

The diagnostic value of hemolysis in cases of cancer / R. Ottenberg and A.A. Epstein.

Contributors

Ottenberg, Reuben, 1882-1959.
Epstein, Albert Arthur, 1880-1965.
Royal College of Surgeons of England

Publication/Creation

Chicago : American Medical Association, 1909.

Persistent URL

<https://wellcomecollection.org/works/wdnf29g6>

Provider

Royal College of Surgeons

License and attribution

This material has been provided by This material has been provided by The Royal College of Surgeons of England. The original may be consulted at The Royal College of Surgeons of England. where the originals may be consulted. Conditions of use: it is possible this item is protected by copyright and/or related rights. You are free to use this item in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you need to obtain permission from the rights-holder(s).

P.C. 9.

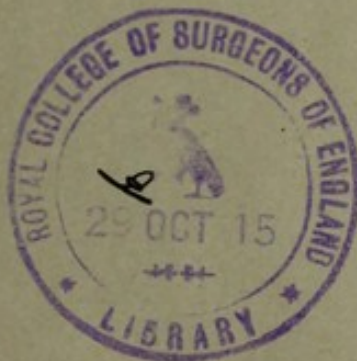
11.

THE DIAGNOSTIC VALUE OF HEMOLYSIS IN CASES OF CANCER

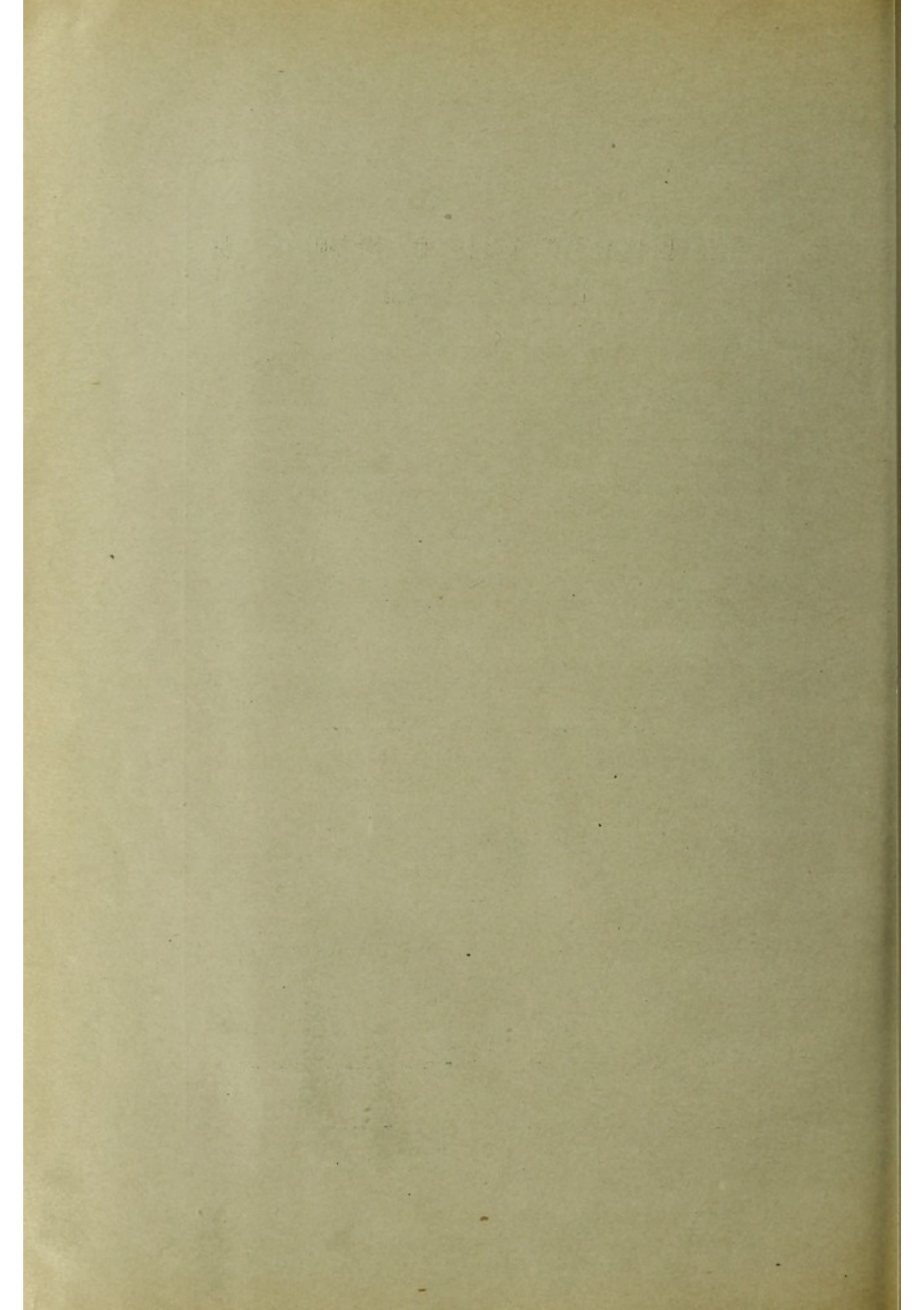
R. OTTENBERG AND A. A. EPSTEIN
NEW YORK

10

Reprinted from The Archives of Internal Medicine.
June, 1909



CHICAGO
AMERICAN MEDICAL ASSOCIATION, ONE HUNDRED AND THREE DEARBORN AVENUE
1909





THE DIAGNOSTIC VALUE OF HEMOLYSIS IN CASES OF CANCER

R. OTTENBERG AND A. A. EPSTEIN
NEW YORK

Recent researches on various biologic properties of the blood in cases of cancer have given hope that a diagnostic blood test could be found. Of these studies none at first seemed more promising than those which dealt with the hemolytic properties of the blood serum.

Within the last year the statements of Crile have aroused much expectation. Crile found the occurrence of isohemolytic serum so very frequent (80 to 100 per cent. of the cases) in carcinoma, and so very rare in other diseases, that from his work there seemed little doubt that the hemolytic reaction would be exceedingly valuable in diagnosis. Other workers, however, have not confirmed his findings, and the whole question as to the value of this method required re-examination.

With the aid of a modified technic, the chief advantage of which is that it enables us to perform a large number of tests readily with a small amount of blood, we examined 100 persons.¹ These were taken in groups of ten or fifteen, the serum of each one of the groups being tried in turn on the washed red blood cells of every other member of the group. The usual controls of each variety of red cells with its own serum and with salt solution were made.

