was found in one of the women in the 3 g./day group it was decided for safety's sake not to give the dose again, although this isolated case may have been merely coincidental. Consequently each of the 20 men was given 1.5 g. a day.

Table III shows a comparison between the results obtained with the control group and those obtained with the patients.

TABLE III

	No.		Positively Reacting	
	Females	Males	Females	Males
Control group ..	20	20	15 (75%)	16 (80%)
Patients	102	38	72 (70.6%)	23 (60.5%)
Total	122	58	87 (71.3%)	39 (67.2%)

If we now summarize the results of this experiment we find that after taking aspirin a large proportion of the persons examined (70%) had a positive benzidine reaction in the faeces (Table IV).

TABLE IV

	No.	Positively Reacting
Males	58	39 (67.2%)
Females	122	87 (71.3%)
Total	180	126 (70%)

Influence of Dosage

The quantity of aspirin given to the patients as a part of the medical treatment varied from 750 to 6,000 mg. a day. The customary doses were 1,500 and 3,000 mg. a day to 68 and 30 patients respectively. We did not find that a positive benzidine reaction occurred more often in those larger doses.

When the positive reactions were divided into slightly positive, positive, and strongly positive, we likewise found no distinctive difference between the results from larger or smaller doses.

No association was found between the ages of patients and their reaction to aspirin. The age of the patients was mostly between 40 and 60 years; there were a few younger and older patients—some of 11 and some of 72 years. On the whole, younger adults were taken for the control group.

As stated in the description of the method applied, the benzidine diet was as a rule prescribed after the patient had been taking aspirin for 14 days, and the first three lots of faeces were not examined.

In order to determine how rapidly the benzidine reaction can become positive we examined the stools of four patients from the very first day on which aspirin was taken. In these four cases the change from negative to positive occurred after three, six, four, and three days respectively (see Cases 1 and 2 in Graph).

Nevertheless the change need not always occur in such a short time. For instance, when we tried to reproduce the condition in a female patient who had originally reacted positively we found no clearly positive reaction even after three weeks of aspirin treatment. When the benzidine reaction was checked again after a space of 60 days it was found to be definitely positive (see Case 4 in Graph).

From the examples given it will be seen that among those persons who were recorded as having reacted negatively during our experiments there may have been some who would have shown a positive reaction during a longer period of observation.

In 70 cases we were able to determine in how many days the benzidine reaction became negative after the administration of aspirin was discontinued. The average period was found to be four to five days, but here again there were some exceptions. In three patients the benzidine reaction was still positive after 20, 23, and 31 days respectively. When the examination was repeated after 56, 43, and 53 days respectively the reaction had become negative.

It appears from our experiments that taking aspirin, even in moderate doses, causes a positive benzidine reaction in the faeces in a high percentage of cases.

It was not possible to find any association between the occurrence of this deviation and the occurrence of subjective complaints. Complaints of a slight feeling of fullness and "burn" in the region of the stomach were made by only a few of our patients. Such complaints were, however, made not only by patients who had reacted positively to aspirin but also by those who had shown a negative reaction. In the case of only one patient, to whom a dose of 3 g. of aspirin a day had been administered, the complaints were of such a nature that treatment had to be stopped. In the female control group, for whom 3 g. a day had been prescribed, complaints of stomach trouble were far more frequent than in the patients who had been given the same doses. Five of the 10 women undergoing the experiment complained of nausea and pains in the stomach. In two cases the pains were so violent that the women were unable to continue with the experiment. It is possible that the frequent occurrence of stomach trouble in this control group was due to a considerable extent to psychological factors. The persons concerned knew that they were undergoing a test, and they may have been expecting gastric troubles. On the other hand, the patients were given aspirin as a medicine, and it is therefore likely that although some of them were troubled they did not complain.

Some research workers have attributed stomach troubles when aspirin was administered to an increase in the value of the gastric acids. We did not carry out any systematic

♀ 63 yrs. C.vdK-H.

R.A. S.M. 102/56

R.A. = Rheumatoid Arthritis

2g. Aspirin
2g. Enterosalicyl

♀ 55 yrs. C. B. - K.