The question of technic, which will only be touched on briefly here, is of considerable importance in comparing the results of different workers. In a preliminary series of 100 cases (over 1,500 individual tests) we attempted to settle for ourselves various questions of technic. We believe that the method which we have finally adopted (and which is described above) gives results strictly comparable with those of the usual method. It may be admitted, as a theoretical possibility, that an exceedingly faint trace of hemolysis might be overlooked in this method, on account of the smaller diameter of the tubes (3.5 to 4 millimeters as compared with the usual 8 to 10 millimeter test-tubes). In practice this source of error is negligible.² The method of preparing the erythro-

1. The majority of these cases were in Mt. Sinai Hospital. The blood of some was kindly supplied us by Dr. R. Weil from the German Hospital, and by Dr. Brewer and Dr. James from patients in Roosevelt Hospital.

2. In these tests, at the suggestion of Dr. Weil, the serum was used in concentrated form—3 parts of serum to 1 of 20 per cent. red-cell suspension, so that the cells were present in 5 per cent. strength in the mixture.

cyte suspension used by Crile, which has not been published, but which Dr. Crile was kind enough to communicate to us by letter, was given up, after having been tried in sixty-nine cases, because of the inconstant results.

The nature of the results can best be appreciated by reference to the accompanying tables. The intensity of the hemolysis in each test is indicated approximately by the number of plus marks. The horizontal columns represent sera, the vertical columns the corresponding blood cells. It will be noticed that even strongly hemolytic sera seldom lake more than half of the different varieties of red blood cells with which they are mixed. In doing the experiments, it should be said, the tubes were numbered by another person in such a way that the person who made the readings was not aware which blood he was examining.

The results, as a whole, without regard to the intensity of the reaction or the number of different kinds of red cells hemolysed by each serum, may be summarized as follows:

Of the 100 subjects 38 were suffering from malignant tumors, 40 had other diseases and 22 were apparently healthy. (The diagnosis in nearly all of the tumor cases was confirmed by operation and microscopic report. The diagnosis in the other cases rested generally on clinical data.)

In the 38 cases of malignant tumor, 28 patients had serum which was hemolytic—a proportion of 76 per cent. In the 40 other diseases, 20 patients had hemolytic sera (50 per cent.). Of these, 6 were cases of tuberculosis—a well-recognized cause of isohemolysis; 5 of the 6 sera were hemolytic. If we exclude the tuberculous cases, 15 cases, that is 42 per cent., of the 35 remaining cases of disease were hemolytic. The diagnoses in these cases were as follows:

- Cases 151 and 75.—Fibroadenoma of breast (two cases).
- Case 95.—Catarrhal jaundice.
- Case 94.—Chronic gastritis (?).
- Case 108.—Postpartum general infection.
- Case 124.—Postoperative adhesions (gall bladder).
- Case 138.—Diffuse lipoma.
- Case 147.—Subacute bacterial endocarditis and streptococcemia.
- Case 162.—Diabetes mellitus.
- Case 164.—Endocarditis (chronic).
- Case 169.—Appendicitis.
- Case 178.—Colloid goiter.
- Case 180.—Plumbism.
- Case 185.—Hodgkin's disease.
- Case 127.—Chronic thyroiditis (tuberculous).

Of the 22 normal persons, 1 showed hemolysis (5 per cent.) This was a patient who had been operated on for hernia several weeks before and in whom no signs or symptoms of any disease could be elicited.

TABLE I.—HEMOLYSIS IN CANCER PATIENTS AND OTHER SUBJECTS

Subjects	Red Blood Cells.											
	131	133	134	135	136	137	138	140	141	142	143	144
Normal	—	—	—	—	—	—	—	—	—	—	—	—
Fibroadenoma breast..	++	—	++++	++++	—	—	—	+	—	++++	—	—
Carcinoma liver	—	—	—	—	—	—	—	—	—	—	—	—
Tuberculosis	—	—	—	—	—	—	—	—	—	—	—	—
Tuberculosis	+	+	—	—	—	—	—	—	—	—	+	—
Tuberculosis	—	+	—	++	—	—	—	+	—	+	++	—
Normal (hernia)	++	+++	+++	++	—	—	—	++	—	—	+++	—
Lipoma	+	++	++	++	—	—	—	+	—	++	++	—
Epithelioma jaw	+	—	++	++	+	—	—	+	—	—	+	—
Carcinoma rectum	—	—	—	—	+	—	—	—	—	—	—	—
Normal	—	—	—	—	—	—	—	—	—	—	—	—
Carcinoma	—	—	—	—	+	—	—	—	—	—	—	—
Rodent ulcer	—	—	—	—	—	—	—	—	—	—	—	—
Rodent ulcer	++	+	—	—	—	—	—	—	—	—	—	—
Normal	—	—	—	—	—	—	—	—	—	—	—	—
Normal	—	—	—	—	—	—	—	—	—	—	—	—
Control	—	—	—	—	—	—	—	—	—	—	—	—

Serum

If we attempt to make the work to some extent quantitative by having regard only to the pronounced hemolyses (indicated by two or more vertical marks in the tables), the percentage of positive results in malignant disease as compared with other diseases is somewhat better. Nineteen of the 27 sera which gave strong hemolysis were from cases of cancer (74 per cent.). That is, 50 per cent. of the 38 cases of cancer gave strong hemolysis. Seven cases (17 per cent.) of the 40 other diseases examined also gave very pronounced hemolyses and the 1 hemolytic case in the group of normals also showed a very strong hemolysis. These actively lytic cases were as follows: Case 94, chronic gastritis (?); Case 127, chronic thyroiditis (tuberculous); Case 137, normal (hernia); Case 138, diffuse lipoma; Case 178, colloid goiter; Case 180, lead-poisoning; Case 181, tuberculosis; Case 75, fibroadenoma of breast. These results are curiously parallel with those obtained by Kelling's method, in which the lytic effect of human sera on chicken red cells is estimated quantitatively and only the strong hemolyses are regarded as positive. (His interesting experiments require confirmation.)

Other methods of analysis give results less favorable (as far as diagnostic possibilities are concerned) than this. Thus taking the mere number of different varieties of red cells out of all those subjected to each serum, and setting up three as an arbitrary standard, we find that of the 42 sera which laked three or more different varieties of red cells, 24 were from cases of malignancy, whereas of the 16 sera which laked only one or two varieties of cells, 10 were from cases of cancer.

Likewise with the method introduced by Weil, "based not only on the reaction of the serum, but also on the degree of resistance of the corpuscles to that serum," it is seen that generally a given hemolytic serum falls into Weil's first group (hemolytic toward non-cancer corpuscles, but not toward cancer corpuscles), or his second group (lytic to both kinds of corpuscles), chiefly according to whether it is a weakly or strongly lytic serum. Of 25 cases belonging to the first group, 14 were cases of malignant tumor; of 29 belonging to the second group, 17 were cancer cases; the grouping therefore seems to have no special significance.