R.A. S.M. 99/55

BENZIDINE

Strongly pos. 4
Slightly pos. 2
Negative 0

Ordinary diet
Benzidine diet

♀ 53 yrs. A.v.A.

R.A. S.M. 31/56

♀ 34 yrs. C.S.-M.

R.A. S.M. 41/56

experiments to determine the gastric acidity when aspirin was taken. As, however, we found five positive reacting patients with an achylia that was refractory to histamine, in addition to a few patients with an increase in gastric acid values after taking aspirin, it may be said that the increase in gastric acid values is possibly not the only factor when stomach troubles occur after the taking of the drug. It has been suggested in the literature that no stomach disorders occur when aspirin is administered as a powder. We have already said why we did not regularly give it in this form. We did, however, give a small control group of four patients and six healthy volunteers 500 mg. of aspirin powder suspended in water three times daily after meals. All these persons had previously shown a positive benzidine reaction after one tablet of 500 mg. had been taken three times a day. In all 10 cases there was once again a loss of blood found in the faeces. There was no clear difference in the strength of the reactions compared with those which occurred when tablets had been taken.

It would appear that the ideal substitute for the ordinary tablets would be coated tablets of aspirin, which would not disintegrate until they reached the small intestine. Talkov *et al.* (1950) do mention the disappearance of subjective disorders after patients had taken such tablets, but this does not imply that there was no occult loss of blood. We carried out a tentative experiment with coated tablets, which we gave to 20 patients who were showing a positive benzidine reaction caused by taking ordinary tablets. In 5 of these 20 cases the benzidine reaction became negative within four to seven days after taking the coated tablets. The reaction of two others became clearly less strongly positive, and in the 13 remaining cases the reaction after an average of 13 days was still unchanged in intensity.

From the data given in the literature it may be concluded that when aspirin is taken in moderation it is highly improbable that hypoprothrombinaemia is the cause of the gastric haemorrhage. Nevertheless, to ascertain whether this was the case four patients with strongly positive benzidine reactions during the administration of aspirin were analysed with regard to their coagulation mechanism. No disorder was found, and notably there was no hypoprothrombinaemia. Time and again normal values for the bleeding-time were found. Therefore in our opinion we need not take into account the possibility of a disorder in the coagulation mechanism of the blood being the cause of the positive benzidine reaction which we had found.

For various reasons we did not carry out a systematic x-ray examination whether or not there was an ulcer in these cases, especially as there were no complaints. The stomach and intestines were radiographed in only four cases in which the patients showed a positive reaction. There was no sign of disorder in any of these x-ray films that would account for the positive benzidine reaction. We did, however, prove by means of x-ray films the presence of a gastric ulcer in a woman in the control group who had been taking 3 g. of aspirin a day for a period of three weeks. This woman had never previously complained of stomach trouble. As she had violent pains coupled with a strongly positive benzidine reaction after taking aspirin we made an x-ray examination of the stomach. Unfortunately we did not have an x-ray film of her stomach taken before she had the aspirin. There is accordingly no proof that the gastric ulcer was brought about by the aspirin. It can be said with greater certainty that the aspirin was the cause of the stomach troubles and of the strongly positive benzidine reaction. For, after the medicine had not been taken for four days the stomach troubles ceased and the benzidine reaction became negative.

We considered the possibility of the positive benzidine reaction, after taking aspirin, being due to a substance other than blood. In order to preclude this possibility the stools of six patients were examined spectroscopically and spectrophotometrically. In cases with a positive benzidine reaction we found a typical blood-absorption curve. The experiment is explained at greater length elsewhere (Stubbs, 1957). Kelly (1956) has stated that the loss of

blood as a consequence of the taking of aspirin may lead to serious anaemia. We on our part found a woman of 23 suffering from extreme anaemia (Hb content 30%), which had been brought about by taking not more than two tablets of 500 mg. of aspirin a day. In the hospital we found the benzidine reaction negative, as no more aspirin was administered after the patient was admitted. When we administered a tablet of 500 mg. of aspirin three times a day during two periods, after we had taken all kinds of precautionary measures, we found signs of melaena after four days and again after seven days, without any complaint on the part of the patient. No disorder could be found when the patient was suffering from melaena, either by x-ray examination or by coagulation tests; the bleeding-time was also normal. After iron had been administered orally it was found that the Hb content had risen to 90% within two months of taking aspirin. These extreme cases are, however, exceptions and are fortunately seldom met with. The occult loss of blood, on the other hand, is a complication very often encountered in aspirin therapy, as we have already said.