If attention is paid only to the resistance of the red blood cells (and the high resistance of cancer red blood cells to all sorts of lytic agents has been recognized for years), it is seen that red blood cells resistant to all the sera applied to them occurred chiefly in those cases whose serum was itself hemolytic, and not much more frequently in cancer than in

TABLE 2.—HEMOLYSIS IN CANCER PATIENTS AND OTHER SUBJECTS

Subjects	Red Blood Cells.*													
	157	154	152	156	148	150	147	155	158	151	153	149	142	140
Carcinoma of stomach.....	157	—	—	—	++	—	+++	+++	+	—	+	—	—	++
Normal	154	+	—	—	—	++	—	—	—	—	—	—	—	++
Sarcoma of scalp.....	152	—	—	+	+++	+	+++	++	—	++	++	++	—	++
Normal	156	—	—	—	—	+++	+++	—	—	+	+	+	—	+++
Normal	148	—	—	—	—	—	++	—	—	—	—	—	—	—
Normal	150	—	+	—	—	—	++	—	—	—	—	—	—	++
Streptococemia	147	—	+	+	+	+	—	—	—	—	+	—	—	—
Normal	155	—	+	—	—	+	+++	—	—	—	—	—	—	++
Tuberculosis	158	—	—	+	—	+	+	—	—	+	+	—	—	+
Fibroadenoma of breast...	151	—	++	+	+	—	+	—	+	—	++	++	—	—
Endothelial sarcoma	153	—	+	++	—	++	++	—	+	—	—	+	—	—
Carcinoma of breast.....	149	—	+	+	—	+	+	—	—	—	—	—	—	—
Carcinoma of lung.....	142	—	+	+	+	++	++	++	—	+	++	++	—	++
Carcinoma of rectum.....	140	—	+	+	—	+	+	—	—	—	—	—	—	—
Saline control	—	+	—	—	—	+	+	—	—	—	+	+	—	+

* Of course those red blood cells which showed hemolysis in the saline controls are not counted in determining which sera are hemolytic. These hemolyses were due to the fact that the red cells used in these cases were more than twenty-four hours old.

other diseases. Thus the twenty-two cases with highly resistant red cells may be classified:

	Cancer.	Not Cancer.
With hemolytic serum.....	11	7
With non-hemolytic serum.....	1	3

But hemolytic serum does not invariably correspond to resistant red cells, as will be seen from the grouping of the forty-eight non-resistant red cells:

	Cancer.	Not Cancer.
With hemolytic serum.....	10	8
With non-hemolytic serum.....	6	24

Of the tumor cases only four can be said to have been in an early stage; these were Case 117, a small carcinoma of the sigmoid; Case 152, sarcoma of the scalp; Case 163, carcinoma of sigmoid; and Case 188, carcinoma of the pylorus. The other patients (which were such as are admitted to a general hospital for operation) showed either large tumors, metastases, glandular involvement, marked anemia, or other symptoms which prevented their cases from being regarded as early. Strangely enough the sera of the four early tumor cases were all-strongly hemolytic.

The origin of the hemolytic property of the blood serum in disease is not yet clear. That it is not the specific product of any one disease process seems, from the variety of conditions in which it occurs, certain. Its probable source in the autolytic products of necrosis, in certain cases, has been pointed out by Weil. In seven of the carcinoma cases in the present series necrosis was observed in the pathologic findings. The serum of all seven of these patients was hemolytic, that of six of them markedly so. The same explanation is applicable to many, but not all, of the other diseases. In all of the seven cases of tuberculosis the tubercle bacilli had recently been demonstrated in the sputum, and there was therefore probably some breaking down of tissue. In the acute inflammatory and septic conditions, on the other hand, the well-known hemolytic products of the staphylococcus and streptococcus are to be considered. In some of the cases, such as those of diabetes, diffuse lipoma, chronic endocarditis, goiter, lead-poisoning, none of these explanations is adequate.

As a result of this work, the chief object of which has been to determine the value of isohemolytic reactions in diagnosis, we are forced to the unsatisfactory conclusion that the method is not at present to be relied on for diagnosis. While it is true that in a majority of cases of

malignant tumor this property of the blood is shown, it is also shown in a considerable proportion of other diseases. The most that can be said is that in a given case, if tuberculosis can be excluded, a strongly hemolytic serum is rather suspicious of carcinoma.

We desire to thank Dr. A. H. Harrigan for his kind assistance.