To obtain an idea of the amount of blood lost in such cases a few patients were given a small quantity of their own blood to drink 10 times a day. In this way we were able to ascertain with what loss of blood the criteria employed for determining the strength of the benzidine reaction approximately corresponds.* It was found that when 4 ml. of blood was administered there was a strongly positive benzidine reaction.

Although this experiment was carried out with only a few patients one might conclude from the results that a patient with a strongly positive reaction loses about 30 times 4 ml. = 120 ml. of blood a month. Those patients who show a strongly positive reaction within the space of a few seconds will probably lose even more blood.

By way of comparison we might take the average quantity of blood a woman loses a month during the menses. According to Wright (1952) the loss amounts to 40 ml. (varying from 10 to 210 ml.).

Discussion

It is known that bleeding may occur in the stomach after a person has taken aspirin. But, considering the enormous quantities of this drug which are consumed and the frequency with which it is taken, such an occurrence may be regarded as an exception.

Subjective complaints of the stomach are not of rare occurrence, but, so far as we know, no one has ever systematically tried to ascertain whether these coincide with organic disturbances. When there are no subjective complaints at all it is generally supposed that objective disorders are out of the question. From our experiments, however, it appeared that about 70% of the persons who took this medicine, and who mostly had no complaints, lost blood with the faeces. It goes without saying that the observance of a positive benzidine reaction is also dependent on the sensitivity of the reaction. The existence of a physiological blood content of the faeces was established in experiments by Hulst (1933) and others.

From this it would appear desirable not to raise the sensitivity of the reaction too high by making the concentration of the benzidine solution too strong. On the other hand, it is of interest clinically to be able to demonstrate the pathological loss of even small quantities of blood. As already stated, we used a benzidine solution of about 0.75% for our experiment, on the basis of data given in the literature. And it appears, from the fact that the reaction was invariably negative during the control periods without the administration of aspirin, that the reaction in the course of the experiment was not too sensitive.

The observations made by Douthwaite (1938, 1954) and other research workers, who with the aid of the gastroscope saw rapid changes occur in the mucous membranes only around the particles of aspirin and not at other places

*A detailed description of the method applied was given in our thesis (Stubbs, 1957).

on the mucous membranes, make it appear very likely that a direct local irritation of the gastric mucosa was the cause of the occult loss of blood. An allergic reaction to aspirin seems highly improbable in view of the frequent occurrence of the loss of blood and the absence of any other allergic symptom in any of the patients and control persons examined by us. It appears from the literature that the occurrence of hypothrombinaemia is very improbable when aspirin is taken in moderation. We could not find a disturbance in the coagulation mechanism during the loss of blood in any of the four cases in which we tried to establish this, and therefore the occult loss would also seem unlikely on this account. Furthermore, one should consider the possibility of increased capillary permeability, due to the taking of aspirin, accompanied or not by changes in the capillaries brought about by the sickness itself, being the cause of the occult loss of blood. In view of this possibility we are carrying out further experiments in this connexion. Provisional data on this subject make it improbable that the loss of blood can be due to capillary permeability of this kind. Although an increase in the gastric acid values during the taking of aspirin has been described by most writers, this does not imply that this increase is a causal factor where there is an occult loss of blood. And this is certainly not evidenced by the fact that we were able to demonstrate the occult loss of blood in five patients with an achylia refractory to histamine.

It has been demonstrated that the loss of blood may not always be ignored; this applies especially to the extent to which the patient is already anaemic and in a bad state generally. The taking of aspirin over a long period is most common in the case of persons suffering from rheumatoid arthritis. Many such patients are anaemic, a state which has also always been regarded as a consequence of the rheumatic process. Now that we know that aspirin can cause bleeding, it may be asked whether this has not likewise often played a more or less important part in bringing about anaemia.

As already stated, we gave patients who were suffering from a rheumatic complaint a coated sodium salicylate (entrosaly), where we thought it necessary, instead of the aspirin. In none of these cases did we ever find a positive benzidine reaction. To 10 patients we gave ordinary sodium salicylate tablets—that is to say, not coated tablets. In these 10 cases also we did not find a single patient with a positive benzidine reaction. This therefore goes to show that the coating is not essential, as sodium salicylate apparently causes no irritation. The drawback of sodium salicylate, however, is that it has a weaker analgesic effect than aspirin. Moreover, when it is not coated it has a very disagreeable taste.

Thus the problem is to find a form for the aspirin which does not cause irritation of the mucous membranes. Consequently it is suggested, for instance, that the drug be given in powder form. But so far as the occurrence of occult bleeding is concerned we could not substantiate that the taking of powder as opposed to tablets made any difference in our examination of 10 patients.

Another possibility is the administration of aspirin in a coated form, in which case the tablet does not disintegrate until it reaches the intestine. Of the 20 patients examined by us after they had taken the coated form of tablet only five showed a negative benzidine reaction. It is not clear why the benzidine reaction was not negative in all 20 of the cases when we administered these tablets. We are not in a position to say whether any of the tablets were imperfectly coated or not. Even with a good coating there is, however, the possibility of occult loss of blood due to irritation of the intestinal mucosa, about which nothing is known.

Conclusions

From the experiments described above it appears that there is a very frequent loss of blood with the stools. The amount of aspirin administered has no evident influence on the occurrence and the seriousness of the disorders. The

administration of aspirin in powder form suspended in water produces the same results as those obtained when tablets are given. Although it has not been definitely established in what way the occult loss of blood is caused when aspirin is taken, our experiments, following on the information already available, tend to show that a local irritating effect on the gastric mucosa is most probable. When patients are treated for a long time with aspirin it is advisable that there be a regular check of the benzidine reaction in the faeces. If the reaction is found to be strongly positive a discontinuance of this treatment seems to be indicated.

When occult blood is found in the faeces without known cause it is necessary, in the first place, to preclude the possibility that this might be occasioned by aspirin before carrying out an extensive analysis with, among other things, a complete x-ray examination. We must also consider aspirin as being the possible causal factor (as in one of our own cases) when a case of serious anaemia occurs in which a negative benzidine reaction can be found due to the discontinuance of the drug.

Summary

Occult loss of blood in the faeces was proved to occur in about 70% of the 180 persons to whom aspirin in the form of tablets had been administered. The details of the conditions of this study and the criteria applied have been given. Results obtained with the 140 patients treated with aspirin in the wards of the rheumatology department were entirely comparable to those found in the control groups, consisting of 40 healthy volunteers.

It was possible to prove conclusively that aspirin was the cause of this loss of blood, as this phenomenon appeared to be reproducible. The quantity of aspirin administered did not have a great influence on the occurrence and the seriousness of the disorder. The most common doses were 1,500 mg. and 3,000 mg. a day. Identical results were obtained when aspirin in powder form suspended in water was administered to a small group and when the same persons were given tablets. Finally, the results obtained when coated tablets of aspirin were administered are recorded.

It was possible to demonstrate spectroscopically and spectrophotometrically that a positive benzidine reaction after the taking of aspirin is indeed due to the presence of blood. In a number of cases it was shown on the basis of the strength of the benzidine reaction that the quantity of blood lost when aspirin was taken may not always be ignored.

These experiments were carried out in the Rheumatological Department "Sole Mio" at Noordwijk and in the Department for Rheumatology and Internal Medicine of the University Hospital at Leyden. I am grateful to the nurses who by their loyal co-operation made these experiments possible, and to those volunteers who came forward to form the necessary control groups. To Miss C. van Heulen, technician in Noordwijk, I am extremely indebted for the manner in which she collaborated in carrying out the tests. The interest and practical assistance of Miss J. H. Pietersen, rheumatologist in Noordwijk, constituted valuable support in the course of these studies.

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